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COMPREHENDING THE ECONOMIC VALUE DRIVERS FOR DIGITAL THERAPEUTICS: A MIXED METHODS BASED APPROACH

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Declaration and Statement of Candidate Contribution

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I take full responsibility for the integrity and quality of the analyses presented. I personally conducted all data analyses, authored each article arising from the research and oversaw their publication process, under the guidance of my supervisor Prof. L. Martin Cloutier at the Université du Québec à Montréal. Prof. Cloutier contributed valuable data and ideas to each paper, ensuring academic rigor.

Each of the three papers (Chapters 4, 5, and 6) has benefited from valuable feedback provided by independant peer reviewers and have been published in the Journal of Medical Internet Research (JMIR), npj Digital Medicine, and JMIR[1], respectively. Each collaborator has granted permission for their joint work to be incorporated into this thesis, with their specific contributions clearly delineated in the author's contribution sections of the respective papers.

Signed:

Date: Aug. 27th, 2025

[1] Chapters 4, 5, and 6 may differ slightly from their corresponding published versions in the Journal of Medical Internet Research (JMIR) and npj Digital Medicine (included in Appendices 1C and 2B). Although each journal has its own editorial and publishing requirements, consistency in these three chapters was prioritized over strict adherence to the original published formats.

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Managerial Summary

Digital Therapeutics (DTx), defined as evidence-based therapeutic treatments powered by high-quality software, are recognized as the “next paradigm” of modern healthcare (Khirasaria et al., 2020). Emerging clinical evidence suggests that DTx can effectively prevent, manage, or treat a spectrum of medical disorders and diseases (Huh et al., 2022). However, despite this promising potential, these therapeutics have yet to become mainstream in healhtcare (Cirkel et al., 2024; Johnson et al., 2024; Prodan et al., 2022; Wang et al., 2023; Williams et al., 2020).

Economic factors increasingly drive healthcare decision-making, particularly influencing regulatory approval, payers’ reimbursement, and pricing decisions for these emerging clinical interventions (Torbica et al., 2020; Yan et al., 2021). These economic considerations also serve as both barriers and facilitators to adoption once DTx become available for physicians to prescribe (Vicki et al., 2020). However, relatively little is known about the capacity of DTx to provide economic value in care (HealthXL, 2021; Kario et al., 2021; Piera-Jiménez et al., 2021; Sapanel et al., 2023). Moreover, the factors driving DTx economic value have not been thoroughly researched, neither in terms of what they are nor how they should be considered (Halminen et al., 2021; Gomes et al., 2022). Recognizing the importance of these economic considerations, recent recommendations for bridging the gap between digital health tool development and implementation emphasize integrating economic considerations into the early stages of technological development (Keogh et al., 2024).

This DBA thesis addresses this important knowledge gap by examining the following main research question: What are the economic value drivers of DTx and how are they considered throughout the product development lifecycle? Through complementary qualitative and mixed method-based approaches, this thesis is structured around three core cascading research studies that include a systematic literature review, group concept mapping (GCM) and a qualitative research approach.

The first paper (Chapter 4) systematically reviews and summarizes the published evidence regarding the cost-effectiveness of clinical-grade mobile app–based DTx. The findings, encompassing 18 studies, indicate that DTx, at least in some use cases and local contexts, can be cost-effective and offer economic value to payers while simultaneously improving care for patients. To date, this study represents the first review reporting costs and factors that influence the economic impact of DTx interventions, such as healthcare resource utilization, pharmaceutical treatment costs, and participants' baseline characteristics. The paper also identifies important methodological shortcomings that must be addressed in future economic evaluations of DTx to reduce the uncertainty surrounding their widespread adoption.

The second paper (Chapter 5) employs GCM, a participatory mixed methods-based approach, to comprehend how healthcare professionals, researchers, industry stakeholders, and public sector representatives collectively conceptualize factors influencing DTx economic value. The study, building upon the initial factors identified in the first paper, extends this foundation by identifying 59 distinct factors, categorized into eight clusters. These factors were evaluated by 62 participants in terms of their importance and current consideration in practice. Three clusters emerged as universal priorities: *DTx Implementation*, *DTx Monetization Models*, and *DTx Associated Costs*. Notably, these areas, while recognized as crucial, are identified as receiving insufficient attention during DTx development, particularly from the research community's perspective. With robust internal reliability estimates and careful examination of external validity threats, the study presents key findings for future research and offers a conceptual framework of priority clusters and factors potentially driving DTx economic value.

Building on these insights from chapters 4 and 5, the third study (Chapter 6) aims to understand why certain economic factors are insufficiently taken into consideration by researchers throughout the DTx development process. The study adopts Critical Realism as an epistemological position to examine the underlying mechanisms and contextual conditions that shape researchers' decision-making processes regarding economic factors in DTx development. Specifically, this study aims to understand why certain economic factors are insufficiently taken into consideration by researchers throughout the DTx development process. Through 17 in-depth interviews with researchers involved in DTx development—including research-engineers, health systems researchers, clinician-researchers, and practitioner-researchers—three interrelated generative mechanisms that systematically influence how researchers approach economic considerations are uncovered: (1) the *Professional Norms* mechanism, operating through a reinforcing loop that systematically prioritize clinical validation while marginalizing economic considerations; (2) the *Researcher Experience* mechanism, revealing how professional training and limited economic literacy create cognitive biases that systematically obscure economic factors; and (3) the *Adoption Uncertainties* mechanism, demonstrating how implementation concerns influence development decisions through both reinforcing and balancing dynamics. The paper discusses the theoretical and practical implications of the findings and provides actionable recommendations for research organizations, individual researchers, and policymakers to enhance economic consideration integration throughout the DTx development lifecycle.

Collectively, the three cascading research studies yield significant theoretical and practical contributions that are important to: (1) understand and characterize the concept of economic value in the context of DTx and identify key factors influencing such economic value, (2) gain a deeper understanding of how these factors are considered early on by various stakeholders involved in DTx development and clinical validation, and (3) develop methodological recommendations to guide these stakeholders in creating conditions that may drive the economic value of DTx. These contributions provide valuable intervention points for strengthening the

DTx development process, moving toward a more comprehensive assessment of clinical, technical, and economic value throughout DTx development, ultimately potentially supporting the adoption of these innovations in healthcare systems.

Key words: digital health; digital therapeutics; economic value drivers; cost-effectiveness, mixed methods-based approach, critical realism, qualitative study, group concept mapping.

Résumé Managérial

Les thérapies digitales (DTx), également connus comme des dispositifs médicaux numériques thérapeutiques fondés sur des preuves de leur bénéfice clinique et alimentés par des logiciels de haute qualité, devraient influencer significativement la prestation et l'utilisation des soins de santé à travers le monde. Les DTx sont considérés comme le "prochain paradigme" des soins de santé modernes (Khirasaria et al., 2020). Il existe en effet des preuves cliniques émergentes que les DTx peuvent prévenir, gérer ou potentiellement traiter un large spectre de troubles médicaux et de maladies (Huh et al., 2022). Cependant, malgré ce potentiel prometteur, ces thérapeutiques n'ont pas encore fait l'objet d'un déploiement généralisé dans le secteur de la santé (Cirkel et al., 2024; Johnson et al., 2024; Prodan et al., 2022; Wang et al., 2023; Williams et al., 2020).

Les facteurs économiques influencent de plus en plus la prise de décision en santé, notamment en ce qui concerne l'approbation réglementaire, les décisions de remboursement des payeurs et les décisions tarifaires pour ces nouvelles interventions cliniques (Torbica et al., 2020; Yan et al., 2021). Ces considérations économiques constituent également à la fois des obstacles et des facilitateurs à l'adoption une fois que les DTx deviennent disponibles pour être potentiellement prescris par des médecins (Vicki et al., 2020). Cependant, la capacité des DTx à fournir une valeur économique dans la prestation de soins de santé n'est pas bien établie (HealthXL, 2021; Kario et al., 2021; Piera-Jiménez et al., 2021; Sapanel et al., 2023). Les facteurs spécifiques qui déterminent de leur valeur économique n'ont pas non plus été rigoureusement étudiés, ni en termes de ce qu'ils sont ni de la façon dont ils devraient être considérés (Halminen et al., 2021; Gomes et al., 2022).

Cette thèse est structurée autour de trois études de recherche séquentielles et interdépendantes incluant une revue systématique de la littérature, une cartographie des concepts en groupe et une approche de recherche qualitative, visant à répondre à la question principale de recherche suivante : Quels sont les facteurs qui contribuent à la valeur économique des DTx et comment sont-ils pris en compte tout au long du cycle de développement du produit?

Le premier article (Chapitre 4) examine et synthétise de manière systématique les preuves publiées sur le rapport coût-efficacité des DTx basées sur des applications mobiles de niveau clinique. Les résultats de 18 études montrent que, dans certains cas d'usage et dans certains contextes locaux, les DTx peuvent être rentables et offrir une valeur économique à de potentiels payeurs, tout en améliorant simultanément la prise en charge des patients. Cette étude constitue la première revue rapportant les coûts et les facteurs influençant l'impact économique des interventions DTx, notamment l'utilisation des ressources de santé, les coûts des traitements pharmaceutiques ainsi que les caractéristiques des participants inclus dans ces études. L'article met également en évidence d'importantes lacunes méthodologiques qui doivent être corrigées dans les futures

évaluations économiques des DTx afin de réduire l'incertitude entourant leur adoption, notamment à grande échelle.

Le deuxième article (Chapitre 5) utilise la cartographie des concepts en groupe, une approche participative mixte, pour comprendre comment les professionnels de santé, les chercheurs, les acteurs de l'industrie et les représentants du secteur public conceptualisent collectivement les facteurs influençant la valeur économique des DTx. L'étude, après avoir repris les facteurs identifiés dans la première étude, va plus loin et identifie 59 facteurs distincts, regroupés en huit clusters. Ces facteurs sont évalués par 62 participants en termes d'importance et de prise en compte au quotidien par ces mêmes acteurs lors du développement d'un DTx. Trois clusters émergent comme des priorités universelles : l'implémentation des DTx, les modèles de monétisation de ces DTx ainsi que les coûts associés. Il est particulièrement important de noter que, bien que ces domaines soient reconnus comme essentiels, ils sont insuffisamment pris en compte lors du développement des DTx, notamment par les chercheurs. Avec des estimations de fiabilité interne et externe solides, cette étude présente des résultats clés pour les recherches futures et propose un cadre conceptuel des clusters prioritaires et des facteurs susceptibles d'influencer la valeur économique des DTx.

Pour comprendre pourquoi certains facteurs économiques sont insuffisamment pris en compte par les chercheurs lors du développement des DTx, le troisième article (Chapitre 6) adopte le réalisme critique comme fondement épistémologique pour examiner les mécanismes sous-jacents et les conditions contextuelles qui façonnent les processus décisionnels de ces acteurs. À travers 17 entretiens approfondis menés auprès de chercheurs impliqués dans des projets DTx – incluant des ingénieurs de recherche, des chercheurs en systèmes de santé, des cliniciens-chercheurs et des praticiens-chercheurs – trois mécanismes génératifs interconnectés influençant systématiquement la prise en compte des considérations économiques sont mis en évidence : (1) Le mécanisme des normes professionnelles en santé, qui fonctionne à travers une boucle de renforcement systématisant la priorité accordée à la validation clinique tout en marginalisant les considérations économiques; (2) Le mécanisme des antécédents et de l'expérience du chercheur, révélant comment la formation professionnelle et une faible littératie économique créent des biais cognitifs occultant systématiquement les facteurs économiques; et (3) Le mécanisme des incertitudes liées à l'adoption des DTx, démontrant comment les préoccupations liées à la mise en œuvre influencent les décisions de développement par le biais de dynamiques de renforcement et d'équilibrage. L'article discute des implications théoriques et pratiques des résultats et fournit des recommandations concrètes à destination des organisations de recherche, des chercheurs individuels et des décideurs politiques afin d'améliorer l'intégration des considérations économiques tout au long du cycle de développement des DTx.

Collectivement, ces trois études de recherche apportent des contributions théoriques et pratiques significatives. Ces contributions visent à : (1) comprendre

et caractériser le concept de valeur économique dans le contexte des DTx et identifier les facteurs clés qui l'influencent ; (2) approfondir la compréhension de la manière dont ces facteurs sont pris en compte en amont par les différents acteurs impliqués dans le développement et la validation clinique des DTx ; et (3) formuler des recommandations méthodologiques permettant d'orienter ces acteurs dans la création de conditions favorisant la valeur économique des DTx. Ces contributions fournissent des leviers d'intervention précieux pour renforcer le processus de développement des DTx, en progressant vers une évaluation plus complète des dimensions clinique, technique et économique tout au long de leur développement, et en soutenant ainsi potentiellement, à terme, l'utilisation de ces innovations au sein des systèmes de santé.

Mots clés: santé numérique; thérapeutiques numériques; moteurs de valeur économique; rapport coût-efficacité; approche par méthodes mixtes; réalisme critique; étude qualitative; cartographie des concepts en groupe.

Publications and Presentations Resulting from this Research

Table 1. Publications resulting from this research

Publication Title	Publication Type	Current Status	Journal Name
A Systematic Literature Review of the Economic Evaluation Associated with Clinical-Grade Mobile Application-Based Interventions	Registration of the systematic literature review research protocol for transparency purposes	**Published on Sept. 19th, 2022** *CRD42022358616*	PROSPERO **PROSPERO** International Prospective Register of Systematic Reviews
Note: PROSPERO, the International Prospective Register of Systematic Reviews, serves as an online repository where researchers document their systematic review protocols prior to initiating the review process. This proactive registration is widely recognized as a best practice in the field, as it enhances the rigor, transparency, and accountability of systematic reviews. PROSPERO is produced by the Centre for Reviews and Dissemination of the University of York and funded by the National Institute for Health Research.			

Paper 1 in this thesis *(Chapter 4):*

Economic Evaluation Associated with Clinical-Grade Mobile App–Based Digital Therapeutic Interventions: Systematic Review	Peer-reviewed scientific article	**Published on Aug. 01st, 2023** *DOI:10.2196/47094*	JMIR Publications Advancing Digital Health & Open Science **Journal of Medical Internet Research** (JMIR) is a Q1 peer-reviewed journal (top 25%) with an **Impact Factor of 7.4** (2023)
Note: The manuscript underwent a rigorous peer review process at the Journal of Medical Internet Research (JMIR), where two independent reviewers evaluated it thoroughly. Following this comprehensive assessment, the journal editor approved the manuscript for publication (see Appendix 1C). For transparency, the original preprint version, published in JMIR Preprint before peer review, is available in Appendix 1B, providing readers insight into the research's evolution throughout the publication process.			

Paper 2 in this thesis *(Chapter 5):*

A Group Concept Mapping Study of Stakeholder Perspectives on Digital Therapeutics Economic Value Drivers	Peer-reviewed scientific article	**Published on Apr. 10th, 2025** *DOI: 10.1038/s41746-025-01600-7*	nature research npj | Digital Medicine **npj Digital Medicine**, published by Nature Portfolio, is a peer-reviewed journal with a **5-year Impact Factor** (2023) of **15.2**
Note: The manuscript underwent a rigorous peer review process at npj Digital Medicine, where three independent reviewers evaluated it thoroughly. Following this comprehensive assessment, the journal editor approved the manuscript for publication (Appendix 2B). For transparency, the original preprint version, published in Preprints with The Lancet before peer review, is available in Appendix 2A, providing readers insight into the research's evolution throughout the publication process.			

Paper 3 in this thesis *(Chapter 6):*

Understanding Economic Decision-Making in Digital Therapeutics Development: A Qualitative Approach	Peer-reviewed scientific article	**Accepted for publication in JMIR on Aug. 21st, 2025,** with publication to follow completion of the copyediting process.	JMIR Publications Advancing Digital Health & Open Science **Journal of Medical Internet Research** (JMIR) is a Q1 peer-reviewed journal (top 25%) with an **Impact Factor of 6.0** (2025)
Note: The manuscript underwent a rigorous peer review process at the Journal of Medical Internet Research (JMIR), where two independent reviewers evaluated it thoroughly. Following this comprehensive assessment, the journal editor approved the manuscript for publication on Aug. 21st, 2025. For transparency, the original preprint version published in Research Square, a preprint platform, is available in Appendix 3A.			

Table 2. Presentations resulting from this research

Presentation Title	Presentation Type	Date and Venue
Are Digital Therapeutics "Value for Money?" *(speaker)*	Digital Therapeutics Europe Conference	Jun. 28th, 2023, London, United Kingdom
Health Technology Assessment in Digital Medicine *(speaker)*	AI in Medicine Cambridge-Singapore Symposium	Oct. 16th, 2023, Cambridge, United Kingdom
Digital Therapeutics applications in the clinical practice, benefits for clinicians, patients, caregivers as well as challenges to overcome *(speaker)*	Advancing Clinical Practice with Digital Therapeutics: A Guide for Clinicians	Nov. 5th, 2024, Asia-Pacific webinar organized by the Digital Therapeutics Association
Realizing the Promise: Translating Digital Health Efficacy into Real-World Effectiveness *(speaker)*	GP+ Primary Care Grand Conference	Nov. 9th, 2024, Singapore, Singapore
Digital Therapeutics: bench to bedside *(keynote speaker)*	InnovFest Suzhou Conference	Nov. 19th, 2024, Suzhou, China
Bridging Academia and Industry: Strategies for Effective Collaboration in Digital Health Solutions *(speaker)*	West Pacific Rim Consortium	Nov. 29th, 2024, Nagoya, Japan
From Promise to Practice: Bridging the Efficacy-Effectiveness Gap in Digital Health *(speaker)*	Systems Thinking for Healthcare Seminar	Mar. 21st, 2025, Singapore, Singapore
Bridging the Efficacy-Effectiveness Gap in Digital Health *(speaker)*	Indonesian Medical Education & Research Institute Visit	May 22nd, 2025, Singapore, Singapore
How can the potential of digital health solutions be realized? *(speaker)*	NUS Med Digital Health Accelerator 2025	August 2nd, 2025 Singapore, Singapore

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Table of Acronyms

ABI	Anchoring-Bridging Index
AHCA	Agglomerative Hierarchical Cluster Analysis
AI	Artificial Intelligence
BDT	Behavioral Decision Theory
BSI	Business Science Institute
CA	Cost Analysis
CAGR	Compound Annual Growth Rate
CBA	Cost Benefit Analysis
CBT	Cognitive Behavioral Therapy
CEA	Cost Effectiveness Analysis
CHEC	Consensus Health Economic Criteria
CLD	Causal Loop Diagram
COREQ	Consolidated Criteria for Reporting Qualitative Research
CR	Critical Realism
CUA	Cost Utility Analysis
CVD	Cardiovascular Disease
DBA	Doctorate of Business Administration
DBP	Diastolic Blood Pressure
DHT	Digital Health Technologies
DiGA	Digital Health Applications
Digi-HTA	Digital Health Technology Assessment
DT	Decision Theory
DTx	Digital Therapeutics
ED	Emergency Department
EE	Economic Evaluation
EUT	Expected Utility Theory
GCM	Group Concept Mapping
HCA	Hierarchical Cluster Analysis
HTA	Health Technology Assessment
HTN	Hypertension
ICER	Incremental Cost-Effectiveness Ratio
IIALY	Incontinence Impact–Adjusted Life Years
INMB	Incremental Net Monetary Benefit

IRB	Institutional Review Board
KPI	Key Performance Indicator
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NL	The Netherlands
NMDS	Nonmetric Multidimensional Scaling Analysis
OUD	Opioid Use Disorder
POC	Proof of Concept
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-Adjusted Life-Year
RCT	Randomized Controlled Trial
RoB	Risk of Bias
RWD	Real-World Data
RWE	Real-World Evidence
SaMD	Software as a Medical Device
SBP	Systolic Blood Pressure
SD	Standard Variation
SDs	System Dynamics
SOC	Standard of Care
ST	Systems Thinking
SV	Stress Value
T2DM	Type 2 Diabetes Mellitus
TW	Taiwan
UC	Usual Care
US	United States
WHO	World Health Organization
WisDM	The Institute for Digital Medicine
WTP	Willingness to Pay

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As I reach this significant milestone in my journey of academic and professional growth, I am filled with profound gratitude for the individuals who have been instrumental in the completion of this Doctorate of Business Administration (DBA) thesis.

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INTRODUCTION 1

CHAPTER 1. INTRODUCTION

This introductory chapter provides a comprehensive overview of the research context, articulating the thesis problem, and outlining the study's objectives.

1.1. Research Context

1.1.1. The transformation of the healthcare system

The world is experiencing an unprecedented rise in chronic and mental health diseases. Globally, one in three adults lives with one or more chronic conditions (Hajat & Stein, 2018). In the United States (US) alone, up to 60% of Americans have one or more preventable chronic diseases (Buttorff et al., 2017), which has numerous consequences.

Firstly, such diseases represent a significant burden to those who live with them, being diabetes, cardiovascular disease, cancer, or mental health, to name a few. The day-to-day experiences of these patients and their families and caregivers, managing these conditions while taking their medication and hoping for better days, have an impact on physical and mental wellbeing, productivity, and household finances, and as such should not be neglected.

Secondly, from a healthcare system perspective, managing these diseases puts an ever-growing pressure on total healthcare costs, which in turn makes healthcare less and less accessible. As a case in point, in the US, 90% of the US$3.5 trillion annual healthcare spending is dedicated to chronic and mental health diseases and this expenditure is projected to continue to outpace GDP growth over the next 15 years (Centers for Disease Control and Prevention, 2022; Lorenzoni et al., 2019). Unfortunately, this upward cost spiral is not unique to the US.

The unprecedented rise in chronic and mental health diseases, coupled with the continually growing costs that accompany them, requires a fundamentally new approach regarding how to conceptualize and deliver care, such as in patients' homes and communities, and away from hospitals. The benefits and utility of this approach were underscored during the COVID-19 pandemic. The COVID-19 pandemic has indeed accelerated digital health adoption. Regulatory barriers and reimbursement challenges alike are coming down. An increasing number of healthcare organizations are making the shift to virtual consultations, remote patient monitoring, e-prescriptions, and a new class of medicine, called digital therapeutics (DTx).

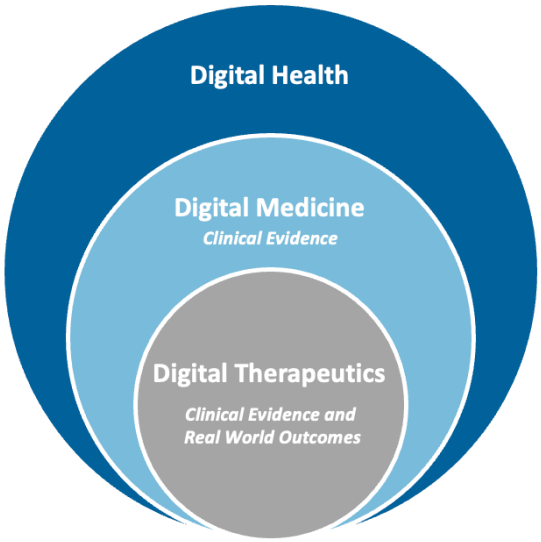
1.1.2. The emergence of DTx

The Digital Health market encompasses a vast array of technological solutions, from basic wellness applications to sophisticated medical interventions. This hierarchy includes Digital Medicine as a more clinically-oriented subset, within which Digital Therapeutics (DTx) represents the most rigorously evidence-based category (Figure 1). While the specific definitions of each technological category will be explored in the next chapter, it is fundamental to keep in mind that DTx occupies a unique position by integrating patient-centric technologies with clinical validation standards to treat, manage, and prevent chronic conditions and disorders.

Unlike conventional drugs, the therapeutic activity of DTx is driven by algorithms and high-quality software (DTx Alliance, 2022). Due to their capability to deliver software-based disease treatments, they should not be confused with digital wellness and lifestyle apps, which cannot and do not make treatment claims. DTx can be prescribed as standalone therapies or in combination with conventional drugs, devices or other therapies (Harvard, 2017). Like drugs, DTx, often regulated as Software as a Medical Device (SaMD), must fulfill stringent requirements that demonstrate their safety and efficacy through rigorous clinical trials before they can be commercialized and prescribed. Simply put, the clinical

evidence required for the regulatory approval of DTx must be the same as for conventional drugs or medical devices (Kirisits & Redekop, 2013).

Figure 1. Relationship between Digital Health, Digital Medicine and Digital Therapeutics.



1.2. Research Problem

On the one hand, DTx are expected to influence significantly healthcare delivery and its consumption across the globe (März et al., 2021). They have the potential to disrupt traditional and often inefficient healthcare business models through delivering better clinical outcomes, while providing a superior patient experience. On the other hand, the financial resources of health organizations and societies as a whole are limited, necessitating ongoing resource maximizing and allocation (dos Santos Silva et al., 2021). Simply put, selecting the optimal mix of services within the system's constraints is of the utmost importance to maximize clinical outcomes at the lowest possible costs (Thomas & Chalkidou, 2016).

Awareness of the economic manifestations of health and diseases as well as the limited resources allocated to healthcare services has brought to the forefront a new discipline - health economics, which is concerned with the efficient allocation of healthcare resources (Goeree & Diaby, 2013), focusing on achieving "economic efficiency," or obtaining the most value for the money spent (Garrison

et al., 2018). From an economic perspective, value is defined as “gross value” (i.e., the willingness to pay for an intervention), and “net value” (i.e., the gross value less the opportunity cost required to obtain that intervention) (Garrison et al., 2018). In healthcare, the cost of an intervention is frequently paid not by the patients but indirectly by their agents, being private or government health insurance, who must assess the value for money of new interventions.

Economic assessments, also known as Health Technology Assessment (HTA), are undertaken to create evidence-based information to assist and improve healthcare resource allocation decision-making. The economic evaluation of healthcare interventions (e.g., new drugs, medical devices and medical procedures) has become crucial in supporting health policy and decision-making for the allocation of limited healthcare resources (Kirisits & Redekop, 2013). The concept of economic value has grown in popularity with scholars and policymakers. Over the last 50 years, the number of economic evaluations of healthcare programs has nearly doubled every five years (März et al., 2021). In the context of this thesis, we will therefore take a health economics approach to the concept of value in healthcare systems.

Even though there is growing evidence that DTx can provide clinical benefits (i.e., measurable changes in symptoms, overall health, ability to function, quality of life, or survival outcomes), in this context of resource optimization, it is critical for governments, payers (e.g., insurance companies) and care providers to assess the potential economic value of DTx compared to alternatives and standard therapies (Kario et al., 2021).

Recent studies have highlighted that economic factors related to a DTx intervention, such as costs, funding, and resources - have indeed been identified as both barriers and facilitators to adoption, the end-stage decision in DTx implementation (Vicki et al., 2020). Recognizing the importance of these economic considerations, recent recommendations for bridging the gap between DTx development and implementation emphasize integrating economic

considerations into early stages of technological development (Keogh et al., 2024).

If economic impacts are indeed key decision elements in supporting health budget allocation decisions and in making a case for or against investment in DTx, only 10% of DTx have published economic studies (HealthXL, 2021), and DTx are yet to become mainstream components of health systems worldwide (Cirkel et al., 2024; Johnson et al., 2024; Prodan et al., 2022; Wang et al., 2023; Williams et al., 2020). Further research is needed to demonstrate their potential impact in the foreseeable future (Khirasaria et al., 2020) and address two critical gaps, which, in essence, justify this research work and the proposed research approach:

1. **Little is known about the capacity of DTx to provide economic value in care.**

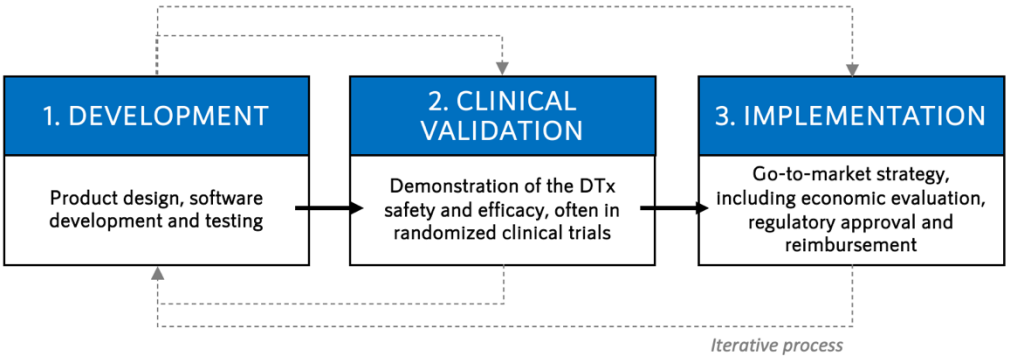
   DTx, like any new drugs or medical devices, must indeed demonstrate that they are medically necessary. Beyond the clinical impact, in a context of increasing demand for healthcare services and the rising costs of providing these services, healthcare organizations broadly speaking – payers, providers and patients - must consider how DTx drive value from a monetary and non-monetary benefit to their organizations and patients or customers. However, the current body of literature does not sufficiently address the economic value of DTx interventions (Kario et al., 2021). For example, to what extent can DTx efficiently use resources and provide “value for money” compared to potential alternative options, or how should the non-monetary benefits arising from the quality care delivery be considered? The absence of evidence on these aspects is in due part to the complexity of defining and assessing economic value in the context of DTx.

2. Little is known regarding the factors that influence or drive DTx economic value.

The distinctive nature of DTx, in which the therapeutic activity is carried out by high-quality algorithms and software, creates a new set of challenges to evaluate such novel technologies that are not well understood (Gomes et al., 2022). The interacting, dynamic and evolving features of DTx, including potential continuous evolving artificial intelligence (AI) models, might impact the design, measurement, analysis and reporting of cost-effectiveness analysis (Gomes et al., 2022). Also, while economic value in healthcare is often defined as “health outcomes relative to monetized inputs”, such a definition reduced to an expression of a solution’s cost-effectiveness may be limited. Beyond the core value elements of “quality-adjusted life-years (QALY)” - a measure of the value of health outcomes - and “net costs”, Lakdawalla et al. (2018) for example, widen the notion of value in healthcare by including ten additional factors of value into cost-effectiveness analysis (i.e., productivity, adherence-improving factors, reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spillovers). The question is also raised as to the QALY approach, the gold standard for the value evaluation of pharmaceuticals, can simply be used to value DTx, or if a new value assessment framework should be considered (Kolasa & Kozinski, 2020). As such, beyond the output of an HTA evaluation, it’s important to understand the specific costs and factors that are driving such economic value, and in which particular context. These costs, specific to medical conditions and disorders under consideration, are often categorized as part of the HTA methodology as direct (e.g., pharmaceutical treatment, cost of the DTx, etc.) or indirect medical and nonmedical costs (e.g., Productivity impact, or the cost related to the maintenance of the DTx intervention).

Finally, as cost-benefit perspectives traditionally vary among stakeholders, and are subject to individual preferences and objectives (McKeering et al., 2017), the question is raised on how stakeholders involved throughout the DTx product development lifecycle (i.e., from development to clinical validation and implementation) consider these aspects related to the DTx economic value.

Figure 2. Three main phases of DTx development cycle



Indeed, while Torbica et al. (2020) emphasized the growing influence of economic factors on healthcare decision-making, there remains a significant research gap regarding how healthcare decision processes impact the potential economic value. Despite extensive research examining healthcare innovation decision-making (Murray et al., 2016; Nghiem et al., 2023), important knowledge gaps persist concerning how stakeholders approach economic decisions in DTx development and clinical validation. Although current literature provides valuable insights into clinical decision-making processes (Keogh et al., 2024; Kim et al., 2024) and technical development frameworks (Carrera et al., 2024; Kim et al., 2024), the intersection of economic considerations with these domains remains understudied.

This knowledge gap is particularly notable given the unique characteristics of DTx development, which represents a complex intervention resulting from intricate interactions among multidisciplinary teams with diverse expertise and numerous decision-making processes (Murray et al., 2016;

Williams et al., 2020; Gomes et al., 2022). DTx development typically involves collaboration between software developers, clinicians, regulatory specialists, behavioral experts, and business strategists, each contributing to different phases of the product lifecycle. This interdisciplinary nature creates complex stakeholder dynamics and distinct decision-making challenges not fully addressed by traditional healthcare innovation frameworks.

As a consequence of the complexities and gaps described above, the current literature on defining and measuring DTx value from a health economics perspective appears fragmented (Halminen et al., 2021; McKeering et al., 2017). The evidence on the potential economic impacts of DTx remains simply insufficient and of uneven quality (Halminen et al., 2021), preventing DTx from being massively adopted by clinicians (i.e., physicians, nurses, pharmacists, or other allied health professionals), payers and ultimately patients.

1.3. Objectives of the Study

The purpose of this study is threefold: (1) to understand and characterize the concept of economic value in the context of DTx as well as identify the factors potentially influencing the “DTx” and “economic value” relationship; (2) to gain a deeper understanding of how these factors, also referred to as economic value drivers, are considered early on by the various stakeholders involved in the DTx development and clinical validation; and finally (3) develop methodological recommendations for guiding these stakeholders to create conditions that may drive the economic value of DTx.

Table 3. Research questions, objectives and corresponding research methods

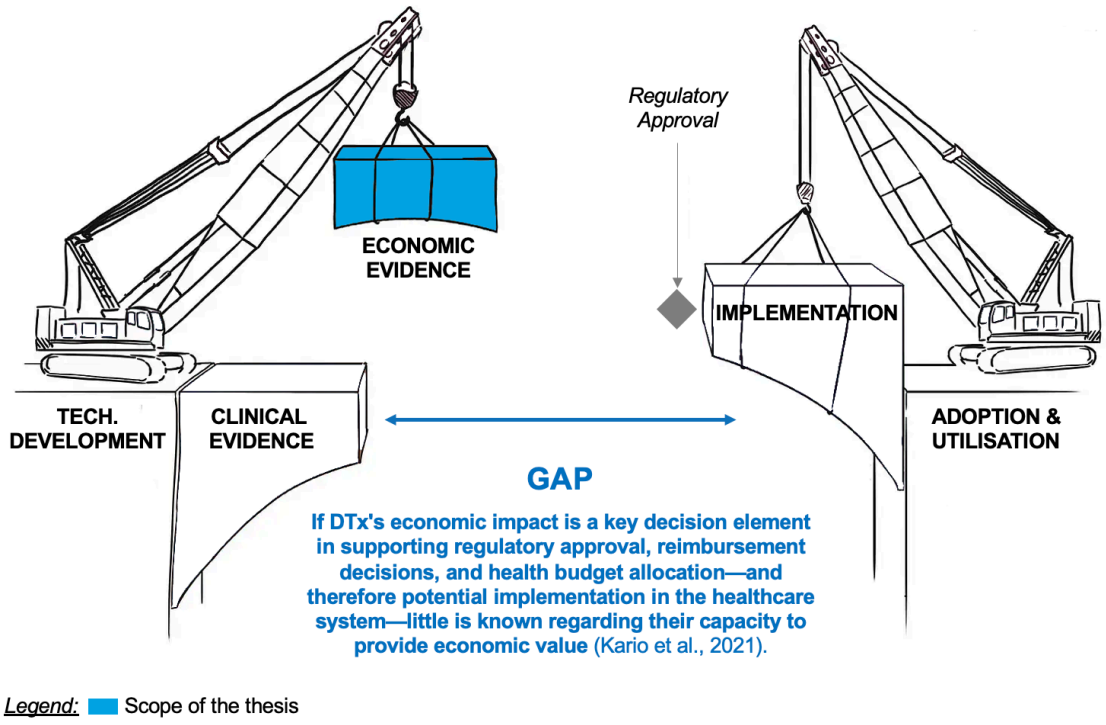
Main Research Question:	**Main Objective:**	**Research Methods:**
What are the economic value drivers of DTx and how are they considered throughout the product development lifecycle?	Develop methodological recommendations to guide stakeholders involved in the DTx development, clinical validation and implementation consider potential economic value drivers.	The research design includes a systematic literature review (Chapter 4), a group concept mapping study (Chapter 5), and a qualitative research study (Chapter 6).
Sub-research Question 1:	**Sub-objective 1:**	**Research Methods:**
How has the emergence of DTx, a new class of medicine, translated to economic value and why?	Understand and characterize the concept of economic value in the context of DTx, as well as factors that might influence the DTx and economic value relationship.	The systematic literature review (Chapter 4) and group concept mapping study (Chapter 5) will contribute to addressing this sub-objective.
Sub-research Question 2:	**Sub-objective 2:**	**Research Methods:**
Do stakeholders involved in the development and clinical validation of DTx consider factors influencing their economic value, and if so, how?	Gain a deeper understanding of how the DTx economic value and its drivers are considered early on in the DTx development and clinical validation.	The group concept mapping study (Chapter 5) and qualitative research study (Chapter 6) will contribute to addressing this sub-objective.

1.4. Research Scope and Focus

While DTx implementation and adoption represent the ultimate goal of healthcare transformation, they depend on multiple foundational pillars including technical development, clinical evidence, and economic evidence. As discussed above and illustrated in Figure 3, there exists a significant gap between the development phases—where the capacity for economic value delivery should be established and demonstrated—and the implementation phase where adoption decisions are made.

DTx adoption is inherently multifaceted, involving numerous success factors for scaling up adoption that spans regulatory, organizational, technological, behavioral, and economic dimensions (Fassbender et al., 2024; Prodan et al., 2022). Given this complexity, this research focuses on one critical foundational element by examining how economic value potential is considered and conceptualized during DTx development and clinical validation phases, as highlighted in blue in Figure 3.

Figure 3. The economic evidence gap in DTx development



1.4.1. Specific Focus on Upstream Developmental Processes

This thesis centers on the technological development and clinical validation phases of the DTx lifecycle (Figure 2) for several critical reasons that address knowledge gaps and practical necessities. In contrast to traditional technology adoption studies that examine downstream adoption decisions, this thesis investigates upstream developmental processes: the strategic decisions and actions during DTx development and clinical validation that ultimately determine their potential for generating economic value in real-world healthcare environments.

Foundational Economic Value Creation: The development and clinical validation phases represent the critical juncture where DTx economic value potential is conceived, designed, and demonstrated. During these phases, fundamental decisions about therapeutic algorithms, clinical endpoints, cost structures, value propositions, and business model considerations are

established. Understanding how stakeholders navigate economic considerations during these formative stages is essential for creating DTx solutions with robust economic foundations.

Regulatory and Market Prerequisites: Economic value demonstration during development and validation phases is a prerequisite to regulatory approval and market access. Healthcare payers increasingly require economic evidence alongside clinical efficacy data for reimbursement decisions (Kolasa & Kozinski, 2020). By focusing on these earlier phases, this thesis addresses the critical need to understand how economic value frameworks can be integrated early enough to support regulatory submissions and payer negotiations.

Stakeholder Decision-Making Complexity: The DTx development and clinical validation phases require unique multidisciplinary collaboration between software developers, clinicians, regulatory specialists, behavioral experts, and business strategists, as will be discussed in the next chapter. Each stakeholder group brings distinct perspectives on economic value, creating complex decision-making dynamics not fully addressed by existing healthcare innovation frameworks. This research captures these intricate stakeholder interactions during the phases where their collective decisions could significantly impact the long term economic outcomes of DTx interventions.

Knowledge Gap Resolution: Current literature reveals insufficient understanding of how economic considerations are conceptualized and integrated during early DTx development. With only 10% of DTx having published economic studies (HealthXL, 2021), there is a documented need to understand the upstream factors that influence economic value creation. This research addresses this fundamental knowledge gap by examining how development-phase stakeholders perceive, evaluate, and integrate economic factors.

A Nascent Technology Context: As this thesis is being developed, DTx are just beginning to take shape, with pilot programs in selected countries, yet to become mainstream or deployed at scale. Germany, the pioneer in DTx implementation since 2020 with a proper regulatory framework for national adoption, represents the most mature market experience available. As of 2025, DTx have achieved regulatory approval in only eight countries worldwide (i.e., Belgium, China, France, Germany, Japan, South Korea, UK and USA), with commercial availability remaining limited.

Consequently, the nascent state of the DTx market presents practical realities that shape what can be studied. For example, most existing studies examining DTx adoption in healthcare systems remain largely theoretical or context specific with limited generalizability. This timing presents a unique research opportunity to understand economic value creation processes during this formative period—before implementation and adoption-related challenges have fully emerged—enabling insights that can inform future DTx development practices.

By concentrating on development and clinical validation phases, this research provides foundational knowledge essential for creating DTx solutions that reach healthcare systems with well-established economic value frameworks. This approach ensures that downstream implementation and adoption decisions can be made based on DTx solutions with robust economic foundations, ultimately supporting more informed healthcare policy decisions and successful healthcare integration (Armeni et al., 2024; Prodan et al., 2022).

1.5. Structure of the Thesis

The DBA thesis structure was designed to create a coherent narrative arc that guides readers from the initial research context through to the conclusions and their significance in the broader academic and practical landscape, while also ensuring readers can engage with individual chapters independently.

Chapter 1 establishes the introductory framework and research context, which transitions into the literature review in Chapter 2. This chapter situates the research within its broader academic landscape. The second chapter also examines the key theoretical foundations of economic evaluations, with a particular focus on economic value in the context of complex interventions, such as DTx (Murray et al., 2016).

The research methodology is explained in detail in Chapter 3, which articulates the interconnections between the approaches used across the research papers and demonstrates the chronological evolution of the study. This methodological framework serves as the foundation for the presentation of the three main papers that form the core of the research.

These three papers, presented in Chapter 4, Chapter 5 and Chapter 6, were submitted to peer-reviewed journals, with the first two already published. The papers function as complementary components, each building upon the findings of the previous study to address the main research question and its sub-questions. While interconnected, each paper stands as a self-contained article, complete with its own abstract, literature review, methodology, results, discussion, conclusions, and references.

Following the presentation of these three core papers, the DBA concludes with a final chapter that synthesizes the key findings and their interpretation. This concluding Chapter 7 demonstrates how the findings collectively address the main research question, proposes managerial recommendations derived from the research outcomes and suggests potential avenues for future research in the field.

1.6. Conclusions

This introductory chapter has established the foundational context for investigating DTx economic value determination within the broader transformation of healthcare systems worldwide. Despite the potential of DTx to address current challenges faced by healthcare systems, a critical research problem arises from two significant knowledge gaps: the limited understanding of DTx capacity to provide economic value in care, and the insufficient knowledge regarding factors that influence or drive such potential value throughout the DTx development lifecycle.

This contextualization and identified research problem lead to the main research question: "**What are the economic value drivers of DTx and how are they considered throughout the product development lifecycle?"** This central question is supported by two complementary sub-research questions that systematically address the identified knowledge gaps. The corresponding research objectives provide a structured framework for generating evidence-based methodological recommendations to guide stakeholders in creating conditions that enhance DTx economic value.

The introductory foundation presented in this first chapter establishes both the rationale and framework for the subsequent literature review, methodological approach, and empirical investigations detailed in the following chapters. This structured approach ensures that the research addresses both theoretical understanding and practical application needs within the evolving digital health landscape, ultimately advancing how DTx solutions are developed and validated.

LITERATURE REVIEW

2

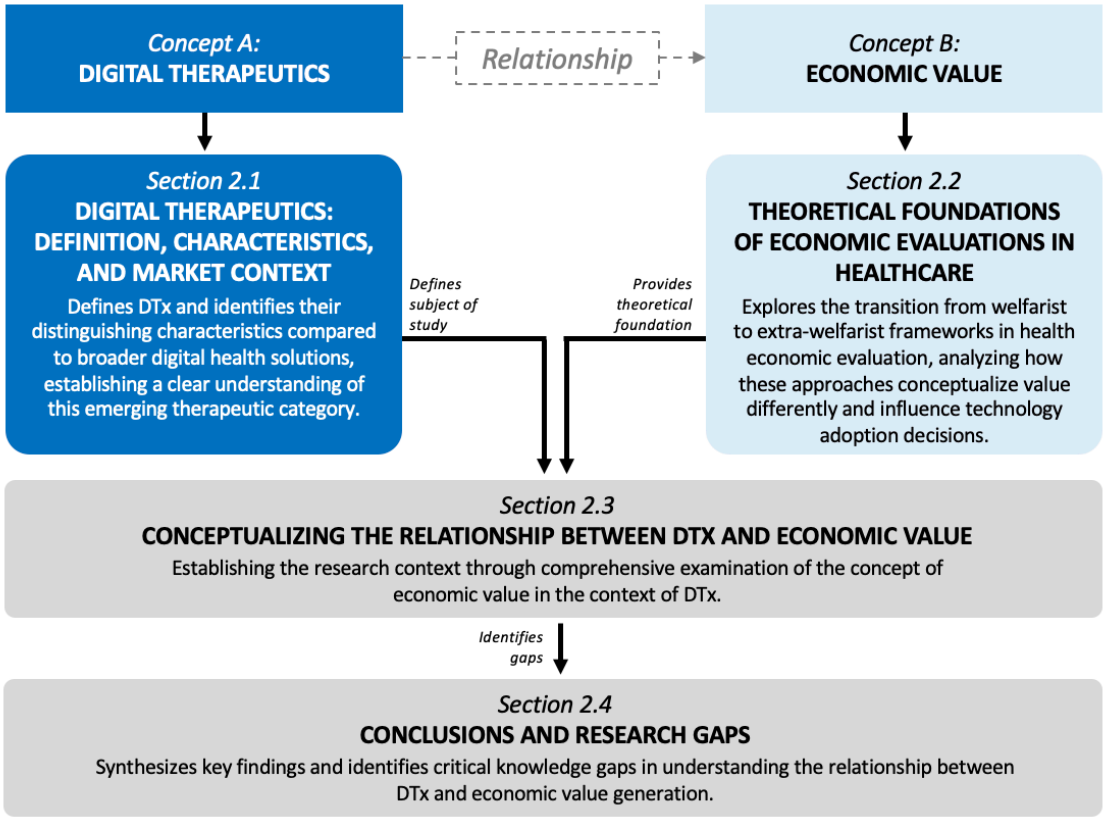
CHAPTER 2. LITERATURE REVIEW

DTx have emerged as evidence-based interventions with significant potential to address mounting healthcare challenges, including resource constraints, aging populations, and rising prevalence of chronic conditions. While their clinical utility has gained recognition, the economic evidence supporting their integration into healthcare systems remains limited (Kario et al., 2021; Gomes et al., 2022).

This literature review examines the complex relationship between DTx and economic value generation, progressing through a logical framework (Figure 4) to understand two fundamental concepts: (1) “DTx”, defining this new class of medicine and their distinguishing characteristics within the digital health landscape, and of (2) “Economic Value”, examining theoretical frameworks for economic evaluation in healthcare systems. Subsequent sections examine the specific challenges and opportunities in conceptualizing DTx economic value across diverse stakeholder perspectives, forming the foundation for addressing the research questions.

By synthesizing evidence across health economics and digital health domains, this literature review contextualizes the research problem and establishes the methodological foundation for subsequent investigations.

Figure 4. Literature review structure contextualizing research framework



2.1. Digital Therapeutics: Definition, Characteristics, and Market Context

DTx represent a novel category of medical interventions that deliver evidence-based therapeutic interventions through software programs. This section provides a comprehensive definition of DTx, distinguishing them from broader digital health solutions, and explores their market trends and implementation challenges, establishing an essential context for research questions.

2.1.1. Defining DTx and their place in digital health

Digital health and DTx are popular terms that are often being used interchangeably, yet critical distinctions between the two exist. Digital health as an umbrella term encompasses all technologies, platforms, and systems across the wellness and healthcare industries that engage consumers for lifestyle,

wellness, and health-related purposes (DTx Alliance, 2019). It includes all trackers and quantified self apps, platforms, or solutions, from consumer wearables, such as sleep trackers and fitness applications to clinically evaluated cardiac health monitors and cloud infrastructure. According to the DTx Alliance (2019), there are three distinct categories of digital health solutions: (1) Wellness & Support, (2) Diagnostic and Monitoring, and (3) DTx, as illustrated in Table 4.

Table 4. Three categories of digital health solutions

	DIGITAL HEALTH SOLUTIONS		
	WELLNESS and SUPPORT	**DIAGNOSTIC and MONITORING**	**DIGITAL THERAPEUTICS**
Overview	Products that capture, store, transmit health data	Products that measure and/ or intervene	Products that deliver therapeutic interventions directly to patients
Clinical Evidence	*Not typically required*	**Required**	**Required**
Real World Outcomes	*Not typically required*	*Not typically required*	**Required**
Regulatory Oversight	*Varies depending on the intended use and function of the solution*	**Required**	**Required**
Examples	• Lifestyle apps & fitness trackers (Fitbit) • Telehealth platforms (Teladoc) • Health Information Technology (Epic MyChart) • Consumer Health information (AI Chatbot)	• Digital diagnostics (AliveCor) • Remote patient monitoring (Medtronic CareLink) • Medication adherence tools (PillPack) • Ingestible sensors (Proteus Digital Health)	• Digital cognitive therapy (Akili Interactive) • Digital behavioral therapy (Sleepio) • Digital physical therapy (Kaia Health)

DTx are by nature patient-focused solutions, designed to be used directly by patients or their caregivers. They offer the possibility of changing the course of disease throughout the care continuum, from diagnosis and early detection to management and treatment of medical disorders, including the possibility of optimizing the effects of medication.

As characterized by DTx Alliance *(2022), "DTx deliver clinical-grade therapeutic interventions to patients [that] may be used independently or in tandem with in-person or remote clinician-delivered therapy to optimize patient outcomes."* According to their mechanism of action, DTx can indeed be subdivided into two broad categories, as potential standalone treatments (also known as drug-replacement therapies) or used in conjunction with other therapies (also known as companion digital therapies) to augment their effectiveness.

2.1.2. Distinguishing characteristics of DTx

DTx present three essential characteristics that distinguish them from the broad spectrum of digital health innovations, establishing them as a unique therapeutic category with significant implications for healthcare delivery and economic evaluation.

First, DTx are characterized by strong clinical evidence supporting their safety and efficacy. The term "therapeutic" specifically signals the presence of clinical-grade evidence, typically demonstrated through randomized clinical trials (RCTs). This evidence-based foundation mirrors traditional medical interventions, as illustrated by the dramatic increase in DTx application trials—from just 12 in 2015 to 58 in 2019 (Burrone et al., 2021). Pioneer products like Pear Therapeutics' reSET and reSET-O exemplify this commitment to rigorous validation, having undergone six RCTs involving over 1,500 patients with substance use disorder before US Food and Drug Administration (FDA) clearance (Pear Therapeutics, 2016).

Second, DTx possess unique capabilities for real-world evidence (RWE) generation that conventional interventions typically lack. By design, these digital solutions collect and analyze real-world data (RWD) in real or near-real time, providing invaluable insights into patient health status and treatment outcomes beyond the controlled environment of clinical trials. This continuous data stream enables iterative refinement through human engineering or machine learning algorithms, creating a feedback loop that optimizes clinical outcomes. The

capacity to generate complementary RWE alongside traditional clinical trial evidence represents a transformative advantage, allowing stakeholders—from patients to clinicians to regulators—to assess DTx's unique value proposition compared to conventional therapies (US FDA, 2017).

Third, DTx operate within established regulatory frameworks, primarily under the SaMD guidelines developed by the International Medical Device Regulators Forum (US FDA, 2017). This regulatory oversight ensures compliance throughout the product lifecycle (HSA, 2019). However, traditional medical device regulatory paradigms do not fully accommodate DTx's unique characteristics, prompting national authorities and payers to develop innovative approaches. These emerging frameworks vary across jurisdictions, with Danev et al. (2021) highlighting significant differences: the United Kingdom mandates cost-effectiveness analysis for DTx, while France and the US adopt more flexible approaches, and Germany progresses toward more economically driven evaluation methods focused on cost-effectiveness ratios and comparison with existing services.

The DTx distinctive characteristics offer a new clinical therapeutic intervention that clinicians can prescribe either as standalone treatments or complementary to existing therapies. While firmly established as a subset of digital health, DTx's evidence-based foundation and regulatory compliance clearly differentiate them from digital wellness and lifestyle applications, creating a new class of medicine.

2.1.3. Market landscape and adoption trends

The DTx market has experienced substantial growth in recent years, driven by technological advancements, the increasing prevalence of chronic and mental health conditions, and a shift toward personalized medicine. Industry research indicates that the global DTx market, valued at US $5.7 billion in 2023, is projected to reach US $36.5 billion by 2032, demonstrating a compound annual growth rate (CAGR) of 23% during the forecast period (Astute Analytica, 2024). This expansion is attributed to factors, such as increasing smartphone

penetration, rising healthcare costs, and growing demand for remote patient monitoring solutions.

The adoption of these digital solutions was significantly accelerated by the COVID-19 pandemic, as noted by Miao et al. (2022). In 2023, the US FDA approved 50% more DTx compared to the previous year, underscoring this rapid growth (Sinapov, 2024). Table 5 provides an overview of DTx approved as of May 2025 in Belgium, China, Germany and the US (Liang et al., 2025), illustrating the diverse range of therapeutic areas benefiting from these digital interventions.

Table 5. Main characteristics of approved DTx in 2025 (Liang et al., 2025)

TARGETED DISEASE	NUMBER OF DTX APPROVED
Diseases of the nervous system	130 [25.64%]
Diseases of the eye and appendages	56 [11.05%]
Mental and behavioral disorders	95 [18.74%]
Diseases of the musculoskeletal system and connective tissue	66 [13.02%]
Endocrine, nutritional and metabolic diseases	94 [18.54%]
Diseases of the circulatory system	54 [10.65%]
Diseases of the respiratory system	26 [5.13%]
Diseases of the ear and mastoid process	18 [3.55%]
Neoplasms	14 [2.76%]
Pregnancy, childbirth and puerperium	10 [1.97%]
Certain infectious and parasitic diseases	1 [0.20%]
Diseases of the blood and hematopoietic organs and certain diseases involving immune mechanisms	2 [0.39%]
Diseases of the digestive system	4 [0.79%]
Factors affecting health status and contact with health-care providers	16 [3.16%]
Diseases of the genitourinary system	4 [0.79%]
Total	**507**[a]

[a]One device may correspond to multiple diseases

Despite promising market growth, widespread adoption of DTx remains limited (Dang et al., 2020; Yan et al., 2021). Challenges include data privacy concerns, the need for more robust clinical evidence, and an evolving regulatory landscape, particularly regarding reimbursement issues (Kario et al., 2021). Armeni et al. (2024, p. 1) attributed this limited adoption to the scarcity of comprehensive research that delves into "*DTx's scope, including its technological underpinnings, potential application areas, and challenges—namely, regulatory hurdles and modest physician uptake.*"

A recent systematic review by Rodrigues et al. (2024) identified technical, organizational, economic, user-related, and patient-related components as crucial factors influencing the ultimate adoption of digital health-related tools by health professionals. Understanding provider perspectives is indeed essential for successful DTx adoption, as they have the ability to prescribe and recommend this new class of medicine to their patients.

Studies among German physicians, one of the pioneering markets for DTx, reveal that only 24–62% would potentially prescribe a DTx (Dahlhausen et al., 2021; Fürstenau et al., 2023), highlighting the need to address specific concerns. Kreuzenbeck et al. (2024) explored the incentives and barriers in healthcare providers' decisions to promote and prescribe DTx, finding that user experience for both patients and healthcare professionals is a significant barrier to usage. Additionally, a substantial portion of physicians expressed direct concerns about costs, extending beyond monetary aspects to include high effort and complex bureaucratic processes for prescribing DTx. Some physicians simply viewed DTx as potential competitors for healthcare funding, indicating concerns about how DTx costs might impact overall healthcare budgets.

These findings suggest that while cost is a significant concern for physicians regarding DTx adoption, it is part of a broader set of barriers that also include administrative burdens and uncertainties about effectiveness and impact on

healthcare resources. Addressing these multifaceted challenges will be crucial for the continued growth and adoption of DTx in healthcare systems worldwide.

2.1.4. Conclusions

This section has established DTx as a distinct therapeutic category characterized by three essential elements: (1) strong clinical evidence supporting safety and efficacy; (2) capacity for continuous real-world evidence generation; and (3) operation within established regulatory frameworks. These distinguishing characteristics position DTx as a novel therapeutic intervention while simultaneously creating unique challenges for economic evaluation and raising questions about their ability to deliver economic benefits, thereby affecting regulatory pathways and ultimately their market adoption. The paradox between projected market growth and limited real-world implementation highlights the need to fully comprehend the complex relationship between DTx and their economic value. The following section addresses the theoretical foundations necessary for establishing a conceptual framework to understand DTx economic value creation.

2.2. Theoretical Foundations of Economic Evaluations in Healthcare

Healthcare spending consistently surpasses overall economic growth (Wager et al., 2022). As a result, achieving a long, healthy life requires the use of scare resources, making it, in part, an economic problem (Harvard, 2017). In this context, the discipline of health economics has emerged as a crucial field, focusing on the efficient allocation of healthcare resources to ensure equitable access to services. This chapter examines the theoretical foundations of economic evaluations in healthcare, exploring how the concept of economic value is defined, measured, and applied within healthcare systems, establishing an essential context for understanding the complex value proposition of DTx in contemporary healthcare environments.

2.2.1. Evolution of health economic theory: from welfare economics to extra-welfarism

Awareness of the economic manifestation of health and diseases and the limited resources allocated to healthcare services have brought to the focus a new discipline - health economics. To assist and improve the decision-making of healthcare resource allocation, economic evaluations are conducted to generate evidence-based information. The economic evaluation of healthcare interventions (e.g., new medicines, medical devices and medical procedures) became critical in supporting health policy and decision-making for the allocation of limited healthcare resources (Kirisits & Redekop, 2013). The concept of economic value has become increasingly popular with scholars and policymakers. Over the last 50 years, the number of economic evaluations of healthcare programs has virtually doubled every five years (März et al., 2021).

To be able to explain decision-making in the context of constrained resources, it is critical to comprehend the principles of economic theories that have shaped healthcare decision-making over the years. It also requires an appreciation of the special economics of healthcare.

Health economics approaches can be broadly categorized into two major frameworks: welfare economics and extra-welfarism. These frameworks differ fundamentally in how they conceptualize and measure value in healthcare interventions, with important implications for the economic evaluation of emerging technologies like DTx. These contrasting approaches represent fundamentally different conceptualizations of value in healthcare decision-making.

Welfare economics in healthcare

For decades, welfare economics has influenced decision-making practices in healthcare, particularly regarding resource utilization and distribution. This approach aims to find the optimal allocation of economic resources, goods, and income to maximize the social welfare of community members in the society at

large. Welfare generally refers to well-being and the key value judgment behind welfare economics is to maximize social welfare (well-being) by maximizing utility (Galea, 2016). Utility is described as "*that property in any object*" which "*tends to produce benefit, advantage, good or happiness*" (Bentham, 1823, p. 3). It is a measure of strength of preference, which is related to desirability (Coast, 2009). The impact of a change in resource allocation is judged by the value individuals place on the alternative states of the world and this value for the change is captured in terms of changes in utilities. In a free market, individuals can maximize their utility by virtue of purchasing goods or consuming services based on their affordability. By choosing A rather than B, an Individual is deemed to get more utility with A and to be better off, having reached a preferred position.

However, healthcare differs significantly from traditional markets in several aspects. First, welfare economics is rooted in the law of supply and demand, with prices determined by the relationship between supply and demand. However, as practically all healthcare services and interventions are considered essential, their perceived utility may be high, by definition, regardless of cost. Patients truly want to receive the best possible care. Contrary to the law of supply and demand, healthcare demand may not decrease with rising prices due to its essential nature (i.e., demand inelasticity). Secondly, patients often lack sufficient medical knowledge to make informed choices (Major et al., 2021). Because of this informational asymmetry between customers and healthcare professionals on price and quality, utility decisions, such as deciding on the optimal course of treatment, may rely on healthcare providers' judgment.

Modern welfare economics helps understand when resource allocation or distribution is efficient, which is essential for achieving fairness and having access to healthcare. For this, the main criterion of "Pareto efficiency" is used, which defines when resources are allocated in the most efficient manner (demand equals supply), and that no economic change can make one individual better off without making at least one other worse off. It suggests that an efficient allocation of resources maximizes the aggregate utility. The welfarist decision

rule of maximizing utility, and thus individual well-being, is theoretically grounded, and this economic state of general equilibrium, or “Pareto efficiency”, is a core pillar of welfare economics. However, utility is subjective and cannot be directly observed or quantified. Economists therefore use willingness to pay (money) as an indirect indicator of utility (He et al., 2024). This concept is crucial for economic evaluation in healthcare, where policymakers need methods to measure and compare benefits across different medical interventions. This substitute measure provides the ability to choose between two or more alternatives based on evidence of cost relative to health gains. Modern economic theory has demonstrated that free competitive market equilibria are “Pareto efficient” (Furubotn, 1991). In other words, if a fully functioning competitive market achieves Pareto efficiency without government intervention, there is no need for economic evaluation or any other method of benefit evaluation, which is not the case in healthcare.

The welfare economics approach has been criticized for decades. Arrow’s impossibility theorem (1951) sparked a body of literature proving essentially that any method of aggregating preferences is necessarily flawed. Feldstein (1963, p. 23) also asked, “*… should not healthcare be allocated to maximize the level of health of the nation instead of the satisfact which consumers derive as they use health services?*” Culyer (1989) also argued that utility is not the only relevant argument, or indeed even the most important argument, in the social welfare function.

An alternative to the welfarism approach has emerged: an extra-welfarist framework that embodies the centrality of health as the outcome of concern (Richardson & Schlander, 2018).

Extra-Welfarism: An alternative approach

In response to the limitations of welfare economics in healthcare, an alternative approach has emerged: extra-welfarism. This approach incorporates two fundamental concepts that do not fit easily into a welfarist framework, (1) the

concept of need (as opposed to demand), and (2) health (as opposed to utility) as a final outcome of concern (Hurley, 2000), as illustrated in Table 6. In other words, value is assessed using utility in welfare approaches; value is assessed using subjective health measures in extra-welfarism approaches. Hurley (2000, p. 58) concluded that "*the health sector has proven fertile ground for extra-welfarist approaches that emphasize non-utility, and in particular health information, in evaluating resource allocations.*"

Table 6. Welfarist versus extra-welfarist approaches

	WELFARIST APPROACH	EXTRA-WELFARIST APPROACH
Primary Value Measure	Utility/consumer preference	Health outcomes
Decision Criteria	Willingness to pay/Cost-benefit	Cost-effectiveness/ Cost-utility
Distributional Concerns	Limited consideration of equity	Explicit consideration of equity
Data Requirements	Preference data, monetary valuations	Health outcome data, utility weights

There are various schools of thought regarding how healthcare resources should be allocated in the most efficient manner to maximize social welfare as well as individual well-being. It has long been debated whether health or utility should be the outcome of concern for health economists and policymakers. Similarly, there is still a lack of broad agreement among patients, clinicians, policymakers, and other healthcare professionals on the concept of "value" as a key concept in healthcare, and especially on which component of value may play a prominent role (Marzorati & Pravettoni, 2017).

Welfarist versus extra-welfarist approaches in DTx evaluation

Unlike traditional welfarism, which primarily focuses on utility maximization, extra-welfarism expands the evaluative criteria to encompass health outcomes directly, as illustrated in Table 6. Therefore, it offers a particularly relevant approach for

evaluating the economic value of DTx, whose interventions specifically target measurable health improvements rather than merely enhancing overall utility or well-being (Table 7). The direct focus on health outcomes in extra-welfarism aligns naturally with DTx's capacity to deliver targeted therapeutic interventions for specific conditions and generate concrete, measurable clinical results that can be systematically evaluated within existing healthcare decision frameworks.

Table 7. Welfarist versus extra-welfarist approaches in DTx evaluation

	Welfarist Approach		Extra-Welfarist Approach	Implications for DTx Evaluation
Primary Value Measure	Utility/consumer preference		Health outcomes	DTx evaluated on health improvement metrics rather than consumer satisfaction
Decision Criteria	Willingness to pay/Cost-benefit	vs.	Cost-effectiveness/ Cost-utility	Enables comparison of DTx with traditional interventions using consistent metrics
Distributional Concerns	Limited consideration of equity		Explicit consideration of equity	Supports evaluation of DTx's potential to address healthcare disparities
Data Requirements	Preference data, monetary valuations		Health outcome data, utility weights	Aligns with DTx's ability to generate rich health outcome data

The extra-welfarist approach also allows for a broader understanding of benefits beyond strictly defined health improvements. Unlike traditional pharmacological interventions, many DTx provide ancillary advantages, such as fostering greater patient engagement, enhancing health literacy, addressing potential equity issues, and data-related value for better personalization of the intervention. By recognizing these additional dimensions of impact, extra-welfarism allows for a more comprehensive evaluation of DTx, acknowledging that the value of these interventions extends into behavioral and educational realms that can significantly influence overall health outcomes. These additional dimensions

significantly influence the economic value assessment of DTx, requiring evaluators to consider a broader spectrum of impacts beyond immediate clinical outcomes.

The theoretical landscape of health economics provides crucial frameworks for understanding and evaluating the economic value of DTx and appreciating its complexity, as discussed in the next section.

2.2.2. Conceptualizing economic value in healthcare systems

Economic considerations are increasingly recognized as fundamental drivers in healthcare decision-making processes (Kario et al., 2021), particularly as healthcare systems worldwide face mounting pressures from resource constraints, aging populations, and a rise in chronic and mental health conditions, as indicated earlier. The economic dimension of healthcare extends beyond simple financial analyses to encompass complex value assessments that inform regulatory approval, resource allocation, policy development, and technology adoption decisions.

The concept of economic value is indeed "*multi-dimensional and not limited to clinical benefit and cost*"(Sarri et al., 2021, p. 599). It extends beyond mere monetary considerations to encompass broader notions of societal welfare and individual well-being. As defined by Bockstael et al. (2000, p. 1384), from a health economics perspective, value refers to the "*contribution made to human welfare, where human welfare is measured in terms of each individual's own assessment of well-being.*" This definition underscores the subjective nature of value and its inherent connection to personal experiences and preferences, such as those of the various stakeholders involved in a DTx ecosystem.

Economic value in healthcare is inherently comparative, serving as a tool to evaluate trade-offs between different situations or interventions. This comparative aspect is crucial in healthcare decision-making, where resources are finite and choices must be made between competing priorities. For instance,

when considering the implementation of a new treatment or technology, policymakers and healthcare providers must weigh its potential benefits against its costs and compare it to existing alternatives.

The need for efficient resource allocation is particularly pressing in healthcare (Hempel et al., 2021). Consequently, the adoption of new technologies is heavily influenced by economic evaluations that compare the costs and health outcomes of novel interventions against existing standards of care (Drummond et al., 2015).

2.2.3. The role of economic value in technology adoption decisions

The adoption of new technologies is indeed significantly influenced by various economic factors, a relationship that has been well documented in social science literature (Adler-Milstein et al., 2014; Gagnon et al., 2012; Greenhalgh et al., 2004; Hall & Khan, 2003). This interplay between economics and technological innovation has been a subject of scholarly interest for decades, shaping our understanding of how new technologies are embraced and integrated into healthcare systems.

One of the earliest contributions to this discourse was made by Griliches (1957, p. 522), who asserted that "*economic variables are the major determinants of the pattern of technological change.*" This foundational idea laid the groundwork for subsequent theories, such as Rogers' (1962) Diffusion of Innovations Theory, which elaborates on how economic considerations can propel the rapid adoption of new technologies. According to this theory, the perceived economic advantages associated with an innovation are pivotal for its adoption rate, suggesting that potential users are more likely to embrace technological solutions that promise tangible economic benefits.

This principle remains highly relevant in contemporary healthcare contexts, where economic costs and benefits continue to be critical determinants for the

acceptance and integration of emerging technologies, including AI and DTx (Cubric, 2020).

The influence of economic considerations on technological adoption is multifaceted. Vicki et al. (2020) identified various economic factors that can either facilitate or hinder the widespread implementation of new interventions. For instance, inadequate funding can impede the uptake of promising technologies, even when their clinical benefits are clear. Conversely, evidence of cost savings or enhanced productivity can accelerate the integration of new technologies into clinical practice.

Regulatory environments also play a crucial role in shaping technology adoption, particularly for emerging technologies like DTx. As mentioned, it is explored in Section 2.1.2 “Regulatory Oversight”, these frameworks significantly influence the adoption landscape by defining the level of clinical and economic evidence required for value assessment (Danev et al., 2021). The interplay between regulatory bodies and emerging technologies creates a dynamic ecosystem that can either accelerate or hinder the widespread implementation of innovative solutions like DTx.

The role of economic value in technology adoption decisions is thus multifaceted and characterized by complex interactions and potential competing priorities. Evidence suggests that adoption decisions are significantly influenced by perceived economic benefits, while insufficient economic data may impede the implementation of even clinically effective technologies. For emerging technologies like DTx, these economic dimensions become particularly crucial, as healthcare systems seek evidence-based justification for resource allocation. These insights regarding the influence of economic value on adoption decisions provide an essential context for understanding how DTx may be evaluated within existing healthcare decision frameworks.

2.2.4. Measuring economic value in healthcare systems

Having established the importance of economic value in decision-making and technology adoption, this section examines how such value can be assessed.

Economic value is defined through HTA, which is a systematic evaluation of the properties, effects, and impacts of health technology (WHO, 2022). HTA evaluates health technologies for their clinical and cost-effectiveness, assessing their impact from the perspective of patients or budget holders (Rejon-Parrilla et al., 2022). HTA agencies typically use various economic evaluation methods to assess the costs and health outcomes associated with new interventions. They aim to establish a sound economic rationale for adopting a new technology, ensuring that it not only delivers clinical benefits but also provides value in a cost-conscious healthcare environment.The economic value in healthcare is often expressed in quality-adjusted life-years (QALY) - a measure of the value of health outcomes, with one QALY is equal to one year of life in perfect health (Lakdawalla et al., 2018). QALY is a generic measure of disease burden, including both the quality and the quantity of life lived. "*Traditionally, health economists proposed maximizing the additional health gain in terms of QALYs to maximize social welfare. Evidence has grown however, that neither potential health gain as a single relevant determinant of value, nor the maximization of this health gain, are sufficient*" (Schwappach, 2002, p. 210). Alternative or complementary approaches to QALYs have therefore emerged, including net costs, productivity, adherence-improving factors, reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spillovers (Lakdawalla et al., 2018).

Measuring economic value in healthcare is complex and context-dependent. The notion of economic value varies drastically depending on the decision context (e.g., mixed private and public insurance like in the US versus single-payer systems like in the UK), the perspectives taken (e.g., the health plan manager, the provider, the patient, society as a whole, etc.) and the objectives that such

economic valuation will inform (e.g., market access, pricing and reimbursement decisions) (Garrison et al., 2018).

Methods for investigating the DTx-economic value relationship

These evaluation methods, rooted in either welfare or extra-welfarist theories, play a crucial role in healthcare resource allocation decisions by systematically comparing intervention costs and outcomes, enabling a comprehensive understanding of their economic value. Frequently conducted alongside both randomized and non-randomized studies (Gomes et al., 2022), they generate evidence-based information to support informed decision-making. The evaluation methods can be broadly categorized into partial and full economic evaluations, each serving distinct purposes in the assessment process and offering unique insights into the economic value of DTx, as detailed in Table 8.

Table 8. Types of economic evaluation methods for DTx

Evaluation Type	Description	Outcome Measure	Application to DTx
Partial Economic Evaluations			
Cost-of-illness analysis	Evaluates the economic burden of a disease/condition	Monetary costs	Establishes the baseline economic impact of conditions targeted by DTx
Program cost analysis	Calculates the total cost of implementing an intervention	Monetary costs	Determines resource requirements for DTx implementation
Full Economic Evaluations			
Cost-benefit analysis (CBA)	Compares interventions by translating all outcomes to monetary	Monetary value (e.g., return on investment)	Captures broader economic impacts, including productivity gains
Cost-effectiveness analysis (CEA)	Compares interventions using natural units of health outcomes	Cost per unit of effect (e.g., cost per symptom-free day)	Evaluates DTx against traditional interventions using condition-specific metrics
Cost-utility analysis (CUA)	Compares interventions using preference-based measures	Cost per QALY gained	Enables comparison of DTx across different therapeutic areas

Partial economic evaluations, such as cost-of-illness analysis and program cost analysis, provide foundational insights into the economic burden of targeted conditions and resource requirements for DTx implementation. Full economic evaluations, including CBA, CEA, and CUA, offer more comprehensive assessments by comparing DTx with alternative interventions (Rabarison et al., 2015).

CBAs translate both costs and benefits into monetary terms, facilitating direct comparisons across diverse interventions. Based on welfarist principles, this approach judges health outcomes by their contribution to societal welfare through individuals' willingness to pay (WTP). While monetizing all benefits presents challenges, CBAs can capture broader impacts, like productivity gains.

In contrast, CEA and CUA follow extra-welfarist principles, aiming to maximize contributions to societal health. CEAs evaluate DTx using natural units or disease-specific metrics (e.g., HbA1c reduction for diabetes DTx), while CUAs incorporate utility functions—typically QALYs—enabling a more comprehensive appraisal of health states. Both approaches express economic value as cost per outcome metrics, such as incremental cost-effectiveness ratios (ICERs), a measure of how efficiently an intervention produces an additional QALY compared to alternatives. Both CUA and CEA are common in the evaluation of DTx (Jiang et al., 2019).

The economic value of an intervention, often referred to as its cost-effectiveness, cost utility, or health-economic effects, is typically expressed as cost per outcome metrics. As mentioned earlier, these metrics include the cost per QALY gained or the ICER per QALY gained, which serves as benchmarks for cost-effectiveness (Buntrock et al., 2021). However, if the use of QALYs allows for standardized comparisons across different types of interventions, capturing the full value of DTx through QALYs can be challenging, as some benefits (like improved patient empowerment) may not be fully reflected in this measure.

In conclusion, economic evaluations remain essential tools for assessing both financial viability and broader societal impacts of DTx, accounting for indirect benefits, such as improved quality of life and potential reductions in future healthcare expenditures.

2.2.5. Measuring patient-centered economic value

In welfarism approaches, the “goodness” of any situation (e.g., resource allocation) is judged solely on the basis of the utility levels attained by individuals in that situation (Hurley, 2000), making the patient perspective crucial for comprehensive economic evaluation. Patients, as end users or consumers of DTx, function as “economic agents” - rational decision-makers who evaluate healthcare interventions based on their individual preferences, constraints, and utility assessments (Yakusheva et al., 2024).

Patients experience and value interventions across multiple dimensions that extend beyond clinical outcomes and system-level cost considerations. Their engagement patterns, preferences, and subjective experiences directly influence the effectiveness and economic value of healthcare interventions (Hibbard & Greene, 2013). This multidimensional valuation becomes particularly significant for DTx, where patient interaction and engagement are prerequisite for therapeutic benefits.

Understanding the importance of capturing patient perspectives requires examining the fundamental differences between welfarist and extra-welfarist approaches from the patient viewpoint. While welfarist frameworks focus on individual utility maximization, they may inadequately account for patients' real-world constraints and experiences. Although the welfarist emphasis on individual utility aligns with patient-centered approaches, it may not provide a good measure in the health sector, given that individuals might value things that diminish their overall health (Seixas, 2017). Extra-welfarist approaches, despite their emphasis on health outcomes, may similarly overlook patient-valued dimensions that influence treatment success but fall outside traditional health

metrics. This gap between theoretical frameworks and patient-experienced value highlights the need for expanded measurement approaches that can capture the full spectrum of patient-centered economic value.

Limitations of current measurement approaches

Traditional economic evaluation methods rely primarily on four conventional value dimensions: QALYs, net costs, productivity impacts, and adherence-improving factors—though the latter are common but inconsistently included (Lakdawalla et al., 2018). These limitations are particularly pronounced for DTx, where patient interaction, as the end user of such digital interventions, directly drives therapeutic benefits. While these four measures provide important insights for healthcare decision-making, they may not fully capture the patient experience of economic value.

The concept QALYs, for instance and as previously discussed, developed by health economists to capture the limitless set of health-related factors (and potential benefits), is far from perfect. QALYs capture “only a subset of benefits that may be produced by a health care intervention” (Lakdawalla et al., 2018, p.133). They have been further criticized for potential cultural bias, inability to capture non-health benefits, and challenges in reflecting patient-valued outcomes such as in palliative care (Andrade, 2025; Pinto-Prades et al., 2014). Similarly, productivity measures typically focus on formal employment, potentially overlooking unpaid care responsibilities and other meaningful activities that patients value.

The underrepresentation of patient-centered value in traditional economic evaluation creates significant methodological challenges, particularly for interventions like DTx where patient engagement is fundamental to effectiveness. Current measurement approaches often struggle to quantify subjective patient experiences that significantly influence treatment outcomes (LaVela & Gallan, 2014). This limitation is problematic for DTx evaluation, where factors such as perceived usefulness, perceived ease of use, and user acceptance - core

components of technology acceptance models (Davis, 1989; Holden & Karsh, 2010)– directly impact attrition rates—which can reach up to 80% in real-world settings (Lewkowicz et al., 2022). High attrition rates consequently affect economic outcomes through reduced effectiveness.

Beyond traditional value dimensions

To fill "in the gaps of the existent measures used in economic evaluations" (de Vries et al., 2016, p.1), Lakdawalla et al. (2018) proposed new concepts that could complement the QALY approach, as mentioned above. These include adherence-improving factors, reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spillovers). Table 9 presents an overview of emerging patient-centered value dimensions particularly relevant for DTx economic evaluation.

Table 9 Emerging patient-centered value dimensions for DTx economic evaluation

Elements of value	Description	From a welfarist and extra-welfarist perspective	DTx Relevance
Equity and access	Fair distribution of healthcare benefits across different population groups; addressing disparities	Health equity impact assessments; geographic and demographic access analyses; digital divide metrics (Curtis et al., 2022; Harris-Roxas et al., 2014)	Potential to reduce geographic barriers; risk of widening digital divide; need for inclusive design
Technology acceptance	Perceived usefulness, ease of use, and trust in digital health technologies, including the notion of privacy and security	Technology Acceptance Model (TAM), Unified Theory of Acceptance and Use of Technology (UTAUT), and user experience metrics (Davis, 1989; Venkatesh et al., 2003)	Critical for engagement and adherence; directly impacts clinical effectiveness
Patient empowerment	Health literacy, self-efficacy, and autonomy in healthcare decision-making	Patient Activation Measure (Hibbard et al., 2004); Health literacy assessments	Enhanced through DTx educational features and self-monitoring capabilities

Financial toxicity	Healthcare-related financial burden including DTx direct costs and indirect costs	COST scale (de Souza et al., 2017); Financial distress questionnaires	Potential for reduced costs through digital delivery; elimination of transportation costs
Well-being	Overall life satisfaction, psychological well-being, and flourishing beyond absence of disease	WEMWBS (Warwick-Edinburgh Mental Well-being Scale)(Tennant et al., 2007); WHO-5 Well-being Index (The WHO-Five Well-Being Index, 2024); and health-related subjective well-being (de Vries et al., 2016)	Many DTx target lifestyle, mental health, and behavioral changes that primarily impact well-being

Implementation challenges and future directions

While these emerging patient-centered value dimensions represent a promising expansion of traditional economic evaluation frameworks, yet significant methodological challenges remain in their implementation and integration. The subjective nature of many of these dimensions—particularly well-being, patient empowerment, and technology acceptance—introduces complexity in measurement standardization and comparability across studies (Huls et al., 2019; Mott, 2018). These measures capture features of individuals' perceptions of their experiences, not their utility as economists typically conceive of it (Kahneman & Krueger, 2006).

Unlike traditional clinical outcomes that can be objectively measured, patient-centered dimensions often rely on self-reported assessments that may be influenced by individual differences, cultural factors, and contextual variables. Furthermore, the relative weighting and aggregation of these diverse value dimensions present methodological challenges, as different stakeholders may prioritize different aspects of patient-centered value.

For DTx evaluation specifically, while these digital interventions offer new opportunities for real-time collection of patient-centered data (unlike traditional

pharmacological treatments), questions remain about how to systematically integrate these measures into formal economic evaluations alongside traditional metrics like QALYs and cost-effectiveness ratios (Gentili et al., 2022).

Critical areas for future research include the development of standardized measurement protocols, validation of patient-centered instruments across diverse populations, and the establishment of methodological guidelines for incorporating subjective measures into economic evaluation represent critical areas for future research. Until these methodological foundations are strengthened, the practical application of patient-centered value dimensions in healthcare decision-making may remain limited, despite their conceptual importance for comprehensive DTx evaluation.

Having established how economic value is conceptualized from both healthcare system and patient perspectives, the following section examines how these value conceptualizations influence technology adoption decisions...

2.2.6. Conclusions

The concept of economic value plays a crucial role in healthcare systems, influencing decision-making processes, resource allocation, and technology adoption. However, measuring and interpreting economic value in healthcare remains complex, especially for digital interventions like DTx, which are often AI-based.

The theoretical foundations of economic evaluations in healthcare have evolved significantly, transitioning from traditional welfare economics to a more nuanced extra-welfarist approach. While the extra-welfarist approach, with its focus on health outcomes, provides a more appropriate framework for assessing DTx value, the unique characteristics of these interventions create challenges for traditional evaluation methods to fully capture DTx's health and non-health impacts. Consequently, the relationship between DTx and economic value

remains intricate, necessitating rigorous investigation to understand its dimensions and implications.

As healthcare systems evolve in response to clinical needs and economic pressures, understanding these dynamics becomes essential for navigating challenges and opportunities at the economics-technology intersection.

The theoretical frameworks of health economics, in this section, provide a critical context for conceptualizing economic value in healthcare. The following section examines how DTx specifically challenge and expand traditional evaluation approaches by investigating the complex relationship between these digital interventions and their diverse economic value dimensions.

2.3. Conceptualizing the Relationship Between DTx and Economic Value

The relationship between DTx and economic value represents a complex interplay of multiple factors that collectively determine their overall economic benefits within healthcare systems. This section systematically examines this relationship through three complementary lenses: (1) current empirical evidence on DTx economic impact across therapeutic areas; (2) unique methodological challenges in capturing DTx economic value; and (3) key factors influencing the DTx-economic value relationship. Additionally, an investigation of diverse stakeholder perspectives—patients, providers, payers, developers, and regulators—reveals how these viewpoints influence and shape economic value conceptualization throughout the DTx lifecycle. Collectively, these multifaceted considerations inform a more nuanced understanding of how economic value is created, measured, and realized.

2.3.1. Current evidence on the economic impact of DTx

As previously highlighted, the relationship between DTx and economic value involves complex factors that determine their cost-effectiveness and economic

benefits. Understanding these factors and their interactions is crucial for healthcare decision-makers allocating resources and for developers optimizing DTx to demonstrate value in resource-limited healthcare settings.

When evaluating DTx interventions, the principle of strong dominance serves as a key consideration. This principle favors interventions that are both less costly and more effective than their comparators. Jiang et al. (2019) found that 43% (6 out of 14) of studies they reviewed demonstrated that DTx for cardiovascular disease management gained higher QALYs with cost savings, indicating strong dominance over comparator treatments. Similarly, Miao et al. (2022) established that DTx for opioid use disorder was cost-effective compared to pharmacological therapies, reducing average hospital costs from $11,141 to $8,733 over a 12-week course while delivering superior clinical outcomes—aligning with the principle of strong dominance.

For interventions that are effective but lead to additional costs, decision-makers must determine whether greater effectiveness justifies increased expenditure. New clinical interventions proposed for approval and reimbursement should result in either cost savings or incremental costs lower than the country-specific WTP threshold—defined as the maximum price at which a healthcare system will purchase one unit of a product.

Evidence increasingly supports the cost-effectiveness of DTx interventions within these established parameters. McManus et al. (2021) and Nomura et al. (2022) concluded that DTx interventions were cost-effective in the UK and Japan, respectively, with incremental costs well below the acceptable threshold value per QALY gained. Buntrock et al. (2021) demonstrated an 89% probability of a DTx intervention being cost-effective from both societal and public healthcare perspectives. These findings align with Piera-Jiménez et al. (2021), who determined that the DTx intervention under study was cost-effective based on the €30,000 WTP threshold typically applied in Spain.

While these promising results suggest economic value potential, evidence in this field continues to emerge, necessitating careful interpretation of value metrics and outcome measures. Understanding the specific factors that influence economic outcomes—positively or negatively—remains critical for developing a comprehensive evaluation framework that can adequately capture the unique characteristics of digital interventions and their implementation contexts. The following section examines these influential factors in greater detail.

2.3.2. Unique challenges in assessing DTx economic value

Traditional evaluation methods, through their inherent methodological assumptions, may not adequately capture the distinct nature, as discussed earlier, of these digital health interventions. For example, Alami et al. (2020, p. 261) suggest that AI-based solutions could bring "*significant changes and impacts at several levels: technological, clinical, human and cognitive (patient and clinician), professional and organizational, economic, legal, and ethical.*" They conclude that an assessment of the value propositions of such solutions should go beyond technical performance and cost logic by performing a holistic analysis of their value in a real-world context of care and services. Gomes et al. (2022) also highlighted significant challenges and methodological concerns for economic evaluations of digital health interventions compared with drugs and medical devices. Conducting HTA therefore requires facing a variety of challenges, from defining the use of different evaluation methods, regulatory context and requirements to product-specific characteristics (Kirisits & Redekop, 2013).

The challenges in assessing DTx economic value stem from their distinctive characteristics, as illustrated in Table 10, as complex interventions with multiple interacting components, significantly impacting their economic assessment (Murray et al., 2016). These complexities necessitate a nuanced approach to evaluation that accounts for the various influencing factors discussed previously.

Table 10. Key characteristics of DTx that impact their economic evaluation

Characteristics	Impact to Economic Evaluations
Clinical Value Dimensions	
User engagement variability	The effectiveness of DTx can be highly dependent on user engagement patterns, which may vary significantly across populations and over time. This variability impacts long-term outcomes and complicates the assessment of sustained benefits in economic evaluations.
Capturing long-term effects	The potential for DTx to influence long-term health outcomes and healthcare utilization patterns presents methodological challenges for economic evaluations, which typically rely on shorter-term data. Modeling these extended temporal effects requires innovative analytical approaches and necessarily introduces greater parameter uncertainty.
Technical Value Dimensions	
Integration with existing healthcare systems	The economic costs and benefits of DTx may be substantially influenced by how effectively they integrate with existing healthcare infrastructure and clinical workflows. This integration aspect often involves non-health outcomes, such as improved operational efficiency or reduced administrative burdens, which are challenging to quantify in traditional health economic frameworks.
Scalability	The marginal cost of delivering DTx to additional users is often minimal, which can significantly impact long-term cost-effectiveness. However, capturing these potential economies of scale in economic models presents methodological challenges. Buntrock et al. (2021) rose for example concerns about maintaining the effectiveness of DTx as solutions are scaled, given that the controlled environment of trials cannot be recreated at scale.
Rapid iteration and updates	Unlike traditional interventions, DTx can be frequently updated, potentially altering their effectiveness and cost structure over time. This rapid technological evolution poses challenges for long-term economic evaluations, as the intervention being assessed may evolve significantly during the study period.
Real-world data generation	DTx often produce vast amounts of real-world data, which can inform ongoing evaluation but also presents challenges in data management and analysis. This continuous data flow offers opportunities for real-time assessment but complicates traditional evaluation timeframes.
Privacy and security considerations	The costs associated with ensuring data privacy and security in DTx may be substantial and ongoing, representing a unique cost category that requires explicit consideration in comprehensive economic evaluations.

Societal Value Dimensions	
Multidisciplinary Stakeholder Engagement	The multiplicity of stakeholders engaged throughout each phase of the DTx product development lifecycle—researchers, software developers, engineers, clinicians, care providers, patients, regulatory agencies, and payers, among others—creates a complex ecosystem where potentially divergent priorities and value frameworks must be carefully aligned for successful implementation and adoption.
Incorporating non-health outcomes	DTx can generate benefits beyond direct health improvements, including increased productivity, improved quality of life, and enhanced patient autonomy and empowerment. Capturing these broader societal impacts in economic evaluations necessitates expanding traditional assessment frameworks to include multidimensional value metrics.

Aligned with our earlier discussions, Gomes et al. (2022) therefore argue for a more comprehensive assessment of DTx that extends beyond conventional health-related outcomes and costs, encompassing non-health benefits and costs that may fall outside the traditional healthcare sector, thus reflecting the broader societal impact of these digital interventions.

To address these challenges, emerging guidelines, such as the Digi-HTA (Digital HTA) framework have been developed to support the introduction of novel technologies, including mHealth, AI, and robotics, into healthcare systems (Haverinen et al., 2019). Digi-HTA is indeed a framework developed in Finland to assess the value of digital health technologies, including DTx. It was created by the Finnish Coordinating Center for Health Technology Assessment in response to the unique challenges posed by digital health interventions.

Similarly, the NICE Evidence Standards Framework for digital health and care technologies in the United Kingdom aims to provide a standardized approach for developers and commissioners, outlining the levels of evidence required for clinical and economic evaluation of digital health technologies (Unsworth et al., 2021).

Despite these promising initiatives, significant methodological deficits persist in current DTx evaluation assessments. Wolff et al. (2020) found that only 6 out of

66 peer-reviewed articles they examined could apply a second step in data analysis, and none included a methodologically sound cost impact analysis. The absence of consistent methodological standards for economic evaluation study designs impacts the reliability and comparability of results. Thase et al. (2020) demonstrated that the difference between control and experimental groups was largely determined by study design, highlighting the need for careful consideration of methodology. Richards et al. (2020) also noted that in the scenario analyses at 6, 9 and 12 months, the probability of cost-effectiveness increases as the time horizon increases.

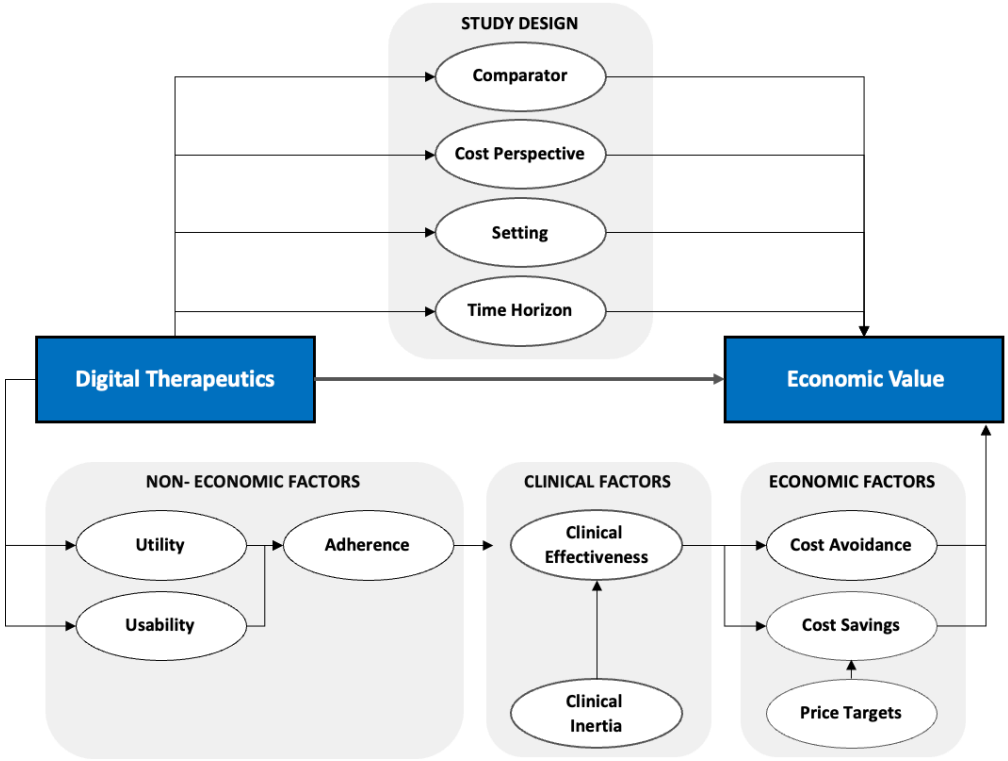
The unique DTx characteristics (Table 10) underscore the need for adapted evaluation frameworks that can address the complexities of DTx economic assessment beyond conventional health-related outcomes and costs (Gomes et al., 2022). More sophisticated economic models capable of comprehensively investigating both short-term and long-term value drivers of DTx in real-world settings are required. Such models would enhance understanding of the intricate relationship between DTx and their economic value while improving the generalizability of findings across various healthcare contexts (Richards et al., 2020). Ultimately, these would provide healthcare decision-makers and stakeholders throughout the DTx lifecycle with more robust evidence to inform regulatory approval, resource allocation and technology adoption strategies.

2.3.3. Factors influencing the DTx-economic value relationship

Building on the previous discussion, the economic value of DTx is influenced by a complex interplay of factors that extend beyond both the unique characteristics of DTx themselves and conventional pharmacological treatments.

To identify these factors and understand how they influence DTx economic value, a review of current literature and published evidence were conducted. Figure 5 summarizes these preliminary identified factors, which collectively shape the relationship between DTx and their economic value, impacting their cost-effectiveness and overall economic benefit.

Figure 5. Factors influencing the DTx and economic value relationship



Cost savings and cost avoidance emerge as primary drivers of a DTx intervention's economic dominance. Baumann et al. (2020) refer to cost savings in terms of reduced healthcare resource utilization, which can manifest as lower medication costs, fewer consultations with healthcare practitioners, or shorter hospital stays (Nordyke et al., 2019). Cost avoidance, in contrast, relates to preventing future expenses, such as averting hospitalizations or rehospitalizations. For instance, Piera-Jiménez et al. (2021) observed that an internet-based cognitive behavioral therapy intervention helped patients transition from severe to mild major depressive disorder, thereby preventing future rehospitalizations and generating substantial economic value through cost avoidance.

The attrition rate of DTx users significantly impacts the ICER ratio, as noted by Lewkowicz et al. (2022) and Nomura et al. (2022). Defined as the percentage of participants who discontinue engaging with the DTx intervention, attrition rates

for DTx apps can reach up to 80% in real-world usage scenarios (Lewkowicz et al., 2022). These attrition or adherence rates have been shown to have the greatest impact on ICER analyses (Nomura et al., 2022) and strongly influence economic outcomes (Lewkowicz et al., 2022). Buntrock et al. (2021) raised concerns about how adherence and effectiveness might be impacted as DTx solutions scale, questioning whether the controlled environment of clinical trials can be recreated in real-world implementation. Examining DTx for low back pain, Lewkowicz et al. (2022) further argued that DTx reimbursement is directly contingent and derivable from (1) the retention and attrition rates while using the DTx, and (2) the effects of the implementing decision-support interventions to provoke behavior change and support long-term coping with low back pain. Importantly, while retention and attrition rates impact the clinical efficacy and effectiveness of DTx, they are themselves influenced by the usability and utility of the proposed solution.

Patient severity distribution also plays a crucial role in determining a DTx economic value. Nordyke et al. (2019) found that the distribution of patient severity between control and experimental groups, along with potential clinical inertia, can limit the economic benefits of digitally delivered behavioral interventions. Clinical inertia, characterized by resistance to deprescribe medications despite improved clinical outcomes, may significantly reduce the estimated economic benefits of DTx by limiting full cost savings potential (Nordyke et al., 2019).

Pricing strategies for DTx also substantially impact their economic value. Lewkowicz et al. (2022) demonstrated that a DTx intervention became the dominant strategy over usual treatment only when the mobile application's cost was reduced to €99 per 3 months or when the attrition rate decreased. This finding underscores the importance of balancing pricing with user retention to achieve cost-effectiveness and highlights the delicate interplay between pricing decisions and value realization.

These factors identified, extending well beyond clinical outcome improvements, underscore the unique challenges and complexity in assessing DTx economic value—complexities that are amplified by divergent stakeholder perspectives, as examined in greater detail in the following section.

2.3.4. Stakeholders' divergent perspectives on DTx economic value

Unlike traditional healthcare interventions, DTx sit at the intersection of healthcare, technology, and consumer products, engaging a broader range of stakeholders with potentially divergent priorities and value frameworks (Ho et al., 2023; Mathews et al., 2019). These divergent perspectives shape how economic value is conceptualized, realized, and measured throughout the DTx lifecycle. This creates a dynamic interplay of opportunities and challenges that evolve as products move from conception to implementation in real-world environments. The DTx development process unfolds across three distinct phases, each characterized by different stakeholder priorities and value considerations (Figure 2).

Phase 1: DTx Development

During the initial development phase, researchers and technology developers—including but not limited to biomedical engineers, data scientists, and behavioral specialists—drive the conceptualization and prototyping process. While instrumental in creating and validating DTx, emerging evidence suggests they may prioritize technical performance and clinical efficacy over economic considerations (Kreuzenbeck et al., 2024). This potential disconnect between researchers and technology developer priorities and market requirements may contribute to adoption challenges, as economic evidence is increasingly demanded by other stakeholders in the healthcare ecosystem.

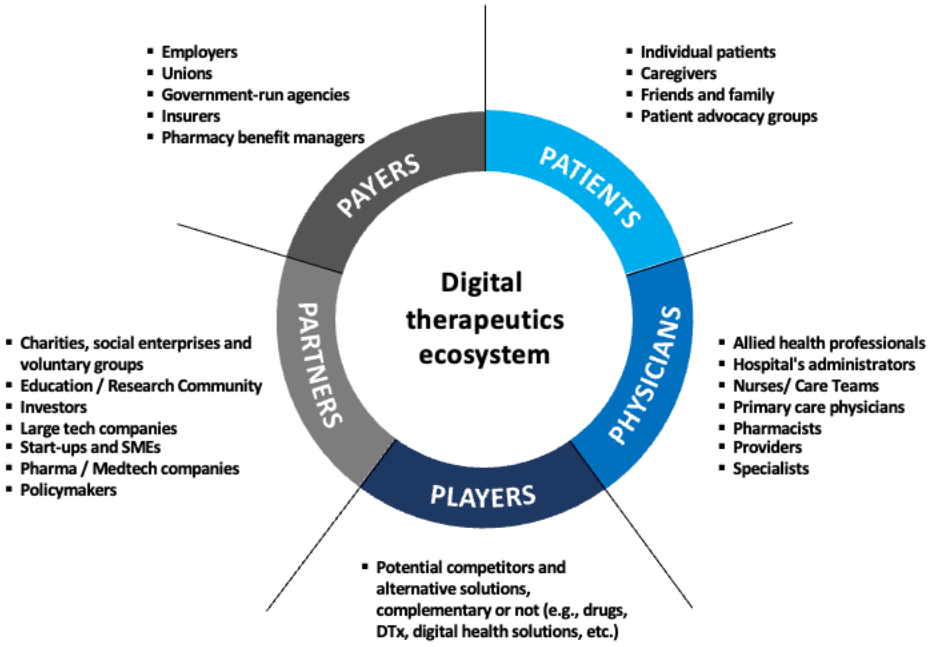
Phase 2: DTx Clinical Validation

The transition from concept to clinical validation marks a shift toward evidence-based validation, where academic assets are transformed into DTx products through pre-clinical phases and clinical trials, typically randomized controlled trials (RCTs). This phase is predominantly clinical-driven, with clinicians leading the process—supported by research teams—to ensure independent collection of safety and efficacy evidence.

Phase 3: DTx Implementation

The implementation phase marks a pivotal expansion of the stakeholder ecosystem as DTx products transition into real-world deployment. This “go-to-market” phase brings new players into the value equation—including regulatory bodies overseeing market approval and healthcare systems managing clinical integration. As this stakeholder network broadens, the assessment and realization of economic value become increasingly complex, with each participant applying their own lens to define and measure what constitutes meaningful value. Ho et al. (2023) identified five broad categories of stakeholders at this third phase: patients, payers, partners, players, and physicians (Figure 6). Each of these stakeholders, woul have varied degree of influences in shaping the potential economic value of a DTx.

Figure 6. The 5Ps in the DTx stakeholder ecosystem



Prescribers (Physicians)

Healthcare providers—including general practitioners and specialists—serve as critical gatekeepers whose economic value assessment significantly influences DTx adoption. Providers typically prioritize clinical outcomes and integration with existing workflows when evaluating DTx. Their assessment of economic value often focuses on time efficiency, reduced administrative burden, and potential for improved patient outcomes (Dahlhausen et al., 2021). As discussed earlier, recent studies reveal that only 24–62% of physicians would potentially prescribe a DTx (Dahlhausen et al., 2021), highlighting significant adoption barriers from the provider perspective. Kreuzenbeck et al. (2024) found that user experience for both patients and healthcare professionals represents a significant barrier to usage, alongside concerns about costs, high effort, and complex bureaucratic processes for prescribing DTx.

Payers

Payers and health system administrators approach economic value from a distinct perspective, emphasizing cost-effectiveness, budget impact, and return on investment as primary considerations (Danev et al., 2021). These stakeholders typically operate within constrained budgetary environments, necessitating careful assessment of new interventions against existing alternatives. Their focus on system-level outcomes often contrasts with the more granular, patient-centered metrics prioritized by other stakeholders.

Patients

From the patient perspective, economic value extends far beyond direct financial costs to encompass experience quality, convenience, accessibility, time savings, and reduced care burden – to name just a few (Sarri et al., 2021). Their willingness to engage with DTx is often contingent on perceived value relative to traditional care options, with considerations, such as time savings and reduced travel costs featuring prominently in their assessment. This patient-centered perspective on economic value may not always align with the metrics prioritized by providers or payers, creating potential tensions in value assessment and realization (Sarri et al., 2021).

Regulatory Bodies (Partners)

Regulatory stakeholders add another layer of complexity through varying economic evidence requirements across jurisdictions. As noted earlier, the UK mandates cost-effectiveness analysis for DTx, while France, the US, and Germany adopt more flexible approaches (Danev et al., 2021). These regulatory variations create a complex landscape for DTx developers seeking multi-market access, potentially necessitating diverse economic evaluation approaches tailored to specific jurisdictional requirements.

Integration of Stakeholder Perspectives

The DTx ecosystem encompasses a diverse array of stakeholders throughout the intervention lifecycle—engineers, data scientists, behavioral scientists, economists, healthcare providers, clinicians, hospital administrators, regulatory bodies, and commercial entities. Ho et al. (2023) characterized this ecosystem as "dynamic and complex," emphasizing the critical importance of understanding each stakeholder's potential impact on technological, clinical, and economic value generation.

The economic evaluation of DTx is inherently influenced by these diverse perspectives, which shape how economic value is conceptualized, measured, and realized across the intervention lifecycle. These diverse and sometimes competing stakeholder perspectives create a complex landscape for economic evaluation of DTx. Lyles et al. (2021, p. 1) identified the "*misalignment of priorities between stakeholder groups*" as a factor that has "*stymied the progress of digital health tool uptake*." Understanding how different stakeholders conceptualize and contribute to the economic value of a DTx throughout its lifecycle is essential for identifying how this value is shaped over time and for identifying potential intervention points when needed.

Ultimately, enabling DTx to become mainstream in healthcare requires understanding the decision-making processes of these stakeholders throughout the DTx lifecycle and determining how to create what Wong et al. (2024, p. 10) describe as "*favorable conditions for technology adoption*." Such understanding can help establish more cohesive pathways from development through implementation to sustained use in clinical practice.

2.3.5. Conclusions

This section has revealed the complex, multidimensional relationship between DTx and economic value. Current evidence suggests promising cost-effectiveness across therapeutic areas, though methodological limitations and inconsistent evaluation approaches constrain generalizability. DTx present

unique evaluation challenges stemming from their characteristics as complex digital interventions. A review of the literature identified multiple factors influencing the DTx-economic value relationship. Additionally, diverse stakeholder perspectives—from patients and providers to payers and developers—create a complex landscape for economic evaluation, with potentially competing priorities and value frameworks that must be carefully navigated throughout the DTx lifecycle. These findings highlight significant knowledge gaps regarding how economic value is created, measured, and realized throughout the DTx lifecycle. Understanding these complexities is essential to capture the full value proposition of DTx while ultimately informing future downstream evidence-based implementation and adoption decisions.

2.4. Conclusions and Research Gaps

This literature review has established DTx as evidence-based digital interventions with significant potential to transform healthcare delivery. Despite their clinical potential and unique capabilities for personalized intervention and real-time data generation, DTx face substantial market access challenges within healthcare systems globally. Central to these challenges is insufficient understanding of their economic value proposition relative to traditional therapeutic approaches.

The review has specifically revealed three critical knowledge gaps that directly align with this thesis research questions:

First, while growing evidence supports clinical benefits of DTx, it remains largely undetermined whether and how these innovative therapies can provide substantial economic value (Piera-Jiménez et al., 2021). The relationship between DTx and economic value is inherently complex, influenced by myriad factors that have yet to be fully identified and investigated. This uncertainty presents a critical barrier to the widespread integration of DTx into healthcare systems and underscores the urgent need for more comprehensive economic

evidence. This gap directly relates to the sub-research question 1: "**How has the emergence of DTx, a new class of medicine, translated to economic value, and why?**"

Second, these factors interact in complex ways across diverse stakeholder perspectives, with patients, providers, payers, developers, and regulators each conceptualize economic value through different lenses and priorities. This multiplicity of perspectives creates additional complexity in how economic value is perceived and realized throughout the DTx lifecycle, yet these perspectives remain inadequately integrated throughout DTx development and implementation processes. This gap corresponds to the sub-research question 2: **"Do stakeholders involved in the development and clinical validation of DTx consider factors influencing their economic value, and if so, how?"**

Third, substantial process gaps exist in how economic considerations are integrated throughout the DTx development lifecycle. The literature suggests that economic aspects are often considered in the later stages of the DTx lifecycle, potentially limiting value creation and demonstration, but lacks detailed investigation of when and how economic value drivers are considered during different development phases. This gap directly addresses the main research question: **"What are the economic value drivers of DTx and how are they considered throughout the product development lifecycle?"**

Addressing these knowledge gaps requires a thorough and in-depth understanding of the relationship between DTx and economic value, as well as the drivers of such value. This research aims to address these critical gaps by identifying economic value drivers and examining how these drivers are considered throughout the product development lifecycle.

The inherent complexity of this research problem necessitates a mixed method-based approach, combining qualitative exploration with quantitative analysis, as detailed in the following chapter. By addressing these evidence gaps, this research aims to advance both academic understanding and practical decision-

making for DTx development, evaluation, and implementation. It aims to bridge the gap between the theoretical potential of DTx and their practical implementation within healthcare systems by providing actionable insights for developers, evaluators, and decision-makers, ultimately facilitating the adoption of DTx.

RESEARCH DESIGN

3

CHAPTER 3. RESEARCH DESIGN

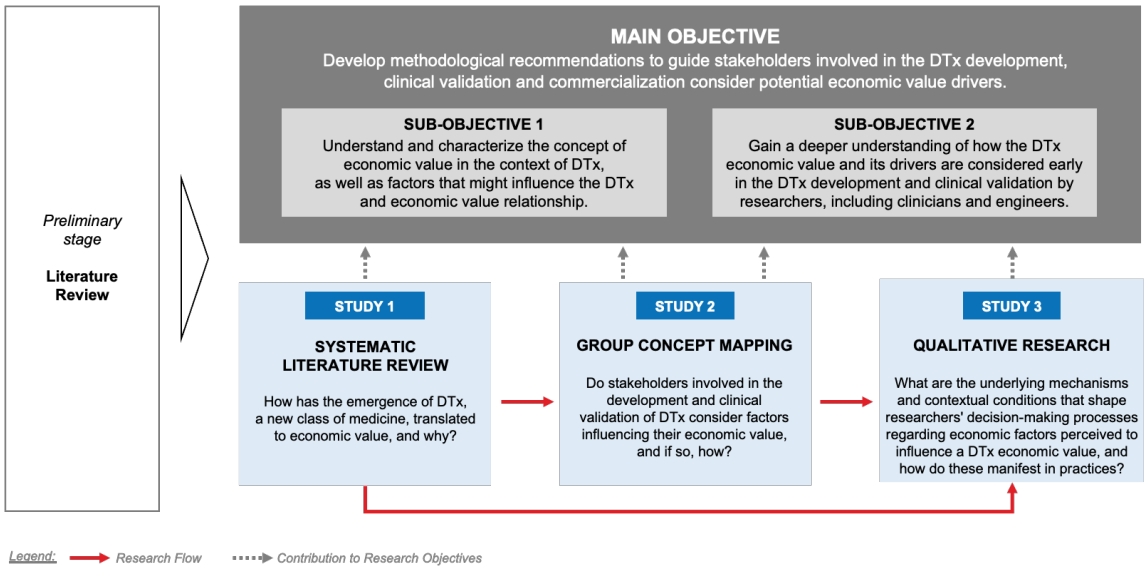
The chapter presents the research framework and methodologies employed in this DBA thesis and related studies. It begins by presenting a comprehensive overview of the research process and outlines the methodological approaches for each of the three cascading papers, which are elaborated upon in their respective chapters.

3.1. Research Approach

To address the complexity of the proposed research problems, this thesis imploys both a qualitative and a mixed method-based research approaches. It involves collecting and analyzing data, integrating findings, and drawing inferences using both qualitative and quantitative approaches within a single study or program of inquiry (Creswell & Tashakkori, 2007). A mixed methods-based approach represents "*a natural choice in order to complement and cater to the increasingly complex needs of contemporary researchers*" (Dawadi et al., 2021, p. 25) and offers several benefits when approaching complex research issues (Fetters, 2016). It enables researchers to view a phenomenon from different perspectives and research lenses (Shorten & Smith, 2017), gaining in-depth and comprehensive understanding of the research phenomenon. In essence, such an approach helps to produce a more complete picture and provides an opportunity for a greater assortment of divergent or complementary views, such as those reflecting the perspectives of various healthcare stakeholders.

Consequently, the research investigates the research questions with a three-study exploratory design that combines studies sequentially (i.e., findings from one approach inform the next one). The research design includes a systematic literature review (Chapter 4), a group concept mapping study (Chapter 5), and a qualitative research study (Chapter 6) as shown in Figure 7.

Figure 7. Proposed study approach: research questions and objectives alignment



3.2. Three Cascading Research Studies

As illustrated in Figure 7, this thesis comprises three interconnected research studies, each culminating in a peer-reviewed publication that forms the core of this investigation. The studies follow a sequential progression, in which each builds upon the findings of its predecessor, enabling progressively deeper exploration of the phenomenon under examination. This structured approach facilitates comprehensive analysis of the primary research question and its associated sub-questions. The three studies were deliberately designed to be complementary, creating a cohesive tripartite investigation that systematically advances understanding of the subject matter through incremental knowledge development.

The following sections outline the research approach and methodology for each core study, while Chapters 4, 5, and 6 provide comprehensive elaboration of the specific protocols, analytical techniques, and findings pertinent to each respective investigation.

3.2.1. Systematic literature review, a narrative synthesis approach (Study 1, Chapter 4)

Systematic literature reviews are employed by researchers seeking to provide a comprehensive review of existing knowledge (Snyder, 2019). These reviews address formulated research questions through systematic and explicit methodological frameworks that identify, select, and critically appraise relevant primary research, followed by rigorous extraction and analysis of included studies' data. The focus of such reviews is to provide an overview of the major themes, similarities, or differences regarding a topic being studied (Snyder, 2019). Systematic reviews may also identify gaps, deficiencies, and trends in the current evidence, as well as produce statements to guide decision-making (Munn et al., 2018). Linnenluecke et al. (2020) also noted that systematic reviews are used to establish the path to productive forthcoming research.

Given the nature of the research problem identified in Chapter 1 and the above methodological criteria, a systematic literature review methodology emerges as the most appropriate design to address the first sub-research question: "**How has the emergence of DTx, a new class of medicine, translated to economic value, and why?**" This study adopts a post-positivist epistemological position that embodies the paradigm's characteristic tension between systematic objectivity and critical reflexivity (Paré et al., 2015). Ontologically, the study assumes that economic value is systematically measurable and comparable across different interventions and contexts, with true causal relationships existing between DTx interventions and their economic outcomes.

This systematic literature review methodology facilitates comprehensive examination of the existing knowledge corpus on DTx economic value propositions relative to standard of care interventions, enabling robust generalization of findings to broader populations. The research adopts a narrative synthesis approach. While this approach may entail statistical data manipulation, it predominantly uses a textual approach to the synthesis process to tell the story of the findings from the studies selected (Popay et al., 2006).

The review examines the existence of relationships between DTx (concept A, measured in terms of presence of a DTx intervention) and various measures of economic value (concept B, measured as the economic impact of the intervention). The review emphasizes the theoretical relationship between these concepts, extracting, characterizing, and explaining such relationship, as well as comprehending contextual factors.

The study protocol detailed in Chapter 4, has been registered in the international prospective register of systematic reviews (PROSPERO), a registry for systematic review protocols, and is publicly available at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=358616. The primary research output derived from this investigation underwent rigorous peer-review evaluation and was subsequently published on August 1, 2023, in the Journal of Medical Internet Research (JMIR).

3.2.2. Group concept mapping, a mixed method-based approach (Study 2, Chapter 5)

Commercialized DTx are frequently the result of multidisciplinary partnerships and collaborative efforts of engineers, clinicians, and healthcare decision-makers, working together to solve DTx-specific problems arising from the novelty and unique characteristics of these digital interventions. To assist DTx economic evaluation for market access, it is crucial to gather diverse experiences and viewpoints of these multiple stakeholders, from all corners of the healthcare ecosystem.

Given these considerations, the research employs GCM methodology - a mixed methods-based approach that engages participants throughout the research process in structured qualitative and quantitative methods (Kane & Rosas, 2018). This approach is often used for the evaluation of interventions in health and social care and research (Rosas & Kane, 2012), making it a natural choice. GCM enables the determination of convergence and divergence among stakeholders

involved in the DTx development, clinical validation and implementation on the multi-factors influencing the DTx economic value.

GCM was introduced by Trochim (1989) as a mixed method-based approach. GCM is designed to harness the knowledge of groups, even those with diverse experience and perspective (Kane & Rosas, 2018), and is well suited to address our second sub-research question, "**How do diverse stakeholders involved throughout the DTx lifecycle collectively conceptualize and perceive the prioritization of factors influencing DTx economic value?**" Additionally, CGM is frequently used in evaluating programs (i.e., planning the deployment of technology in healthcare) to help evaluators and evaluation stakeholders articulate their implicit theories, program activities and outcomes, and potential measures (Kane & Rosas, 2018), which naturally supports the proposed research activities.

Cloutier et al. (2019, p. 528) also emphasize that "*GCM differs from other approaches in that it is part of a stepwise process, the one of producing group or collective or coconstructed knowledge based on multivariate and non-parametric statistical methods*." CGM therefore incorporates detailed qualitative data in addition to robust multivariate statistical techniques.

This study adopts a realist stance, treating stakeholder perspectives on DTx economic value as legitimate and discoverable knowledge that can inform real-world decision-making (Allmark & Machaczek, 2018). Epistemologically, the study embraces an interpretivist approach through GCM, whereby knowledge is gained through systematic interpretation of stakeholder meanings and experiences (Klein & Myers, 1999). The methodology is designed to reveal the subjective understandings that different groups bring to DTx economic value assessment, deliberately embracing researcher-participant collaboration as essential to understanding complex social phenomena (Trochim, 1989).

Building upon these philosophical and methodological foundations, the GCM project is structured around three interconnected objectives that operationalize

the interpretivist approach: (1) increasing understanding of the factors that contribute to the economic value of DTx, (2) learning more about how stakeholders involved in DTx development consider these factors throughout the product development lifecycle (i.e., development, clinical validation, and implementation), and (3) comprehending how these stakeholders contribute to or create conditions that may drive the economic value of DTx.

The manuscript resulting from this study underwent peer-review evaluation and was subsequently published in npj Digital Medicine on April 10th, 2025, underscoring the methodological rigor and scientific contribution of the findings to the digital medicine field.

3.2.3. Qualitative research method, a critical realism approach (Study 3, Chapter 6)

Building upon findings from the systematic literature review (Study 1) and GCM investigation (Study 2), this research examines gaps in economic related factors consideration between researchers and non-researchers, and the underlying mechanisms that shape researchers' decision-making processes regarding economic considerations throughout DTx lifecycle.

The father of qualitative research, Lazarsfeld (1971), demonstrated how psychology could provide a framework for interpreting human behavior. He advocated for in-depth interviewing, probing for answers to ‘why?’ type questions (Bailey, 2014), which is essentially the question that must be answered. Furthermore, as Green and Thorogood (2018) pointed out, qualitative designs are most effective in understanding what people do and their different perspectives, as well as how health practices are implemented in everyday life by multiple stakeholders. In other words, a qualitative approach amplifies stakeholders’ perspectives on the DTx and economic value relationship.

Green and Thorogood (2018) also emphasize the “logical position” of a qualitative study as a follow-up to quantitative or mixed method-based research,

providing “depth” to the findings. For example, they argue that “*a survey data might identify a relationship between variables, for instance, but may not be able to uncover the mechanism*” (Green & Thorogood, 2018, p. 19).

The study adopts a critical realist (CR) epistemological stance that embraces a stratified ontology recognizing three interconnected domains of reality: the empirical, the actual, and the real (Fletcher, 2017). This ontological foundation enables the study to move beyond surface-level descriptions of researchers' behaviors to uncover the deeper generative mechanisms that shape researchers' decision-making. These mechanisms would have been invisible through purely empirical approaches (Bhaskar, 2008; Wynn & Williams, 2012). Central to this approach is CR’s core epistemological principle is that knowledge advances through theoretical identification of underlying causal powers rather than through empirical correlation alone (Bhaskar, 2008). Consequently, the CR approach assumes that while researchers' decision-making patterns are empirically observable, the causal structures producing these patterns operate independently of researchers' awareness or interpretation, thereby embodying CR's commitment to ontological realism coupled with epistemological relativism.

Addressing the thesis's second sub-question—”**Do stakeholders involved in the development and clinical validation of DTx consider factors influencing their economic value, and if so, how?**”—the research gathered data through semi-structured in-depth interviews with 17 researchers involved in DTx development. Participants included research-engineers, health systems and social science researchers, clinician-researchers, and practitioner-researchers, selected through purposive sampling based on relevant experience criteria. The interview guide covered topics ranging from participants' roles and priorities to contextual conditions and practical implementation issues influencing economic decision-making.

The data analysis followed a structured three-step analytical approach aligned with CR principles. First, coding and identification of demi-regularities used a

deductive yet flexible coding framework (Fletcher, 2017) combining Decision Theory concepts with DTx literature, yielding three core themes. Second, abduction following Sætre & Van de Ven's approach (2021) identified puzzling patterns in researchers' decision-making, revealing how researchers prioritize clinical evidence while deprioritizing economic considerations despite acknowledging their importance. Third, retroduction using Danermark's framework (2019) identified three primary generative mechanisms explaining researchers' approaches: *Professional Norms* (institutional forces systematically prioritizing clinical validation), *Researcher Experience* (intrapersonal factors including professional training and cognitive biases), and *Adoption Uncertainties* (implementation challenges affecting development decisions).

The study applies System Dynamics (SDs), particularly Causal Loop Diagrams (CLDs), to visualize and analyze complex relationships between identified mechanisms, mapping variables and causal links to reveal how reinforcing and balancing loops create persistent decision-making patterns. Methodological rigor was enhanced through triangulation across multiple data sources, systematic comparison with previous findings, and critical discussions with both the research team and DTx experts.

This qualitative approach provides depth to findings from the previous two studies by exploring why certain factors are considered or not, uncovering explanatory mechanisms for observed patterns, providing rich contextual understanding of decision-making processes, and triangulating findings to strengthen the overall research program's validity. The study answers Green and Thorogood's (2018) call for depth following quantitative research by identifying not just relationships between variables but also underlying mechanisms, creating a comprehensive understanding of economic decision-making in DTx development. The details of this third study's approach, including details of data collection, analysis and reporting, are presented in greater details in Chapter 6. The manuscript resulting from this study underwent peer-review evaluation and

was subsequently accepted for publication in the Journal of Medical Internet Research (JMIR) on August 21, 2025.

3.3. Conclusions

This chapter has outlined the comprehensive methodological framework underpinning this thesis, employing a mixed methods approach through three sequential and complementary studies that collectively address the complex research questions surrounding DTx economic value. The cascading three-study approach ensures systematic progression from broad foundational understanding to detailed mechanistic insights, with each investigation strategically aligned to address specific research objectives and sub-questions.

The systematic literature review (Study 1) directly addresses the first sub-research question regarding how DTx emergence has translated to economic value, establishing the empirical foundation necessary to meet the objective of comprehensively examining existing knowledge on DTx economic value propositions. The GCM approach (Study 2) specifically targets the second sub-research question concerning how diverse stakeholders conceptualize and prioritize factors influencing DTx economic value, fulfilling the objective of capturing multi-stakeholder perspectives across the healthcare ecosystem. The qualitative investigation (Study 3) addresses the third sub-research question by exploring how stakeholders consider economic factors throughout DTx development, achieving the objective of uncovering underlying decision-making mechanisms.

This methodological design ensures that each study contributes distinct yet complementary insights toward answering the overarching research question while systematically addressing all research objectives. The integration of quantitative, mixed methods, and qualitative paradigms provides methodological triangulation specifically calibrated to the complexity of the research problem. The following Chapters (4, 5, and 6) present the detailed methods, analysis, and

findings of each respective study, demonstrating how this approach generates comprehensive insights into DTx economic value propositions and stakeholder decision-making processes.

4 ECONOMIC EVALUATION ASSOCIATED WITH CLINICAL-GRADE MOBILE APP-BASED DIGITAL THERAPEUTIC INTERVENTIONS: SYSTEMATIC REVIEW (STUDY 1)

CHAPTER 4. ECONOMIC EVALUATION ASSOCIATED WITH CLINICAL-GRADE MOBILE APP-BASED DIGITAL THERAPEUTIC INTERVENTIONS: SYSTEMATIC REVIEW (STUDY 1)

DTx represent an emerging class of medicine that delivers software-based therapeutic interventions directly to patients. Despite growing interest in their potential to transform healthcare delivery, the economic value proposition of these innovations remains inadequately characterized, impeding widespread adoption across global healthcare systems.

This chapter presents the first study in our three-part investigation, a systematic review examining the economic value evidence for mobile app-based DTx interventions. This comprehensive analysis synthesizes literature on DTx cost-effectiveness, identifies methodological approaches and limitations in current economic evaluations, and extracts key factors influencing DTx economic outcomes.

The findings establish an evidence-based foundation regarding economic evaluations for DTx while highlighting methodological challenges affecting result interpretation and generalizability. This systematic review serves as the foundation for the broader research agenda, with subsequent chapters employing mixed methods-based approaches to develop a more nuanced understanding of how economic value is conceptualized throughout the DTx development lifecycle.

Publication Status

Published in the Journal of Medical Internet Research (JMIR) on August 1, 2023 (Appendix 1C). JMIR is a Q1 peer-reviewed journal ranking in the top 25% of medical informatics publications with an Impact Factor of 7.4 (2023). The manuscript underwent rigorous evaluation by two independent peer reviewers prior to acceptance. Since then, as of May 20th, 2025, it has been cited eighteen times in peer-reviewed journals and once in a book/policy document.

4.1. Abstract

Background: DTx, a class of software-based clinical interventions, are promising new technologies that can potentially prevent, manage, or treat a spectrum of medical disorders and diseases as well as deliver unprecedented portability for patients and scalability for healthcare providers. Their adoption and implementation were accelerated by the need for remote care during the COVID-19 pandemic, and awareness about their utility has rapidly grown among providers, payers, and regulators. Despite this, relatively little is known about the capacity of DTx to provide economic value in care.

Objective: This study aimed to systematically review and summarize the published evidence regarding the cost-effectiveness of clinical-grade mobile app–based DTx and explore the factors affecting such evaluations.

Methods: A systematic review of economic evaluations of clinical-grade mobile app–based DTx was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines. Major electronic databases, including PubMed, Cochrane Library, and Web of Science, were searched for eligible studies published from inception to October 28, 2022. Two independent reviewers evaluated the eligibility of all the retrieved articles for inclusion in the review. Methodological quality and risk of bias were assessed for each included study.

Results: A total of 18 studies were included in this review. Of the 18 studies, 7 (39%) were nonrandomized study–based economic evaluations, 6 (33%) were model-based evaluations, and 5 (28%) were randomized clinical trial–based evaluations. The DTx intervention subject to assessment was found to be cost-effective in 12 (67%) studies, cost saving in 5 (28%) studies, and cost-effective in 1 (6%) study in only 1 of the 3 countries where it was being deployed in the final study. Qualitative deficiencies in methodology and substantial potential for bias, including risks of performance bias and selection bias in participant recruitment, were identified in several included studies.

Conclusions: This systematic review supports the thesis that DTx interventions offer potential economic benefits. However, DTx economic analyses conducted to date exhibit important methodological shortcomings that must be addressed in future evaluations to reduce the uncertainty surrounding the widespread adoption of DTx interventions.

Keywords: digital health; digital therapeutics; economic evaluation; cost-effectiveness; mobile phone; systematic review.

4.2. Introduction

4.2.1. Background

The continued rise in chronic and mental health conditions, and commensurately in their associated healthcare costs, is not a new phenomenon. What is new—and reinforced by the COVID-19 pandemic—is the realization of a need for novel approaches to deliver care for these conditions closer to where individuals live and work, such as in their own homes and communities. As healthcare organizations and providers rush to adapt to this new reality, the adoption of digital technologies has accelerated rapidly (Perdana & Mokhtar, 2022).

Under the umbrella term digital technologies, it is crucial to distinguish between 3 separate categories, which are sometimes conflated or used interchangeably: *wellness and support* solutions, referring to products designed to capture, store, and transmit health data (e.g., telehealth platforms); *diagnostic and monitoring* solutions, involving products that measure or track individuals' health status or both (e.g., connected drug delivery devices); and *digital therapeutics (DTx)*, a new class of medicine that delivers therapeutic interventions directly to patients (e.g., digital behavioral therapy) (DTx Alliance, 2021).

Powered by computer software, DTx can deliver evidence-based therapeutic interventions that prevent, manage, or treat a spectrum of medical disorders and diseases directly to patients (DTx Alliance, 2021). Evidence supporting the potential of DTx in optimizing patient care and health outcomes (Huh et al., 2022) through a more personalized approach to healthcare, with greater patient education and empowerment, is mounting (Masanneck et al., 2023). As such, DTx have recently been described as the "next paradigm" of modern healthcare (Khirasaria et al., 2020).

Interest in DTx began to surge in 2017 when the US FDA approved the first DTx for the treatment of opioid use disorders (Shen, 2017). Subsequently, in 2019,

Germany became the first country to establish a Fast-Track Process for integrating DTx into the German reimbursement market (Federal Institute for Drugs and Medical Devices (BfArM), 2020). Shortly thereafter, Belgium (INAMI, n.d.), France (Lovell, 2021), Japan (Business Wire, 2022), South Korea (Ministry of Food and Drug Safety, Republic of Korea, 2020), and the United Kingdom (Ofori & Monnickendam, 2022) began to implement DTx-specific approval and reimbursement processes. Globally, there are currently approximately 400 DTx available or under development (ResearchAndMarkets.com, 2023).

Although considered a rapidly emerging class of medicine, the economic value of DTx is yet to be understood, resulting in an important knowledge gap that limits its widespread uptake (Kyaw et al., 2023; Yan et al., 2021). There is currently limited consensus on whether these technologies are cost-effective compared with traditional treatments. Because cost-effectiveness is an important consideration in payers' reimbursement and pricing decisions (Yan et al., 2021), questions regarding the potential economic impact of DTx merit exploration (Rahimi, 2019).

In the context of budgetary constraints and the enduring need for optimal resource allocation in healthcare, determining the best mix of health services and treatments to optimize clinical outcomes while minimizing costs is critical (dos Santos Silva et al., 2021; Thomas & Chalkidou, 2016). If DTx can demonstrate its economic value to decision makers (e.g., public and private payers, regulators, and care providers), such evidence is important to facilitate decisions around market access, pricing, and reimbursement for these technologies (Kolasa & Kozinski, 2020). Therefore, we sought to systematically answer the question of whether this recently emerged class of medical intervention, DTx, has yet been translated to economic value.

4.2.2. Objective

Given the growing body of evidence supporting the potential clinical benefits of DTx, the aim of this systematic review was to evaluate the published evidence regarding the cost-effectiveness of clinical-grade, mobile app–based DTx interventions and explore the costs and factors that drive such economic evaluation (EE).

4.3. Methods

This study adopts a post-positivist epistemological position, assuming that DTx economic value can be systematically measured and compared across interventions, while acknowledging the inherent limitations and context-dependent nature of such knowledge (Avenier & Gavard-Perret, 2018; Paré et al., 2015). The methodology emphasizes systematic, quantifiable evidence while simultaneously embracing key post-positivist principles: the fallibilist nature of knowledge, recognition of limited generalizability due to scope and context, and acknowledgment that research conclusions are provisional rather than definitive (Santos et al., 2022). This methodological self-awareness—critiquing bias through quality appraisal while maintaining systematic rigor—exemplifies post-positivism's attempt to balance scientific objectivity with critical reflexivity about the research process itself (Avenier & Gavard-Perret, 2018). The approach aligns with Paré et al.'s (2016) advocacy for the twin concepts of systematicity and transparency in information systems literature reviews.

4.3.1. Search strategy

The protocol for this review was registered with PROSPERO *a priori* (CRD42022358616, Appendix 1A). A search of the relevant literature was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines (Page et al., 2021). Databases searched for eligible studies included PubMed, Cochrane Library, Web of Science, Embase, Business Source Ultimate (EBSCO), CINAHL

(EBSCO), Scopus, ProQuest Business Premium Collection, and the Wiley Online Library. The search was conducted between September 5, 2022, and October 28, 2022, and was not constrained by the year of publication. In addition, secondary searches were executed in the International Network of Agencies for Health Technology Assessment International Health Technology Assessment database and the *International Journal of Technology Assessment in Health Care*. The search strings were tailored according to each database requirement. The following keywords were searched in publication titles and abstracts, as identified by the setting, perspective, intervention, comparison, and evaluation framework (Booth, 2006) and in consultation with a research librarian from the National University of Singapore:

(A): “digital therapeutic*” OR “digital health*” OR “digital tech*” OR “mobile health” OR “mhealth” OR “mobile tech*” OR “mobile medical app*” OR “mobile app*” OR “wearable tech*” OR “connected medical devices”; AND

(B): “economic evaluation” OR “economic value” OR “cost-benefit” OR “cost-utility” OR “cost-effectiveness” OR “cost-effective” OR “Quality-Adjusted Life-Years” OR “Markov Chains” OR “Models, Economic.”

4.3.2. Eligibility criteria

DTx delivery mechanism (e.g., mobile apps, web-based systems, or virtual reality) can significantly impact its economic proposition. Therefore, because DTx primarily leverage mobile apps as a delivery mechanism (Santoro et al., 2021), and “smartphone apps” are regarded as the top 2 (after telemedicine) technology developments anticipated to create the most disruption for established healthcare practices (NHS Health Education England, 2019); hence, this review focuses on clinical-grade mobile app–based DTx. Thus, studies were included based on the following inclusion criteria: (1) published in a peer-reviewed journal within any time frame, (2) the study analyzed a mobile app–based intervention, (3) the therapeutic intervention was delivered directly to patients, (4) the intervention demonstrated its clinical benefits through at least 1 case-control study, (5) the

study included a partial or full EE, and (6) the publication was available in English. Internet-based and virtual reality–based interventions, solutions for screening, diagnostic and monitoring purposes, telemedicine and remote patient monitoring solutions, and clinical decision support solutions were excluded. Furthermore, non–peer-reviewed publications (e.g., white papers and editorials), abstract-only papers, and those with unavailable full text were also excluded.

The reference lists of studies that met the inclusion criteria were subjected to an additional “backward reference search” to identify additional relevant studies.

4.3.3. Study selection, data extraction, and data synthesis

After duplicate records were removed, 2 reviewers (YS and XT) independently screened the titles and abstracts of all remaining identified studies for inclusion using the systematic review software Covidence (Veritas Health Innovation). Eligible studies that met the inclusion criteria, according to both reviewers, then underwent a full-text review. Conflicting outcomes were discussed between reviewers, and a third researcher (AR) was involved to help reach a consensus when necessary.

Data were extracted using a bespoke web-based Microsoft Excel 365 spreadsheet. Full data extraction was completed by 1 reviewer (YS) and verified by a second reviewer (XT). The extracted information from each study included country, targeted disease, product’s primary purpose, study design, perspective, costs considered, time horizon, intervention group sample size, type of control group, clinical outcomes, cost savings, scholars’ conclusion on the intervention’s cost-effectiveness, uncertainty consideration (discounting and sensitivity analysis), and sources of funding or conflicts of interest. Additional factors directly considered in the EE and factors reported by scholars as impacting the DTx’s economic impact, through sensitivity analysis or explicitly in the studies’ discussion sections, were also extracted. After extraction, the data were narratively synthesized to evaluate their meaning (Popay et al., 2006). The

additional extracted factors impacting the DTx were clustered into main categories and organized into a concept matrix (Webster & Watson, 2002).

4.3.4. Quality assessment

Quality assessment of the included studies was conducted using the Consensus Health Economic Criteria (CHEC) list (Evers et al., 2005). Each study received a score of 1, 0.5, or 0 for satisfying, partially satisfying, or not satisfying, respectively, the 19 independent evaluation criteria. The cumulative percentage of criteria satisfied was calculated as an overall "score" for each article (maximum possible score: 19/19 criteria or 100%).

The risk of bias (RoB) was calculated for each article according to its methodology. For randomized controlled trials (RCTs), the Cochrane Collaboration RoB tool (Higgins et al., 2011) was used, rating each study as unclear, low, or high risk for selection bias. For nonrandomized studies, the Risk of Bias in Non-Randomized Studies of Interventions tool was used to rate the RoB owing to confounding, bias in selection of participants into the study, bias in the classification of interventions, bias owing to deviation from intended interventions, bias owing to missing data, bias in measurement outcomes, and bias in selection of the reported result (Sterne et al., 2016). Each of these features was rated as low, moderate, or serious RoB, and each study's overall bias was conservatively calculated as the highest-risk measure in any category. Finally, bias in modeling studies was calculated using the Bias in Economic Evaluation checklist, and rated as "Yes," "No," "Partially," "Unclear," or "Not applicable" referring to a study's ability to address each of 22 independent criteria (Adarkwah et al., 2016). We elected to consolidate the Bias in Economic Evaluation ratings into the scale's 4 overarching categories: overall checklist for bias in EE, bias related to structure, bias related to data, and bias related to consistency. For uniformity with the other RoB assessment tools, we rated the bias in each category as low, moderate, or high risk, equivalent to the highest-risk single evaluation for any component criterion, considering "Yes" and "Not

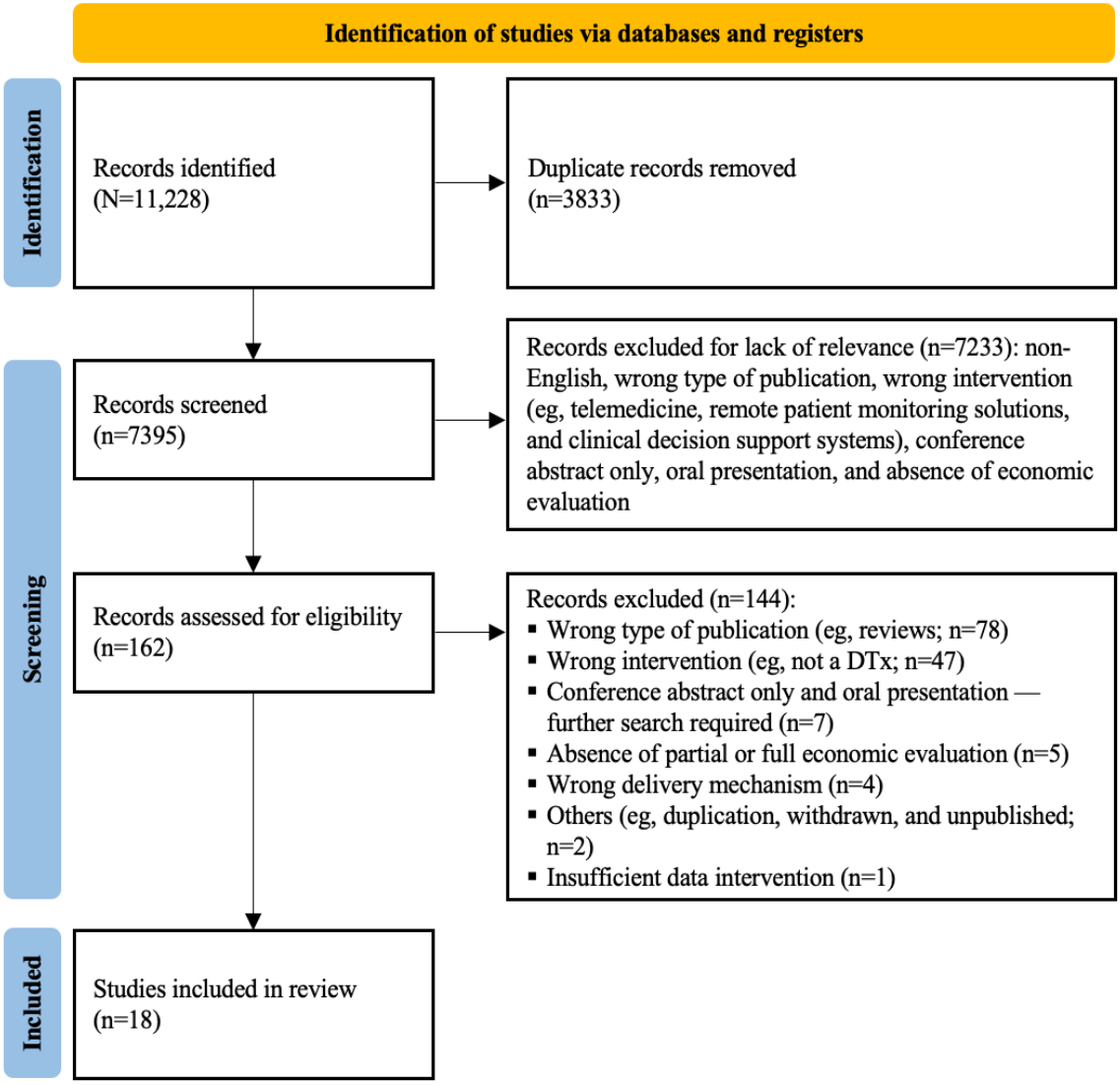
applicable” to be equal to low risk, “Partially” and “Unclear” to be equal to moderate risk, and “No” to be equal to high risk.

4.4. Results

4.4.1. Study selection

After duplicate removal and eligibility screening, 18 studies were included in this review (Figure 8).

Figure 8. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram



4.4.2. Study characteristics

Please note that for enhanced readability, individual references for each study characteristic have been omitted in this section. For a comprehensive list of references corresponding to each characteristic, please consult Appendix 1C in the final paper published in the Journal of Medical Internet Research (JMIR), in accordance with the journal's publication requirements.

Table 11 summarizes the characteristics and main health economic outcomes associated with the included studies. Overall, the 18 studies in this review were conducted between 2016 and 2022. Of the 18 studies, 10 (56%) were conducted in the US; 2 (11%) in the Netherlands; 2 (11%) in Sweden; 1 (6%) in Germany; 1 (6%) in Japan; 1 (6%) in the United Kingdom; and 1 (6%) jointly in the Netherlands, Spain, and Taiwan. Furthermore, of the 18 studies, 10 (56%) were industry funded, 6 (33%) were publicly funded, and the remaining 2 (11%) received mixed funding.

The targeted diseases for DTx in the included studies, all among adult patient populations, were urinary incontinence (3/18, 17%), diabetes (2/18, 11%), opioid use disorder (2/18, 11%), hypertension (2/18, 11%), generalized anxiety disorder (1/18, 6%), chronic insomnia (1/18, 6%), osteoarthritis (1/18, 6%), lower back pain (1/18, 6%), obesity (1/18, 6%), behavioral health conditions (1/18, 6%), cardiovascular disease (1/18, 6%), both diabetes and cardiovascular disease (1/18, 6%), and both type 2 diabetes and hypertension (1/18, 6%).

Regarding the type of EE performed, of the 18 studies, 7 (39%) involved nonrandomized study–based EE, 6 (33%) involved model-based EE, and 5 (28%) involved RCT-based EE. Of the 18 studies, 12 (67%) used a payer perspective, whereas 6 (33%) used a societal perspective, with 2 (11%) of the latter group also taking a payer perspective. The time horizon used for the EE was between 6 and 12 months for 56% (10/18) of the studies, 24 months for 6% (1/18) of the studies, 36 months for 17% (3/18) of the studies, 60 months for 6% (1/18) of the studies, 120 months for 6% (1/18) of the studies, and lifetime for 11% (2/11) of the studies. The intervention group sample sizes ranged between

60 and 305 participants for RCT-based EE and between 248 and 4790 participants for nonrandomized study–based EE. The interventions were compared with usual care (13/18, 72%), preintervention (2/18, 11%), an informative but noninterventional “control” app (1/18, 6%), patients who filled their prescription but did not engage beyond week 1 and patients who did not fill the prescription (1/18, 6%), and traditional cognitive behavioral therapy or no therapy (1/18, 6%).

Of the 18 studies, 14 (78%) assessed the impact of the DTx intervention on clinical outcomes. Of the 14 studies, 11 (79%) found superior clinical outcomes, 2 (14%) found no improvement compared with usual care, and 1 (7%) found superior clinical outcomes in only 1 of the 3 countries in which the intervention under study was delivered.

Half (9/18, 50%) of the studies included in this review conducted a cost-effectiveness analysis (CEA), with 4 (22%) also including a cost-utility analysis (CUA). Of the 18 studies, 8 (44%) conducted a cost analysis, with a strong emphasis on cost differences using, for example, pre-post intervention claims data, and 1 (6%) study focused solely on CUA. Of the 10 studies using CEA and CUA methods, 7 (70%) presented incremental cost-effectiveness ratio (ICER) values based on the cost per quality-adjusted life year (QALY) gained to assess the cost-effectiveness of the DTx intervention. Meanwhile, 20% (2/10) of the CEA and CUA studies showed ICER values based on cost per incontinence impact–adjusted life years gained and cost per mm Hg reduction in blood pressure. In total, 10% (1/10) of the studies did not report an ICER but an incremental net monetary benefit.

Of the 10 studies that conducted a full EE, 9 (90%) found the DTx intervention to be cost-effective in the context of the study, whereas 1 (10%) study found the intervention to be cost-effective in only 1 of the 3 countries in which it was studied. Specifically, DTx accounted for QALY gains along with cost savings in 20% (2/10) of the studies, QALY gains along with higher costs at an acceptable

ICER in 50% (5/10) of the studies, QALY losses with cost savings in 20% (2/10) of the studies, and no demonstrable effectiveness difference with cost savings in 20% (1/10) of the studies.

Figure 9 represents the 15 different DTx interventions under assessment in the 50% (9/18) of the studies that reported cost and QALYs as the outcome measures across the quadrants of the cost-effectiveness plane. The horizontal axis of the plane indicates differences in effects (ie, health outcomes), whereas the vertical axis represents the differences in costs between the DTx interventions and their respective comparators.

Of the 8 studies based on partial EE, all 8 (100%) found the DTx intervention under evaluation to be cost saving.

Table 11. Study characteristics

Study; country	Targeted disease (categories of DTx[a,b])	Type of evaluation	Perspective	Time horizon (months)	Intervention group sample size	Intervention versus comparator	Did the intervention lead to superior clinical outcomes?	Did the intervention lead to cost savings (in US $)?	Is the intervention cost-effective (ICER, in US $)?	Consensus Health Economic Criteria (%)
Randomized clinical trial–based economic evaluations										
Ekersund et al., 2022; Sweden	Urgency and mixed urinary incontinence (manage)	CEA[c] and CUA[d]	Societal	12	60	Tät II versus information app	Yes (0.0115 QALY[e] gained)	No (+144)	Yes (12477/QALY)	92
Pelle et al., 2022; NL[f]	Osteoarthritis (manage)	CEA and CUA	Healthcare payer	6	214	Dr Bart versus UC[g]	No difference	Yes (−23)	Yes (56 iNMB[h])	76
McManus et al., 2021; United Kingdom	HTN[i] (manage)	CEA	NHS[j] payer	12	305	Home and Online Management and Evaluation of Blood Pressure versus UC	Yes (a mean difference in SBP[k] of −3.4mm Hg, and −0.5 mm Hg in DBP[l])	No (+46)	Yes (13/mm Hg reduction)	100
Sjöström et al., 2017; Sweden	Stress urinary incontinence (manage)	CUA	Societal	12	62	Tät versus UC	Yes (0.00849 QALY gained)	No (+69)	Yes (8071/QALY)	95

Loohuis et al., 2022; NL	Stress, urgency, or mixed urinary incontinence (manage)	CEA and CUA	Societal	12	131	URinControl versus UC	No (0.025 QALY loss and 0.043 IIALY[m] gained)	Yes (−170)	Yes (−3918/IIALYs)	87
Nonrandomized studies–based economic evaluations										
Horstman et al., 2021; United States	Overweight and obesity (manage)	CA[n]	Payer	36	4790	Real Appeal versus UC	Yes (3% greater weight loss on average per participant)	Yes (−771/participant)	—[o]	55
Forma et al., 2022; United States	Chronic insomnia (treat)	CA	Payer	24	248	Pre-post Somryst treatment intervention	Yes (37.2% insomnia severity index score declined/participant)	Yes (−2059/participant)	—	39
Sweet et al., 2020; United States	Diabetes (prevent)	CA	Employer and payer	12	2027	Omada versus UC	Yes (4.3% average weight loss)	Yes (−1169/participant)	—	55
Abhulimen et al., 2018; United States	Behavioral health condition[p] (manage)	CA	Public and payer	11	799	myStrengh versus UC	—	Yes (−382/participant)	—	53
Velez et al., 2022; United States	OUD[q] (treat)	CA	Payer	12	901	reSET-O versus UC	—	Yes (−2791/participant)	—	63

Velez et al., 2021; United States	OUD (treat)	CA	Payer	9	444	reSET-O versus nonengagers	—	Yes (−2708/participant)	—	50
Whaley et al., 2019; United States	Diabetes (manage)	CA	Employer and payer	12	2261	Livongo program versus UC	—	Yes (−1056/participant)	—	55
Model-based economic evaluations										
Piera-Jiménez et al., 2020; NL, Spain, and TW[r]	CVD[s] (prevent)	CEA (RCT[t] informed and Markov model)	Societal and healthcare payer	60	120	Do change 2 versus UC	NL: yes (0.011 QALY gained); Spain: no (0.134 QALY loss); TW: no (0.094 QALY loss)	NL: no (+1456); Spain: yes (−2666); TW: no (+1127)	NL: no (131959/QALY); Spain: yes (19895/QALY); TW: no	76
Lewkowicz et al., 2022; Germany	Low back pain (manage)	CEA and CUA (RCT informed and Markov model)	Societal	36	RCT: 53 model: 10,000	Kaia versus UC	Yes (0.0221 QALY gained)	No (+129)	Yes (5815/QALY)	87
Nomura et al., Japan, 2022	Hypertension (treat)	CEA (RCT informed and Markov model)	Public healthcare payer	Lifetime	199	CureApp and UC versus UC	Yes (0.092 QALY gained)	No (+962)	Yes (10434/QALY)	92

Kumar et al., 2018; United States	Generalized anxiety disorder (prevent/treat)	CEA (pilot study informed and Markov model)	Societal and payer	Lifetime	Pilot: 89 model: 100,000	Mobile CBT[u] versus traditional CBT (model A) and mobile CBT versus UC (model B)	Model A: yes (34,108 QALYs gained); model B: yes (81,492 QALYs gained)	Societal: model A: yes (−2.23 billion); model B: yes (−4.54 billion); payer: model A: yes (−339 million); model B: yes (−605 million)	Societal: model A: yes (−65380/QALY); model B: yes (−55710/QALY); payer: model A: yes (−9939/QALY); model B: yes (−7424/QALY)	74
Nordyke et al., 2019; United States	Diabetes and HTN (manage)	CEA (decision tree model)	US commercial payer	36	—	DTx+UC versus UC	T2DM[v]: yes (0.0427 QALY gained); HTN: yes (0.0827 QALY gained)	T2DM: yes (−5220); HTN: yes (−3480)	T2DM: yes (−122,248/QALY); HTN: yes (−42,080/QALY)	55
Chen et al., 2016; United States	Diabetes and CVD (prevent)	CA (best available evidence and Markov model)	Public and payer	120	1121	Pre-post Omada program intervention	Yes (6.8% reduction in body weight per participant)	Yes (from 11,550 to 14,200 per participant)	—	76

[a]DTx: digital therapeutics.

[b]Classified as “manage” medical disorders and conditions (e.g., manage chronic conditions that can be controlled but not cured, including symptoms management), “treat” (e.g., toward permanent recovery, such as for addictions and chronic insomnia), or “prevent” (e.g., secondary prevention of cardiovascular diseases).

[c]CEA: cost-effectiveness analysis.

[d]CUA: cost-utility analysis.

[e]QALY: quality-adjusted life year.

[f]NL: the Netherlands.

[g]UC: usual care.

[h]iNMB: incremental net monetary benefit, which is easier to interpret than the incremental cost-effectiveness ratio when differences are small.

[i]HTN: hypertension.

[j]NHS: National Health Service.

[k]SBP: systolic blood pressure.

[l]DBP: diastolic blood pressure.

[m]IIALY: incontinence impact–adjusted life years.

[n]CA: cost analysis.

[o]Not available.

[p]Including depression, anxiety, insomnia, and substance use disorders.

[q]OUD: opioid use disorder.

[r]TW: Taiwan.

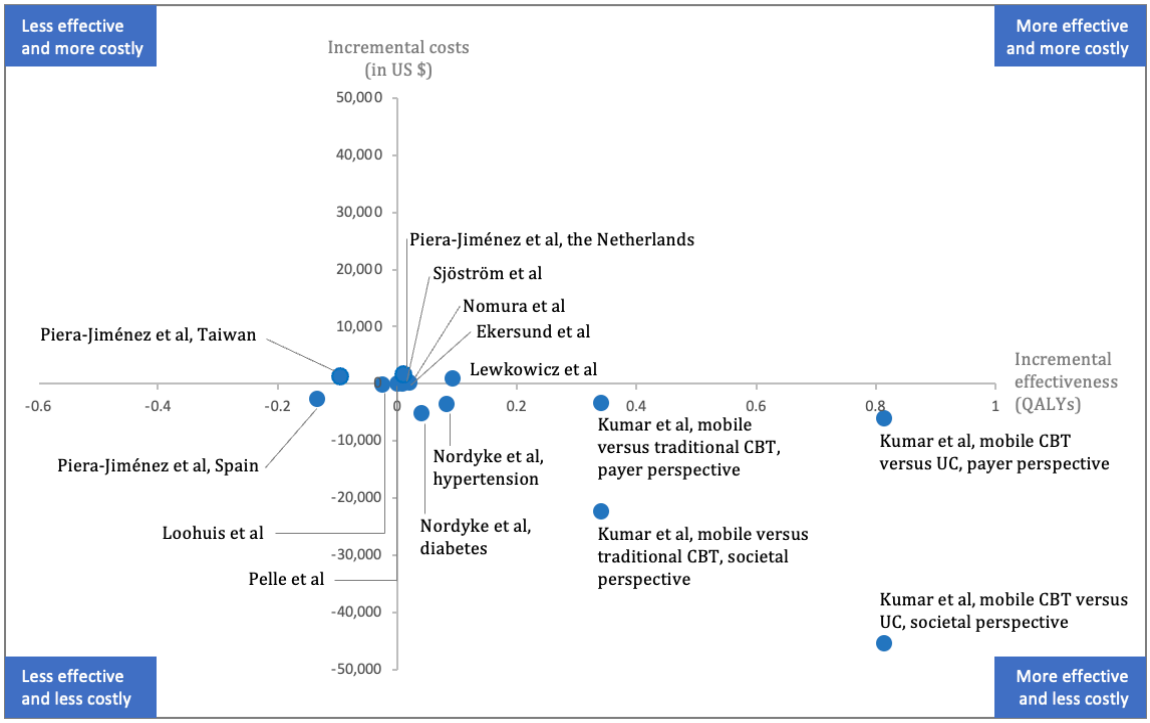
[s]CVD: cardiovascular disease.

[t]RCT: randomized controlled trial.

[u]CBT: cognitive behavioral therapy.

[v]T2DM: type 2 diabetes mellitus.

Figure 9. Cost-effectiveness plane of studies with cost and quality-adjusted life years as the outcome measures



CBT: cognitive behavioral therapy.

QALY: quality-adjusted life year.

UC: usual care.

4.4.3. Quality assessment

The level of methodological detail presented in the included studies varied but was overall high. The mean study quality score, determined using the CHEC list, was 71% (Standard Deviation (SD) 0.18%; Appendix 1D). Quality was the highest among EE based on RCTs and the lowest among those based on nonrandomized studies (Appendix 1D). Common areas for point deduction included no mention of ethical and distributional considerations, the single most common quality issue, limited descriptions of interventions' alternatives (i.e., of any interventions received by control groups), unjustified decisions to use narrow methodological perspectives (e.g., healthcare resource use rather than societal perspectives), a lack of incremental analysis of costs and outcomes (i.e., an ICER), and no discussion of generalizability to other settings and patient populations. In contrast, most of the

included studies measured and valued outcomes appropriately, clearly described study populations, and explicitly acknowledged the potential conflicts of interest. Study quality was not significantly associated with the year of publication.

Although all RCT-based EE (5/5, 100%) performed sensitivity analyses (i.e., univariate and multivariate scenarios as well as one-way and multiway deterministic sensitivity analyses), only 29% (2/7) of the nonrandomized study–based EE did so (i.e., multiway deterministic sensitivity analyses). In total, 83% (5/6) of model-based EE performed sensitivity analyses (i.e., one-way and multiway deterministic sensitivity analyses as well as probabilistic sensitivity analyses).

RoB was similarly heterogeneous for RCTs, nonrandomized studies, and modeling studies, with important overall risks of bias across studies. None of the RCTs were classified as having a low RoB in any of the 6 categories. Owing to the digital nature of the DTx, participants (or personnel) were not blind to assignment and could therefore expect to receive either an active treatment or a placebo. Consequently, most RCT-based studies (4/5, 80%) were classified as having a high risk of performance bias. One study used an “information app” for the comparator group, and without clear consequence on the potential performance bias, it was classified as unclear. In total, 40% (2/5) of the studies were classified as high risk for attrition bias related to incomplete outcome data resulting from a high degree of participant attrition that was not fully accounted for in the analyses (Appendix 1E). Common sources of “other bias” were potential selection biases in participant recruitment, leading to potential imbalance between groups in baseline variables (such as age, educational level, or disease severity).

Among the nonrandomized studies, none received an overall low-risk classification (Appendix 1F): 57% (4/7) were graded as moderate risk and 42% (3/7) as high risk, in all cases owing to moderate- or high-risk classifications in 1 to 3 (out of 7) scoring categories. All nonrandomized studies demonstrated a low RoB in the classification of interventions, potential deviation from intended interventions, measurement of outcomes, and selection of reported results. The greatest source of potential bias

among these nonrandomized studies was the selection of participants in the study, as patients often self-selected or were recruited into intervention groups based on potentially confounding factors. For example, 2 studies of the opioid abstinence tool reSET-O were graded as serious risk in this category because the intervention group comprised patients who sought a reSET-O prescription or filled one provided by a prescriber, whereas the control group comprised patients who did not actively seek treatment in the same way.

Finally, among the modeling studies, RoB was classified as unclear in the category of bias related to internal consistency in all 6 studies, none of which explicitly reported exploring this (Appendix 1G). The highest RoB among these studies tended to arise from part A of the checklist: the “overall checklist for bias in economic evaluation.” Within this category, 66% (4/6) of the studies were graded as high RoB and 16% (1/6) as moderate RoB. Common sources of potential bias among modeling studies were narrow perspectives without justification, a lack of ordinal ICER, and a short time horizon relative to the outcome of interest.

4.4.4. Costs and factors impacting the economic value of DTx

Overview

The costs and factors associated with the economic impact of the DTx interventions, which were obtained through sensitivity analysis or outlined in the discussion sections of the individual studies as having an impact on DTx economic value, were extracted from the selected studies (Table 12). These costs and factors reflect, above all, the medical conditions and disorders under consideration as well as the study design and methods for measuring economic outcomes. Nevertheless, there are some common key findings that are worth noting.

Table 12. Costs and factors impacting the economic value of DTx

	Societal perspective studies						Payer perspective studies											
	Loohuis et al., 2022	Sjöström et al., 2017	Ekersund et al., 2022	Kumar et al., 2018	Piera-Jimenez et al., 2022	Lewkowicz et al., 2022	Sweet et al., 2020	Whaley et al., 2019	Chen et al., 2016	Horstman et al., 2021	McManus et al., 2021	Nomura et al., 2022	Nordyke et al., 2019	Velez et al., 2022	Velez et al., 2021	Pelle et al., 2022	Forma et al., 2022	Abhulimen et al., 2018
Direct medical and non-medical costs																		
Pharmaceutical treatment[a]	●[b]	○[c]	○	○	-[d]	○	○	●	●	-	○	○	●	-	-	-	○	-
Cost of the DTx	-	-	-	○	●	●	○	-	-	○	-	●	-	-	-	-	-	-
HRU[e]: Primary care[f]	○	-	-	-	○	○	-	-	-	-	○	-	-	-	-	○	-	-
HRU: Outpatient care[g]	○	-	-	●	○	○	○	●	●	●	○	-	-	○	○	○	○	○
HRU: Inpatient care[h]	○	-	-	●	●	-	●	○	●	○	○	○	●	●	●	○	●	●
HRU: ED[i] visits	○	-	-	○	-	-	○	○	○	-	○	-	-	●	●	-	●	●
HRU: Health support intervention[j]	○	○	○	-	○	●	-	-	-	-	○	-	-	-	-	-	-	-
Intervention-specific training[k]	-	-	-	-	○	-	-	-	-	-	○	-	-	-	-	-	-	-
Participants' time spent on the DTx[l]	-	●	●	-	○	-	-	-	-	-	-	-	-	-	-	-	-	-
Indirect medical and non-medical costs																		
Productivity impact[m]	○	-	-	●	-	○	-	-	-	-	-	-	-	-	-	-	-	-
DTx maintenance	○	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Influencing factors																		
Participants' baseline characteristics[n]	●	○	-	○	●	-	-	○	●	●	○	-	●	○	○	-	-	○
Reimbursement rate	-	-	-	-		●	-	-	-	-	-	-	-	-	-	-	-	-
Treatment adherence	-	-	-	-	-	-	-	-	-	-	○	-	-	○	○	-	-	-
Attrition rate[o]	-	-	-	-	-	●	○	○	○	●	○	●	●	○	-	-	-	○
Degree of clinical inertia	-	-	-	-	-	-	-	-	-	-	○		●	-	-	-	-	-
Sustained DTx clinical effectiveness[p]	-	-	-	○	-	●	-	-	○	-	○	○	●	-	-	-	-	-

[a]Including core costs originating from spending related to treatment of medical disorders and diseases, such as diabetes, or materials and aids, as in the case of incontinence.

[b]Factors considered and directly cited by researchers as impacting the cost-effectiveness of DTx.

[c]Factors reported by researchers as having an "important" or "significant" impact on, or which were deemed as "decisive" to, the cost-effectiveness of DTx.

[d]Not applicable.

[e]HRU: healthcare resource use.

[f]General practitioners, physical therapists, occupational therapists, exercise therapists, dieticians, or other primary care practitioners.

[g]Outpatient or ambulatory care visits, medical specialist consultations, physician services, and pathology and laboratory services.

[h]Including partial hospitalizations.

[i]ED: emergency department.

[j]Health assistance interventions and support provided by healthcare workers.

[k]Training and educational sessions related to the optimal implementation of the intervention, including in-person or web-based sessions, for either patients or clinicians.

[l]Costs associated with the time spent by study participants using the DTx.

[m]Productivity losses, such as absenteeism and disability days.

[n]Demographic and risk factor profiles of the study participants, such as race, age, gender, ethnicity, disease evolution, and severity or presence of comorbidities.

[o]Including study participants' engagement level with the DTx.

[p]Medium- to long-term relative effectiveness of the DTx intervention, including its effect on preventing or delaying disease onset.

Healthcare resource use

Healthcare resource use, which includes primary care, outpatient care, inpatient care, emergency department visits, and health support intervention, was the most frequently examined and reported cost across studies (18/18, 100%). Of the 18 studies, inpatient care–related costs were shown to have a potential impact on the economic impact of DTx in 15 (78%) studies. Inpatient care was further categorized as a "decisive factor" (i.e., having a significant impact on the economic impact of DTx) in half (9/18, 50%) of the studies.

Pharmaceutical treatment

The expenditures originating directly from treating medical conditions or disorders, such as those related to the consumption of drugs (e.g., frequency and dose) or materials and aids, were considered in 67% (12/18) of the studies.

In some cases, DTx interventions have been shown to improve treatment adherence and, as a result, might increase some expenses, such as overall drug

therapy costs or costs associated with higher rates of use of certain clinician services (e.g., psychiatry services, outpatient visits, and pathology or drug testing). However, in many cases, these expenses were largely compensated by the cost savings in the included studies, especially in healthcare resource use. For example, in a trial by McManus et al. (2021), participants who used DTx were more likely to have their antihypertensive drugs adjusted during the study (i.e., dosage or change in drugs).

In other cases, the clinical benefits of DTx treatments may be able to reduce or eliminate the need for pharmacotherapies, thereby lowering total medical expenditures. However, Nordyke et al. (2019) and McManus et al. (2021) noted that despite evidence of DTx clinical efficacy, there may be a delay in deprescribing drugs from healthcare professionals—a phenomenon known as clinical inertia, which may reduce the potential economic benefits of DTx.

Participants' baseline characteristics

More than half (12/18, 67%) of the studies pointed out that participants' baseline characteristics, such as age, gender, ethnicity, education level, baseline disease severity, risk factors, and costs, had an impact on the economic value of the intervention. Loohuis et al. (2022) conducted a subgroup analysis that revealed differences in DTx effects and costs not only by disease severity but also by recruitment type: participants recruited via social media incurred lower associated costs and experienced a lesser treatment effect than those recruited by a general practitioner.

Whaley et al. (2019) hypothesized that individuals with higher healthcare needs who accepted the program invitation generally had higher baseline levels of comorbidity and healthcare spending than those who did not enroll and therefore were more motivated to try a new intervention and more likely to voluntarily enroll in a digital intervention. Piera-Jiménez et al. (2021) also noted that the willingness of individuals to adopt an intervention strongly impacts the success of a DTx intervention.

Attrition rate

More than half (10/18, 56%) of the studies considered the potential causal effect of attrition rate, which can be a critical factor, on the DTx economic impact. Discrepancies in the manner in which such factors were evaluated should be noted. First, as highlighted by Lewkowicz et al. (2022), a DTx intervention's attrition rates in RCT-based EE might simply not be reported or may not "*represent real-world engagement and program dropout rates*." Second, some studies defined a minimum level of engagement for participants' data to be included for extraction and analysis; for example, in the study by Pelle et al. (2022), an RCT-based EE, 63 participants were excluded for suboptimal level of engagement. Finally, in claims-based EE, the impact of a DTx intervention was evaluated based on a patient population that, by definition, filled their prescription and engaged with the therapeutic, which might have led to bias in the selection of participants in the study (Appendix 1F). As Nomura et al. (2022) highlighted, "*achieving good cost-effectiveness for DTx might require sensitive handling to balance the appropriate DTx app usage duration with DTx costs and expected attrition rate*." The attrition rate may have also resulted in incomplete outcome data, a potential RoB in half of the RCT and nonrandomized study–based EE (Appendices 1C and 1D).

4.5. Discussion

4.5.1. Main findings

The EE of new therapies and clinical interventions is critical for market access and potential adoption because they provide decision makers with important information regarding their "value for money." This systematic review included 18 studies that evaluated the EE of clinical-grade, mobile app–based DTx. The relatively small number of included studies (which is consistent with other recent systematic reviews of digital health solutions (Jiang et al., 2019) attests to the paucity of published literature on DTx, which also explains the scarcity of evidence pertaining to the economic value of these intervention modalities (Wilkinson et al., 2023).

All 18 included studies were conducted in high-income countries, with 12 supported by industry funding and 6 by public organizations. Although the prevalence of industry-funded research may potentially introduce commercial bias, which is acknowledged in this review, it also underscores the contributions of both public and private organizations in generating evidence for informed treatment decision-making when DTx options are available.

4.5.2. Heterogeneity among included studies

The included studies exhibited significant heterogeneity with respect to DTx intervention, type of EE, and methodology (Table 11). This review combines EEs based on both clinical trial results and decision modeling to examine DTx applications for a spectrum of diseases across various settings and for different payers. Specifically, 4 studies did not report the clinical outcomes of the intervention, only 10 reported an ICER, and only 7 reported cost and QALYs as the outcome measures. As a result of this heterogeneity, a robust meta-analysis of these data was not feasible, making it impossible to provide numerical answers regarding the cost-effectiveness of DTx interventions. The study heterogeneity also hinders the comparability and generalizability of the findings and makes the EE results difficult to interpret.

In addition to this challenge, the context-specific nature of DTx interventions is evident in a multisite RCT conducted by Piera-Jiménez et al. (2021), who evaluated the economic impact of the same intervention implemented in 3 different countries: the Netherlands, Spain, and Taiwan. The study found that DTx led to QALY gains in the Netherlands but not in Spain or Taiwan, whereas cost savings were observed in Spain but not in the Netherlands or Taiwan.

4.5.3. Methodological characteristics of the included studies

With a mean CHEC score of 71% (SD 17.9%) across all 18 studies, the methodological rigor across the included studies was of moderate quality, ranging from an average of 90% (SD 8.2%) for RCT-based EE to 77% (SD 11.7%) for model-based EE to 53% (SD 6.7%) for nonrandomized study–based EE. In particular, the evaluations based on nonrandomized studies, all of which were funded by industry, adopted a payer-only perspective, which may be too narrow to broadly inform implementation decisions because it excludes direct patient out-of-pocket costs, indirect costs, such as productivity loss, and other factors that can impact the long-term utility of an intervention. Furthermore, none of the EE based on nonrandomized studies performed an incremental analysis of costs and outcomes of the alternatives to DTx (e.g., standard therapy). Finally, only 29% (2/7) of nonrandomized study–based EE performed sensitivity analysis, which is the best practice for quantifying uncertainty and testing the robustness of a study's conclusions (Ramsey et al., 2015).

Another methodological deficit stems from the fact that although the majority of DTx interventions were reported to have significant impacts on costs and outcomes over a patient's lifetime, most studies used a short time horizon to capture all or most clinical and economic impacts of the respective intervention. Specifically, the average time horizon of the RCT-based EE was 10.8 months, whereas that of the nonrandomized study–based EE was 17.8 months. Only 2 studies adopted a lifetime horizon, and only 6 studies included modeling decisions to extrapolate the outcome measures over time. This incongruity between the claimed lasting impacts of DTx and the limited time horizons over which they were evaluated implies that DTx should be assessed over longer periods. In turn, determining the long-term economic effects of DTx and advancing understanding as to where their adoption may add value requires more comprehensive modeling (McGhan et al., 2009).

Modeling can also ensure that trial populations reflect patient groups treated in real-world clinical practice, which is an important consideration because this review

identified various biases in participant recruitment. Such biases might result in imbalances in the relevant baseline characteristics between patient groups, which can also hinder health equity considerations. As a case in point, in 11 studies, participants were required to have internet access, a smartphone or a tablet, the skills necessary to use a PC, medical insurance, or employment to participate—requirements that may limit the participation of members of marginalized groups or groups considered socioeconomically disadvantaged. In contrast, only 3 studies addressed the ethical and distributional issues inherent in the implementation of digital technologies.

Across studies using the same perspective, disparities in the costs taken into account were also noted (Table 11). The importance of the time and expertise required for patient education on using and managing DTx technology (Prodan et al., 2022) was only considered in 2 studies. Similarly, only 1 study factored in the ongoing maintenance costs of the DTx. Highlighting the criticality of taking stock of all costs, Lewkowicz et al. (2022) applied a societal perspective and reported that their model accounted for 61% of costs related to conventional treatment for low back pain when only direct costs were considered and for 81% when indirect costs were included, using a publicly available cost-of-illness study as a benchmark. Future DTx EE will therefore benefit from a more transparent, systematic, and exhaustive consideration of all the costs that implementing DTx interventions entails, including long-term healthcare costs that may not be directly disease- or intervention-related as per the Professional Society for Health Economics and Outcomes Research recommendations (Ramsey et al., 2015).

Altogether, the studied DTx interventions were found to be cost-effective in 9 (90%) of the 10 studies that performed a full EE and cost saving in the remaining 8 studies that performed a partial EE. In 5 (28%) of the 18 studies, the DTx interventions presented a trade-off between costs and effects (i.e., intervention being more effective and more costly than the comparators). However, in 3 (60%) of these 5 studies, the highest ICERs obtained through sensitivity analysis fell below the WTP

threshold established in the countries in which they were performed, providing reassurance about their potential economic benefits.

The findings from this review indicate that DTx, at least in some use cases and local contexts, can be cost-effective and offer economic value to payers while simultaneously improving care for patients. However, consistent with the existing literature (McGhan et al., 2009; Wilkinson et al., 2023), qualitative deficits in methodology and significant potential biases in EE should be addressed going forward.

This review emphasizes the importance of adhering to established best practices and developing a robust, consistent methodological framework that incorporates the unique features that distinguish DTx interventions from conventional therapies or the current standard of care (Wilkinson et al., 2023). In the future, DTx EE analysis will need to adhere to local and international guidelines, use generalizable tools and metrics for enhanced comparability of the findings, and be both long-term focused and all-inclusive when factoring in value and cost. Such efforts are crucial for minimizing providers', payers', and patients' uncertainties surrounding the adoption of DTx interventions.

4.5.4. Limitations

Although we aimed to provide a comprehensive and systematic review of the economic value of clinical-grade mobile app–based DTx, there are several limitations to be acknowledged. First, only studies written in English were included. These studies were identified using a finite list of specific search terms; however, widely varying terminologies exist in the literature with reference to DTx, such as medical apps, digital therapies, or simply digital health technologies. As a result, it is possible that not all relevant studies assessing the economic impact of DTx may have been identified. Second, DTx interventions can be delivered through different modalities, including, but not limited to, virtual reality devices, mobile apps, web-based platforms, or a combination of these. To draw robust conclusions about mobile DTx as an emerging category of technologies in the clinical arena, this

review focused exclusively on mobile app–based DTx and excluded multimodal DTx or those not primarily using a mobile app as the core delivery mechanism.

4.5.5. Conclusions

The systematic review has provided valuable insights into the current state of DTx economic evaluations, identifying key factors that influence economic outcomes and highlighting significant methodological challenges. While these findings offer an important evidence-based foundation, they represent only the published literature—largely from the perspective of health economists and researchers. To develop a more comprehensive understanding of DTx economic value drivers, Chapter 5 extends this inquiry through a GCM approach, engaging diverse stakeholders across the DTx ecosystem. This mixed methods-based investigation moves beyond identifying economic value factors to understanding how these factors are conceptualized, prioritized, and considered by those directly involved in DTx development, validation, and implementation.

5

A GROUP CONCEPT MAPPING STUDY OF STAKEHOLDER PERSPECTIVES ON DIGITAL THERAPEUTICS ECONOMIC VALUE DRIVERS (STUDY 2)

CHAPTER 5. A GROUP CONCEPT MAPPING STUDY OF STAKEHOLDER PERSPECTIVES ON DIGITAL THERAPEUTICS ECONOMIC VALUE DRIVERS (STUDY 2)

This chapter presents the second study in our three-part investigation, utilizing GCM to explore how stakeholders across the DTx ecosystem collectively conceptualize, perceive, and prioritize factors influencing economic value. Moving beyond the published literature, this mixed methods-based approach directly engages healthcare professionals, researchers, industry stakeholders, and public sector representatives to generate a comprehensive framework of factors perceived to impact DTx economic value.

By examining convergences and divergences in how these diverse stakeholders consider economic factors throughout the DTx lifecycle, this study bridges the gap between theoretical economic evaluation frameworks identified in the systematic review and the practical considerations that shape real-world DTx development and implementation decisions.

Publication Status

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5.1. Abstract

Background: DTx, defined as software as a medical device intended to treat or alleviate a disease, disorder, condition, or injury by delivering a medical intervention, present a promising avenue for addressing the increasing burden of a range of conditions, including chronic diseases, mental health conditions, and substance abuse disorders, among others. In a context of budgetary constraints and enduring need for optimal resource allocation, the implementation and adoption of this emerging class of medicine are contingent upon their capacity to provide economic value. However, comprehensive analysis of the factors influencing the capacity of DTx to deliver economic value and how these factors are considered in the DTx development, clinical validation, and implementation remain limited.

Objectives: This study aims to comprehend how diverse stakeholders involved in the DTx lifecycle collectively conceptualize, perceive, and prioritize the factors influencing its economic value. By examining these factors, the study seeks to provide deeper insights into the complex decision-making processes that shape DTx economic outcomes.

Methods: Group concept mapping (GCM), a participatory and mixed methods-based approach was used to delve into a comprehensive identification and understanding of the factors that are conceptualized and perceived to impact the economic value of DTx. It involved semi-structured interviews, group discussions and web-based tasks. Participants included healthcare professionals, researchers, industry stakeholders, and public sector representatives. Participants sorted the identified factors based on their similarities (n=37), rated their importance for DTx in generating economic value (n=62), and assessed the extent to which these factors are considered in their own field or practice (n=62). Analyses included multidimensional scaling and hierarchical cluster analysis to develop abstract conceptual data into visual representations.

Results: 59 factors influencing the economic value of DTx were identified and grouped into eight clusters. There was broad agreement among stakeholders on the significance of the DTx Impact on Patient Outcomes and DTx Implementation as the most influential clusters affecting the economic value of DTx. The DTx Associated Costs and DTx Monetization Models clusters were reported as not receiving potentially sufficient consideration throughout the DTx development lifecycle, particularly among researchers. Convergences and divergences among stakeholder groups regarding factors impacting the economic value of DTx were noted.

Conclusions: The results illustrate how stakeholders conceptualize, perceive, and consider factors impacting DTx economic value throughout its lifecycle. They reveal the complex interplay of multiple stakeholders and factors influencing DTx economic value, highlighting areas requiring prioritization at each stage. Consequently, a conceptual framework of priority clusters and factors potentially driving DTx economic value is proposed. It should be interpreted within the context of each

stakeholder group, to support current and future efforts toward the widespread deployment and adoption of DTx interventions.

Keywords: digital health; digital therapeutics; economic evaluation; cost-effectiveness; group concept mapping.

5.2. Introduction

An aging population, burdened by increasing chronic and mental health conditions among others, coupled with a surge in the utilization of healthcare resources, highlights the imperative to enhance the effectiveness and efficiency of healthcare systems. All these factors have accelerated the emergence of DTx as a new class of medical treatment. DTx are health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has a demonstrable positive therapeutic impact on a patient's health (DTx Alliance, 2023; Miao et al., 2024). While these software as medical devices are set to significantly improve the delivery of healthcare, stakeholders, such as healthcare providers as well as public and private payer organizations are yet to fully embrace and realize the potential of DTx. They require a large body of evidence that demonstrates the clinical benefits and value of these solutions, including their impact on patients, such as improvements in quality of life, as well as their effect on the burden of disease and ethical and equity considerations (Nascimento et al., 2023; Stern et al., 2022). Health economic data, along with considerations regarding software interoperability, data security, and privacy, are also critical factors that come into play (Keogh et al., 2024; Kreuzenbeck et al., 2024; Sapanel et al., 2023).

Given the context of budgetary constraints and the ongoing need for optimal resource allocation, health economic data are crucial for payment, reimbursement and adoption decisions (Kario et al., 2021), if sufficient clinical benefits and value are demonstrated. These data determine the cost-effectiveness of a DTx compared to standard treatments or alternatives, providing decision-makers with important information regarding their "value for money" (Gomes et al., 2022).

However, research on the economic value of DTx remains limited. Kario et al. (2021) noted that little is known about DTx capacity to provide economic value, while Gomes et al. (2022) emphasized the complexity of defining and assessing this value. A 2023 systematic review of clinical-grade mobile app-based DTx further underscored the challenges in reaching definitive conclusions about their economic benefits, largely due to heterogeneous study methods and data collection processes (Sapanel et al., 2023). These findings highlight a critical need for more robust evidence to support market access decision-making and ultimately the potential adoption of DTx (Keogh et al., 2024; Kreuzenbeck et al., 2024).

It is also crucial to recognize that the development, clinical validation, and implementation of DTx involve numerous stakeholders, including researchers, software developers, engineers, clinicians, care providers, patients, regulatory agencies, and payers, among others. Each stakeholder decisions—from designing user interfaces to prioritizing specific features—are interrelated and influence the potential clinical value and economic benefits of DTx for the healthcare system, providers, and patients.

Given that economic impacts are crucial in supporting health budget allocation, reimbursement decisions, and the eventual mass adoption and use of DTx, a significant research gap exists. There is a pressing need to address the following research question: **How do diverse stakeholders involved throughout the DTx lifecycle collectively conceptualize and perceive the prioritization of factors influencing DTx economic value?** It is essential to comprehend how various stakeholders contribute to and shape DTx economic value generation, while also providing a deeper understanding of the complex decision-making processes that impact DTx economic outcomes throughout its lifecycle.

To address this multifaceted research challenge, this study adopts a realist stance, treating stakeholder perspectives on DTx economic value as legitimate and discoverable knowledge that can inform real-world decision-making (Allmark & Machaczek, 2018). Epistemologically, the study embraces an interpretivist

approach through GCM. The participatory nature of GCM reflects a shift toward collaborative knowledge construction that values stakeholder knowledge as legitimate and experiential, moving beyond traditional researcher-subject hierarchies (Cornwall & Jewkes, 1995). Knowledge is gained through systematic interpretation of stakeholder meanings and experiences (Klein & Myers, 1999), with the methodology designed to reveal the subjective understandings that different groups bring to DTx economic value conceptualization. While maintaining realist ontological assumptions about the existence of economic value phenomena, the study deliberately embraces researcher-participant collaboration as essential to understanding complex social phenomena (Trochim, 1989).

Building upon these philosophical and methodological foundations, this study employs a collective conceptualization stakeholder approach to examine factors which influence the economic value of DTx. Specifically, it aims to explore how these factors are conceptualized by stakeholders involved in DTx from development to implementation, while also investigating how they are perceived and considered throughout the DTx lifecycle by the same stakeholders. Building on this analysis, this study aims to develop an evidence-based conceptual framework of priority areas. This framework will provide a comprehensive roadmap for stakeholders, outlining considerations throughout the technology lifecycle that can ultimately influence a DTx ability to generate economic value.

5.3. Methods

5.3.1. Study design

To meet the objective, GCM is used to delve into potential convergences and divergences in stakeholders' perspectives and considerations on factors influencing the economic value of DTx. This methodological approach provides a structured way to synthesize complex, multifaceted concepts and associated conceptualizations and perceptions into a coherent analytical framework (Kane & Rosas, 2018). The choice was motivated by the GCM's participatory nature and its

ability to combine diverse perspectives from a broad group of participants. Napier-Raman et al. describe CGM as "*particularly useful when examining complex, multifaceted issues, particularly those in public health*" (2023, p.904).

Initially introduced by Trochim (1989), GCM engages a diverse group of stakeholders as participants in collaborative efforts to generate, structure and visualize conceptual information. It facilitates the conceptualization of abstract constructs, delving into complex social phenomena, examine relationships among factors, and compare perspectives and priorities across different participant groups (Burke et al., 2005; Rosas, 2017). The GCM research design transforms abstract conceptual data into visual representations or maps, and leads to the creation of a collective conceptual framework for comprehending a specific topic of interest (Kane & Rosas, 2018; Trochim, 1989).

The participant-oriented and collaborative nature of GCM has resulted in its widespread application across various disciplines and research areas, encompassing public health, social sciences (Napier-Raman et al., 2023), planning and evaluation (Kane & Trochim, 2007), chronic diseases prevention (Wutzke et al., 2017), and dissemination and implementation science (Waltz et al., 2015). In essence, GCM is a robust method and tool for participatory research, providing researchers with actionable, participant-determined research outcomes (Napier-Raman et al., 2023).

The study received approval from the Ethics Boards of the National University of Singapore (certificate number: NUS-IRB-2023-399) and the University of Quebec in Montreal (certificate number: UQAM-CIEREH-2024-6028). Participants provided written informed consent to engage in either face-to-face sessions, group discussions, or web-based tasks described below. The Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist was used to guide the reporting of this study (Appendix 2K) (Tong et al., 2007).

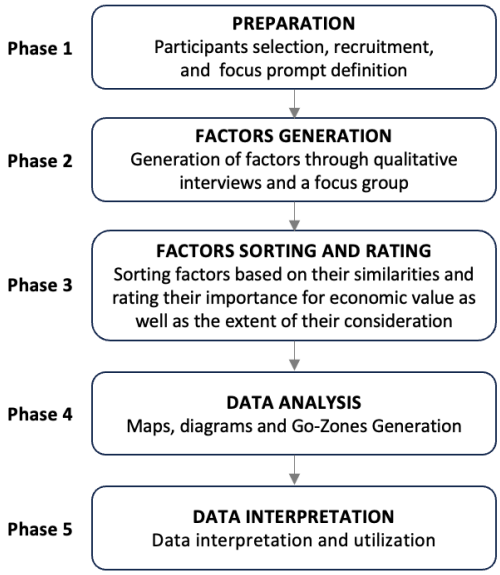
The study was conducted between March 2023 and August 2024. Data collection occurred from September 2023 to February 2024, with analysis, interpretation,

external validation, and manuscript preparation conducted from February to August 2024.

5.3.2. Overview of group concept mapping process

The GCM approach comprises five phases (Trochim, 1989): (1) identifying relevant stakeholders and developing the focus prompt, (2) generating factors that may impact the economic value of the DTx, (3) structuring factors through sorting and rating, (4) analyzing data and creating the visual representations, and (5) interpreting and utilizing the results (Figure 10).

Figure 10. Steps involved in a group concept mapping approach



The figure illustrates the five key phases of the GCM methodology used in the research study. It represents the systematic flow progression from (1) Preparation, (2) Factors Generation, (3) Factors Sorting and Rating, (4) Data Analysis, and finally (5) Data Interpretation.

Phase 1: Preparation

The preparation phase includes all aspects of planning, including ethics review board approvals (Appendix 2C) and participants' recruitment, and focus prompt definition and interview guides (Appendix 2G). Participants were recruited through purposive sampling based on their relevant experience according to three inclusion criteria: (1) experience in DTx development, clinical validation and/or

implementation; (2) geographic diversity to ensure broader perspectives; and (3) fluency in English or French.

This purposeful sampling approach used an iterative selection process that enabled responsive participant recruitment based on emerging analytical insights (Robinson, 2014). Data collection employed a “two-phase” recruitment strategy over six months, designed to capture diverse perspectives from “information-rich informants” while maintaining methodological rigor consistent with purposeful sampling principles (Palinkas et al., 2015). This iterative process allowed the second phase of interviews to explore adjacent concepts and emerging codes identified during the initial phase, ensuring theoretical saturation and depth of understanding.

Participants were identified through the research team's professional network. The final participant pool comprised four key stakeholder groups: (1) Healthcare professionals involved in care delivery and experienced with digital health solutions, (2) Industry stakeholders often leading the commercialization efforts of DTx interventions, (3) Public stakeholders responsible for DTx-related policy and regulatory aspects, and (4) Researchers early engaged in the DTx lifecycle, that is, in the development of these technologies (i.e., biomedical engineers, clinical researchers, healthcare management and economics researchers, behavioral scientists, and regulatory scientists). To provide context, a sociodemographic questionnaire was used to collect non-personal information, including demographic and professional information from participants (Table 13).

Table 13 presents a comprehensive overview of participants’ professional profiles, international geographic zones, and experience across the DTx lifecycle. Four major categories of participants were recruited: (1) Healthcare professionals involved in care delivery and experienced with digital health solutions, (2) Industry stakeholders often leading the commercialization efforts of DTx interventions, (3) Public stakeholders responsible for DTx-related policy and regulatory aspects, and (4) Researchers early engaged in the DTx lifecycle, that is, in the development of these technologies. Notably, 77% of participants reported at least five years of

experience in their respective fields, thus ensuring a high level of expertise among participants.

Table 13. Participant characteristics

	Participants, n (%)
Number of participants at GCM Phase 3	
Step 1: Factor sorting	37
Step 2: Factor rating for the importance scale	62
Step 3: Factor rating for the extent of consideration scale	62
Participants' professions	
Healthcare professionals Healthcare administrator/management Healthcare professional	12 (19%) 4 (6%) 8 (13%)
Industry stakeholders Healthcare consultant Entrepreneur and/or investor Market access, pricing models, and/or reimbursement expert Medical technology and pharmaceuticals leader	24 (39%) 4 (6%) 11 (18%) 6 (10%) 3 (5%)
Public stakeholders Non-for-profit professional and trade associations Public payer and/ or healthcare decision-maker	7 (11%) 5 (8%) 2 (3%)
Researchers Research engineer Healthcare management and economics researcher Behavioral scientist Regulatory scientist	19 (31%) 9 (47%) 6 (32%) 3 (16%) 1 (5%)
Participants' years of experience	
< 5 years	14 (23%)
6-10 years	12 (19%)
11-20 years	26 (42%)
>20 years	10 (16%)
Participants' experience in the DTx lifecycle[a]	
DTx technological development	28
DTx clinical validation	32
DTx deployment and commercialization	44
Participants' international geographic zone	
Asia-Pacific	37 (60%)

North America	6 (10%)
Western Europe	19 (30%)

a Some participants reported having experience in one, two, or all three phases of the DTx lifecycle.

Phase 2: Factors generation

Factors influencing the DTx economic impact were initially extracted from the literature (Kolasa & Kozinski, 2020; Sapanel et al., 2023; van Kessel et al., 2022, 2023; Wilkinson et al., 2023; Yan et al., 2021; Gomes et al., 2022). Subsequently, four in-depth face-to-face semi-structured interviews were conducted with DTx experts, defined as individuals having at least five years of experience in DTx development and/or implementation, and a group discussion was conducted with six additional DTx experts. The interview guide and complete transcripts are available in Appendices 2G and 2H, respectively, while details of the group discussion are documented in Appendices 2I and 2J. The purpose of the interviews and group discussions was to identify and exchange ideas related to a central prompt question: "*What factors may impact the ability of DTx to provide economic value or benefits?*" In total, 223 potential factors influencing the economic value of DTx were identified. In GCM, the term "statement" is used to refer to ideas obtained from the literature, during interviews, and group discussions to denote formalized specific ideas to be included in the list for sorting and rating (phase 2). For consistency with participant terminology and to reflect the conceptual nature of these elements, this paper adopts the term "factor", encompassing the various aspects both identified and evaluated by the participants during the GCM process.

Thematic-conceptual coding (Williams & Moser, 2019) was conducted to analyze the factors identified and a list of 59 factors was established (Table 13), which was pretested by two additional DTx experts. For example, the factors "The degree of contextualization and personalization in the intervention," "The level of personalization in interventions delivered to the patients," and "The use real-world data to personalize the therapeutic intervention" were synthesized into "The degree of personalization of the DTx intervention at the individual patient level." Each factor

randomly placed in the list and was attributed an identifying number for the traceability of empirical results.

Phase 3: Factors sorting and rating

At this phase, participants were invited to engage in three key activities through groupwisdom™, a web-based platform for GCM data collection, analysis, and results visualization (The Concept System, 2021). First, participants (n=37) were asked to sort the factors at Phase 2 into virtual piles based on their perceived similarity in meaning and to assign a name to each one. Second, participants who took part in factor sorting, along as additional ones (n=62), were tasked to rate the factors on two distinct 5-point Likert-type scales:

- **Importance scale:** Participants rated the importance of each factor for a DTx to generate economic value, based on their experience. The scale ranged from 1 (not important) to 5 (very important).
- **Extent of consideration scale:** Participants assessed the extent to which each factor is considered in their field or practice regarding DTx development, clinical validation, or implementation. This scale ranged from 1 (not considered) to 5 (very considered).

A total of 91 potential participants were initially contacted for this Phase 3, primarily via email between November 2023 and February 2024. Of these, 62 individuals completed the study, while 24 did not respond, 3 declined to participate, and 2 agreed but did not complete the required tasks.

Phase 4: Data analysis

The sorting results of the sorters (n=37) were analyzed using nonmetric multidimensional scaling (NMDS) to produce a point map (Everitt et al., 2011). This map displays the individual factors in two-dimensional (x, y) space. Factors frequently sorted together into piles by participants are plotted in Euclidean proximity on the point map, while factors not frequently sorted together into piles are spatially positioned farther away. The estimated stress value (SV) for this study

stands at [0.27 < 0.276 < 0.29; p-value < 0.05], and falls within the 95% confidence interval for internal statistical reliability from meta-analytic studies in GCM (Rosas & Kane, 2012). Similarly, test results obtained for SV for sample split-half-1 [0.27 < 0.288 < 0.29; p-value < 0·05] and SV for sample split-half-2 [0.27 < 0.290 ≤ 0.29; p-value < 0.05]. This "goodness-of-fit" statistic confirms a strong fit between the sort data (i.e., collected data) and the results of the estimated point map (i.e., processed data) (Rosas & Kane, 2012). Subsequently, agglomerative hierarchical cluster analysis (AHCA), using Ward's algorithm (Kruskal & Wish, 1978) was employed with the NMDS-estimated x-y coordinates of each factor used as an input. This spatially groups factors in polygons on a cluster map that are closest and non-overlapping. From NMDS estimates, anchoring and bridging Index (ABI) values are in the interval [0,1] and generated for each factor and their mean values calculated for each cluster (Kane & Rosas, 2018; Laustsen et al., 2021). The mean ABI provides insight into how factors within a cluster relate to each other and to factors in other clusters. Lower ABI values (toward "0") indicate that factors were more frequently sorted together by participants, thus they are more tightly associated within their cluster and reflect agreement among participants, while higher values (toward "1") suggest factors may serve as bridges to other clusters, and less agreement as to their spatial location on the concept map.

To determine the optimal number of clusters, i.e., the number of clusters which define the concept map solution, the study team systematically evaluated each cluster solution, ranging from 12 to 8 clusters. Each step involved examining which factors were grouped together as informed by the AHCA, and ABI values for consideration, to decide the best conceptual fit for the concept map, related to the intended purposes of the study (Mirabal et al., 2024; Rosas & Kane, 2012). The result was a final configuration of eight clusters (Figure 11), each containing between 5 and 10 factors. There is no single *a priori* correct number of clusters or statistical method to determine the single best cluster solution (Kane & Trochim, 2007; Mirabal et al., 2024; Rosas & Kane, 2012), an examination of data found the mean number of sorted piles by participants is 7.91 (SD 2.14) and the median is 8. Regarding scale ratings, the 'importance' and 'extent of consideration' ratings were

averaged for each factor and by cluster. To establish the internal reliability of rating consistency, the inter-rater reliability test estimate of participants obtained using the Pearson-Brown Prophecy formula (Nunnally, 1978) for the importance of the factor for generating DTx economic value [0.91 < 0.92, p-value < 0.05] and for the extent of consideration of the factor in the DTx field of practice [0.84 < 0.90 ≤ 0.90, p-value < 0.05] provide quite strong internal reliable and valid scale evaluation results with the 95% confidence interval or higher based on the criteria established in GCM meta-analyses on reliability (Rosas & Kane, 2012).

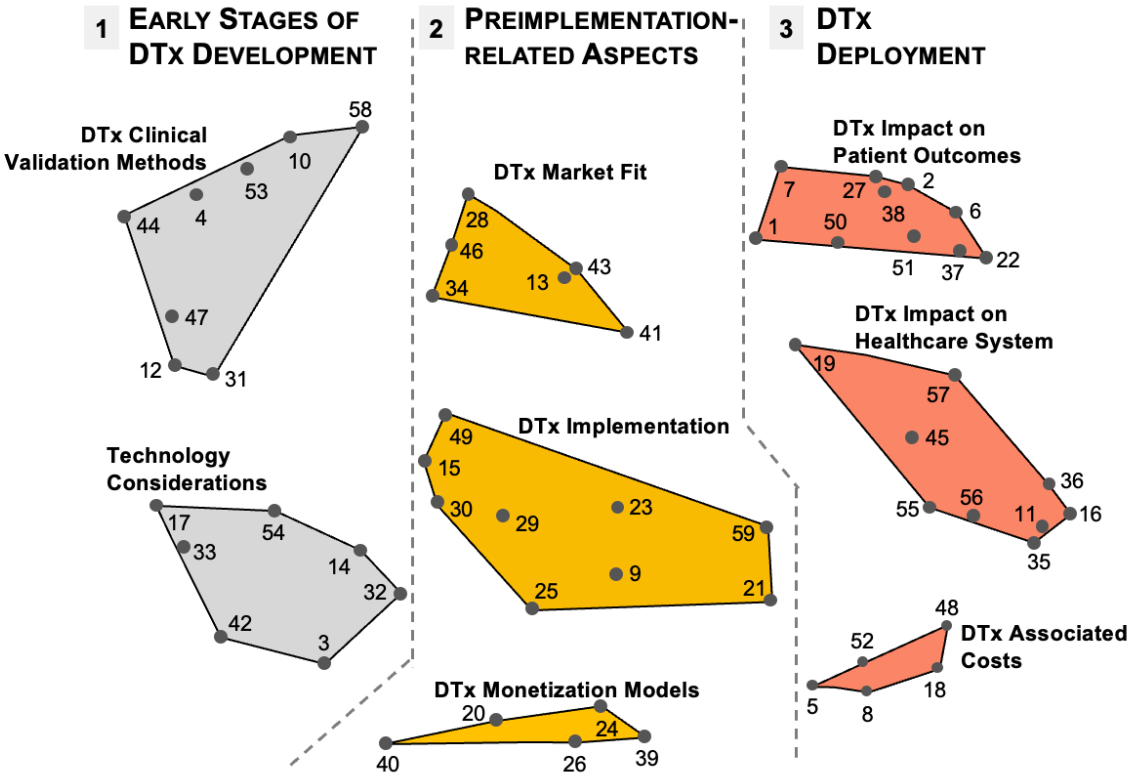
Phase 5: Data interpretation

At this final stage, semi-structured interviews/discussions involving five DTx experts were organized to interpret the findings. These experts, each with at least five years of experience, represented diverse profiles covering all aspects of DTx development, clinical validation, and implementation. These sessions involved a comprehensive review of the point map, point cluster map, as well as the ratings for importance and extent of consideration. These ratings for each factor and cluster, both within and among each group of stakeholders, were thoroughly examined and compared to comprehend potential convergence and divergence among factors. The goal was to interpret these variances and derive meaningful findings.

5.4. Results

The cluster map, showcasing eight clusters, serves as a visual representation of the factors that participants have grouped together (Figure 11). A dot on the map represents a single factor. The distance between the dots reflects how frequently participants sorted these factors into the same piles. These clusters delineate distinct themes spanning the entire DTx lifecycle, from inception to widespread deployment, with 59 factors conceptualized to influence the DTx ability to deliver economic value.

Figure 11. Cluster point map of all 59 factors perceived to influence the economic value of DTx, grouped into eight-cluster map (n=37)



The cluster point map reveals the interconnected nature of 59 factors that contribute to the economic value of DTx, organized into eight non-overlapping clusters, as shown by the polygons, where each one represents a key aspect of DTx development and implementation. Through spatial conceptual relationships, the map illustrates how participants consistently grouped certain factors together, with closer proximity represented within the perimeter of each polygon to indicate stronger association among them.

The mapping of 59 factors into eight clusters reveals three main themes along a horizontal axis in the NMDS map, representing a time axis that follows the traditional DTx development cycle from conception to deployment. These themes are:

- **Early stages of DTx Development:** This theme encompasses clusters of factors more pertinent to the initial phases of DTx development and clinical validation, leading toward approvals and/or market authorization by a regulatory body;

- **Preimplementation-related Aspects:** This theme includes clusters associated with various considerations and preparations necessary before the actual implementation of a DTx intervention; and

- **DTx Deployment:** The final theme consists of clusters containing factors pertinent to the implementation and ongoing management of DTx in a real-world environment.

In the EARLY STAGES OF DTX DEVELOPMENT, the *Technology Considerations* cluster includes aspects, such as data privacy and security requirements, the technological complexity, and development-related costs of the DTx, as well as the level of healthcare provider support and their readiness for a DTx intervention. The *DTx Clinical Validation Methods* cluster delves into critical aspects of clinical validation in DTx, encompassing comparator selection, trial types, and quality. It evaluates the time required for clinical development and validation, emphasizing patient and healthcare provider involvement. Early-stage user engagement, usability studies, and the representativeness of the DTx clinical trial population to real-world scenarios are also key considerations.

In the PREIMPLEMENTATION-RELATED ASPECTS of DTx, three clusters of factors become apparent. The *DTx Monetization Models* cluster encompasses considerations, such as potential go-to-market and monetization models, including potential coverage or reimbursement by public and/or private payers. The *DTx Implementation* cluster delves into the practical aspects of implementing a DTx. It includes considerations, such as digital literacy of providers and patients, the necessary healthcare resources to support the intervention usage as well as the question of the intervention's technological interoperability and integration with existing healthcare IT systems. The third cluster, *DTx Market Fit*, under this second theme, focuses on the relevance and relative importance of targeted clinical unmet needs and the profile of patients being targeted by the DTx. This encompasses their acceptance and willingness to use a DTx intervention.

Subsequently, in the DTx DEPLOYMENT, factors were organized into three clusters. The *DTx Impact on Patient Outcomes* cluster revolves around the clinical efficacy and effectiveness of the DTx intervention in improving short and long-term patient outcomes. It also encompasses the intervention's influence on driving behavioral change in patients, considering patient adherence and compliance with the DTx intervention. The *DTx Impact on Healthcare System* cluster examines the broader impact of a DTx intervention on current and future usage of outpatient and inpatient care resources, primary care healthcare resources, overall healthcare productivity, and efficiency. It also considers the long-term societal impact associated with the DTx intervention. Finally, the *DTx Associated Costs* cluster focuses on various expenses associated with a DTx intervention, including time spent by patients and healthcare providers, out-of-pocket expenses, and potential cost-saving effects. Additionally, it explores the DTx impact on indirect costs, such as patient and caregiver productivity and transportation expenses.

Any cluster size (Figure 11) reflects the extent to which its contributing factors are related. A smaller cluster, like *DTx Associated Costs* or *DTx Monetization Models*, suggests a focused scope with similar factors. By contrast, *DTx Implementation* and *DTx Clinical Validation Methods* encompass a diverse range of broader conceptual factors.

Table 14 presents all 59 identified factors forming these eight clusters, along with the standard deviation for each cluster and the average anchoring and bridging index (ABI) for each factor, as well as for each cluster. A low average bridging index (ABI), closer to 0, indicates that a factor is firmly anchored to its position on the map, meaning it has been sorted with factors that are in the same area on the map (Laustsen et al., 2021). For instance, factor 2 – "The DTx impact on short-term patient outcomes", with an ABI of 0, exemplifies such factors. Conversely, a high ABI, closer to 1, suggests that a factor has been sorted with factors located further away on the map, thus bridging to other areas. Factor 42, "The DTx technological complexity and development-related costs", with an ABI = 1, serves as an example of a bridging factor. Additionally, factor 54 – "DTx product-market fit", which

assesses the cultural appropriateness of the solution, with an ABI = 0.55, is also a bridging factor. It was frequently sorted with items not only in the *Technology Considerations* cluster but also with items in the *DTx Market Fit* cluster.

Table 14. Overview of the eight clusters with their respective factors

	Average bridging index	Average importance ratings	Average extent of consideration ratings
THEME 1: EARLY STAGES OF DTX DEVELOPMENT			
Technology Considerations	**0.61**	**3.86**	**3.51**
3. The DTx competitive market landscape and presence of existing treatment options	0.77	3.55	3.16
14. The support level from healthcare providers for a DTx intervention	0.32	4.39	3.82
17. The DTx manufacturers' ability to operate in an agile manner with iterative development cycles and continuous feedback loops with key decision-makers	0.57	3.61	3.08
32. The readiness of DTx for implementation by the healthcare provider(s)	0.37	3.85	3.50
33. The data privacy and security requirements to be complied with for a DTx intervention	0.73	4.11	4.23
42. The DTx technological complexity and development-related costs	1.00	3.03	3.13
54. The DTx product-market fit	0.55	4.02	3.45
DTx Clinical Validation	**0.40**	**3.77**	**3.66**
4. The selection of the comparator(s) in DTx clinical trials	0.24	3.84	3.61
10. The types and quality of DTx clinical trials	0.16	3.98	3.85
12. The time required to develop and validate clinically the DTx intervention	0.82	2.92	3.07
31. The extent to which patients and healthcare providers were involved in the development and implementation of the DTx	0.53	3.84	3.61
44. The types of data and the methods used for data collection in DTx clinical trials	0.29	3.43	3.82
47. The early-stage user engagement and usability studies in the development of DTx	0.59	3.77	3.57
53. The nature of the clinical and digital endpoints chosen in DTx clinical trials	0.17	3.95	3.85
58. The representativeness of the DTx clinical trial population to real-world populations	0.40	4.02	3.77
THEME 2: PREIMPLEMENTATION-RELATED ASPECTS			
DTx Market Fit	**0.49**	**3.72**	**3.74**
13. The degree of real-time personalization of the DTx intervention at the individual patient level	0.32	3.38	3.26
28. The relevance and relative importance of the targeted clinical unmet needs, including size of the affected population	0.74	4.06	4.08
34. The DTx as a standalone treatment or combined with an existing treatment	0.66	2.90	3.36
41. The patient's acceptance and willingness to use a DTx intervention	0.29	4.61	4.25
43. The overall DTx treatment duration, frequency and intensity	0.45	3.56	3.71
46. The profile of patients being targeted by the DTx	0.51	3.60	3.60
DTx Implementation	**0.32**	**3.94**	**3.59**
9. The interoperability of DTx with existing healthcare IT systems	0.29	3.76	3.49
15. The health and digital literacy of the healthcare providers and/ or patients	0.25	3.89	3.55
21. The level of healthcare resources required to support the DTx implementation	0.28	3.74	3.49
23. Healthcare providers' willingness to prescribe DTx interventions or adjust treatment plans	0.25	4.34	3.84
25. Healthcare provider leadership support for DTx intervention	0.27	3.82	3.30
29. The need for education and training of patients and healthcare providers on the DTx intervention	0.22	3.97	3.68
30. The availability and accessibility of DTx to patients	0.39	3.92	3.51
49. The presence of HTA frameworks for evaluating DTx interventions	0.70	3.71	3.19
59. The level of integration of DTx into clinical practice and existing workflows	0.23	4.11	3.73
DTx Monetization Models	**0.48**	**3.93**	**3.45**
20. The presence of DTx regulatory and reimbursement pathways	0.45	4.27	3.77
24. Government prioritization and budget allocation for DTx-covered disease areas	0.30	3·71	3.30
26. The maintenance-related costs of DTx	0.66	3·40	2.87
39. The level of the DTx coverage or reimbursement by public and/or private payers	0.37	4·15	3.68
40. The DTx go-to-market and monetization models	0.59	3·94	3.29

THEME 3: DTX DEPLOYMENT			
DTx Impact on Patient Outcomes	**0·16**	**4·00**	**3.84**
1. The patient's adherence and compliance with the DTx intervention	0·28	4·55	4.16
2. The DTx impact on short-term patient outcomes	0·00	3·92	4.08
6. The DTx impact on the health and well-being of family members and caregivers	0·14	3·29	2.76
7. The clinical efficacy and effectiveness of the DTx intervention	0·36	4·68	4.59
22. The DTx impact in the secondary and tertiary prevention of medical conditions	0.29	3.26	3.00
27. The DTx impact on long-term patient outcomes	0.05	4.15	3.85
37. The DTx impact on current potential treatments	0.19	3.69	3.62
38. The DTx impact on patient quality of life	0.02	4.11	4.13
50. The DTx potential to drive actual patients' behavioral change	0.20	4.03	3.71
51. The DTx impact on the severity and recurrence of potential adverse events	0.11	3.94	3.81
DTx Impact on Healthcare System	**0.38**	**3.86**	**3.47**
11. The DTx impact on overall healthcare productivity and efficiency	0.25	3.94	3.48
16. The DTx impact on current and future usage of outpatient care resources	0.28	3.77	3.25
19. The perceived utility and usability of the DTx intervention by healthcare providers and patients	0.43	4.26	3.82
35. The impact of DTx on the healthcare workforce shortage and their existing workload	0.25	3.79	3.39
36. The DTx impact on current and future usage of inpatient care resources	0.32	3.77	3.28
45. The degree of change (or disruption) of the intervention to the current care delivery	0.42	3.82	3.65
55. The impact on long-term societal costs associated with the DTx intervention	0.48	3.71	3.03
56. The DTx impact on current and future usage of primary care healthcare resources	0.28	3.76	3.42
57. The ability of the DTx to address health disparities in access to healthcare	0.68	3.52	3.08
DTx Associated Costs	**0.37**	**3.93**	**3.41**
5. The costs associated with the time spent by patients and healthcare providers using the DTx	0.37	3.69	3.37
8. The out-of-pocket costs potential patients may incur for the DTx intervention	0.44	3.84	3.13
18. The potential cost-saving or cost-offset effect associated with the DTx intervention	0.39	4.24	3.54
48. The impact on the total indirect costs associated with the DTx intervention	0.39	3.71	3.19
52. The impact on total medical expenses associated with the DTx intervention	0.28	4.06	3.31

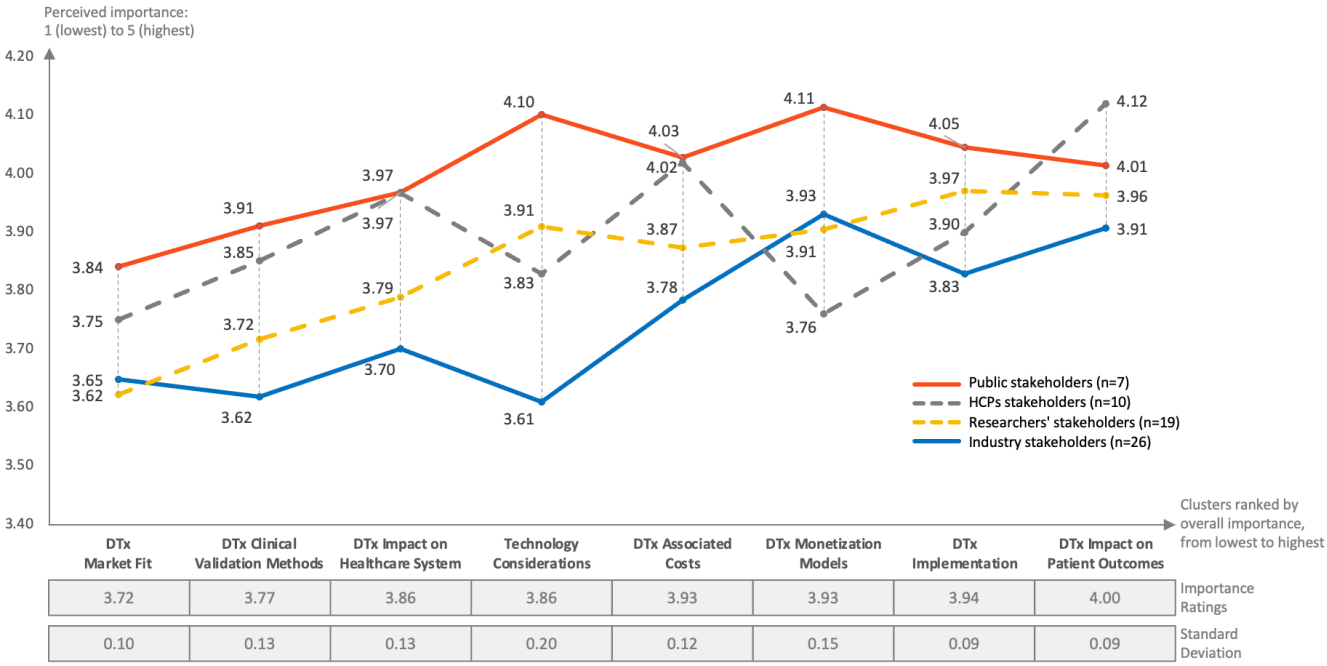
A low average bridging index (ABI), closer to 0, indicates that a factor is firmly anchored to its position on the map, meaning it has been sorted with factors that are in the same area on the map (Laustsen et al., 2021). For instance, factor 2 – "The DTx impact on short-term patient outcomes", with an ABI of 0, exemplifies such factors. Conversely, a high ABI, closer to 1, suggests that a factor has been sorted with factors located further away on the map, thus bridging to other areas. Factor 42, "The DTx technological complexity and development-related costs", with an ABI = 1, serves as an example of a bridging factor. Additionally, factor 54 – "DTx product-market fit", which assesses the cultural appropriateness of the solution, with an ABI = 0.55, is also a bridging factor. It was frequently sorted with items not only in the *Technology Considerations* cluster but also with items in the *DTx Market Fit* cluster.

Table 14 reveals a notable pattern. Seven out of eight clusters show higher mean ratings for importance than for extent of consideration. This suggests these clusters may be under considered in fields of practice relative to their perceived importance in influencing the overall DTx economic value. The sole exception is the *DTx Market*

Fit cluster, where the importance rating (3.72 / 5.00) closely aligns with its extent of consideration rating (3.74 / 5.00).

In what follows, cluster results for each rating are examined, and then compared to draw broader insights. The mean ratings for importance provided by the participants for each factor and by cluster are presented in Figure 12. SD are computed for each cluster to assess the degree of convergence or divergence among stakeholder responses, with a mean value of 0.13.

Figure 12. Perceived importance of the clusters of factors perceived to influence the economic value of DTx among stakeholder groups (n=62)



The figure shows how different stakeholder groups (Healthcare Professionals, Industry, Public, and Researchers) rated the importance of each cluster. DTx Impact on Patient Outcomes and DTx Implementation emerged as the most important clusters overall, with mean ratings of 4.00 / 5.00 and 3.94 / 5.00, respectively. Public stakeholders consistently gave higher importance ratings across clusters compared to other groups.

The two clusters of factors impacting the economic value of DTx, reported as the most important by stakeholders, are the *DTx Impact on Patient Outcomes* (rated at 4.00 / 5.00) and *DTx Implementation* (rated at 3.94 / 5.00). The SD values, of 0.09 for both clusters, indicate a narrow rating, thus a strong agreement among stakeholders.

Following closely are the *DTx Monetization Model* (rated 3.93 / 5.00) and *DTx Associated Costs* (rated 3.93 / 5.00), ranking as the third most important clusters. The *DTx Market Fit* cluster was consistently ranked lower than any other cluster by all stakeholder groups, except for Industry stakeholders, who rated it as the third lowest.

The convergence and divergence in perception among stakeholder groups merit attention. Statistical analysis using the Kruskal-Wallis on ranks test confirmed significant between-group differences for importance ratings ($p<0.01$), establishing the statistical independence of each stakeholder group and relevance of subsequent comparative analyses (Appendix 2L). Public stakeholders consistently assigned higher importance ratings across clusters, with a mean rating of 4.00 / 5.00, compared to HCPs (with a mean rating of 3.90 / 5.00), Researchers (mean rating of 3.84 / 5.00), and Industry stakeholders (mean rating of 3.75 / 5.00).

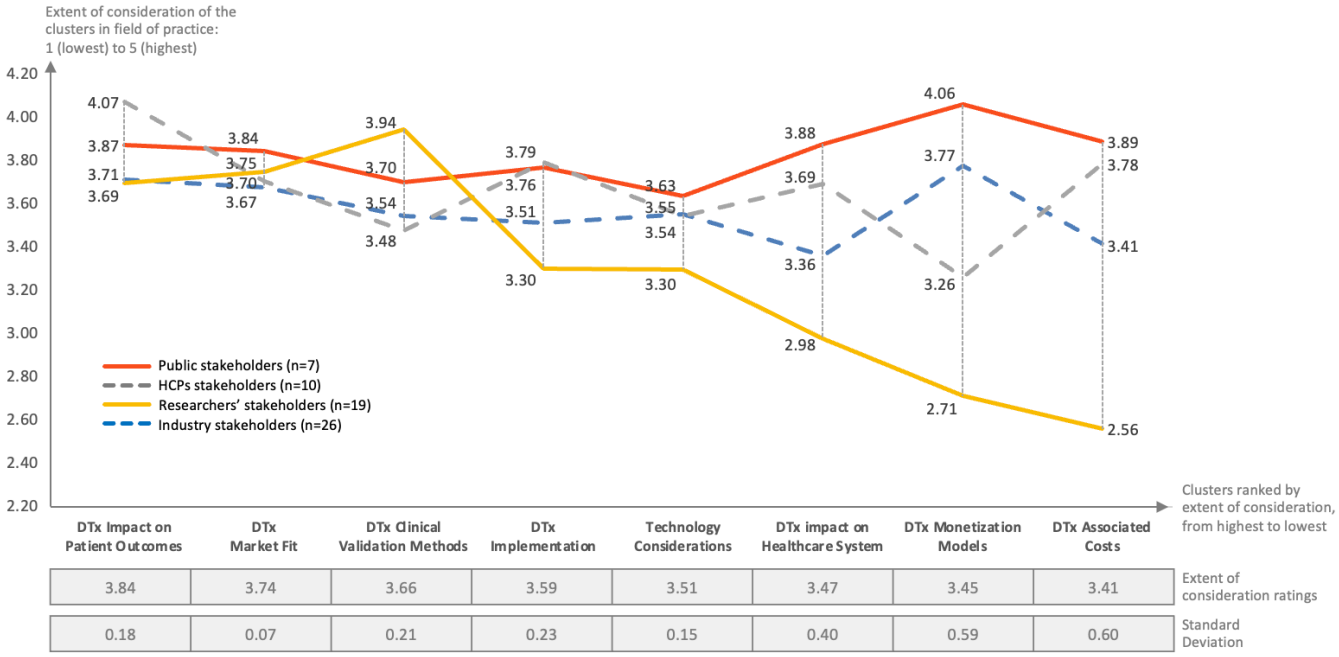
The most significant convergence of perspective is toward the importance of the *DTx Impact on Patient Outcomes*, with a SD of 0.09. However, while the *DTx Impact on Patient Outcomes* emerges as the most important cluster of factors for HCP stakeholders—an outcome most likely aligned with expectations— it ranks only fifth in importance for Public stakeholders.

The most notable divergence of perspective relates to the *Technology Considerations* influencing a DTx ability to deliver economic value, with a SD of 0.20. This cluster ranked as the second most important for Public stakeholders (with a mean rating of 4.10 / 5.00), contrast sharply given it is rated as the least important for Industry stakeholders (with a mean rating of 3.61 / 5.00). The interpretation of these convergences and divergences in perception among stakeholder groups is further examined in the discussion section.

In addition to evaluating the relative importance of clusters influencing the economic value of DTx, stakeholders were asked to rate the extent to which each factor was considered into their respective field of practice (Figure 13). This includes aspects like day-to-day decision-making and prioritization within their roles. The mean SD

for extent of consideration across clusters is 0.30. Consistent with the importance ratings, extent of consideration also showed significant between-group differences (Kruskal-Wallis, $p<0.05$), further emphasising the relevance of the comparative analyses (Appendix 2L).

Figure 13. Extent of consideration of the clusters of factors perceived to influence the economic value of DTx among stakeholder groups (n=62)



The figure illustrates the extent to which each stakeholder group rated these clusters in their practice. DTx Associated Costs was the least considered cluster (3.41 / 5.00), followed by DTx Monetization Models (3.45 / 5.00), despite their high importance ratings. DTx Impact on Patient Outcomes was reported as the most considered cluster (3.84 / 5.00)

.

Among all stakeholders, Figure 13 reveals that *DTx Associated Costs* is the least considered cluster of factors (rated at 3.41 / 5.00), followed by *DTx Monetization Models* (rated 3.45 / 5.00), despite both being reported as the third most important clusters (Figure 12) – results partially driven by the ratings of the group of Researchers (Table 15). A strong consensus exists among stakeholders in considering *DTx Impact on Patient Outcomes* perceived as the most considered cluster (rated at 3.84 / 5.00). Once again, Public stakeholders consistently assigned higher consideration ratings across clusters with a mean rating of 3.83 / 5.00.

Table 15 compares how Researchers and other stakeholder groups reported the perception of the different clusters in their professional practice. Researchers prioritize factors related to the EARLY STAGES OF DTX DEVELOPMENT (rated 3.62 / 5.00), PREIMPLEMENTATION-RELATED ASPECTS (3.25 / 5.00), and DTX DEPLOYMENT (3.08/5.00). This aligns with Researchers' typical involvement in the early stages of the DTx lifecycle. The *DTx Associated Costs* cluster reveals a significant perception gap between Researchers and other participants. Researchers rated it considerably lower (2.56 / 5.00), while other participants gave it a higher score (3.69 / 5.00). This disparity underscores the divergent views among stakeholder groups on how factors affecting DTx economic value are considered. Notably, this cluster also shows the highest SD (0.60) across both importance and extent of consideration ratings and clusters.

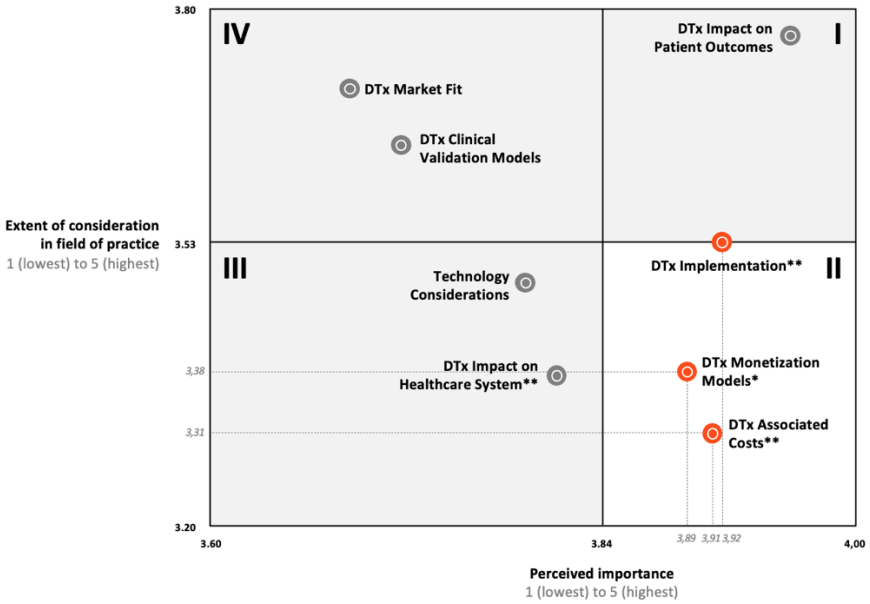
Table 15. Comparison of extent of consideration ratings: Researchers vs. other stakeholder groups by cluster

	Mean extent of consideration rating, excluding Researchers (n=43)	**Mean extent of consideration rating for Researchers (n=19)**	**Significance**
Theme 1: Early stages of DTx Development	**3.57**	**3.62**	
Technology Considerations	3.58	3.30	$p > 0.05$
DTx Clinical Validation Methods	3.57	3.94	$p > 0.05$
Theme 2: Preimplementation-related Aspects	**3.71**	**3.25**	
DTx Market Fit	3.74	3.75	$p > 0.05$
DTx Implementation	3.69	3.30	$p < 0.05$
DTx Monetization Models	3.70	2.71	$p < 0.005$
Theme 3: DTx Deployment	**3.74**	**3.08**	
DTx Impact on Patient Outcomes	3.88	3.69	$p > 0.05$
DTx Impact on Healthcare System	3.64	2.98	$p < 0.005$
DTx Associated Costs	3.69	2.56	$p < 0.001$

To further explore these results, both the ratings of importance and extent of consideration were compared not in isolation, but rather in conjunction. It led to the

plotting of clusters based on stakeholders' mean ratings, resulting in an aggregate scattered bivariate plot by cluster, referred to as a go-zone graph GCM analysis (Figure 14 and Figure 15). These graphs are divided into quadrants, above and below the mean value of each factor ratings. Thus, it facilitates the overall identification of priority clusters.

Figure 14. Bivariate go-zone plot of aggregate means by cluster as perceived by stakeholders of the importance and extent of consideration in the field of practice (n=62)



This quadrant analysis plots clusters based on the importance (x-axis) versus the extent of consideration (y-axis). The scattered plot identifies three priority clusters that are highly important but receive insufficient consideration (Quadrant II), these are, DTx Implementation, DTx Monetization Models, and DTx Associated Costs. A single asterisk (*) indicates a p-value < 0.05, and double asterisks (**) indicate a p-value < 0.001. The non-parametric Wilcoxon Rank-order test for matched pairs indicates a statistical difference (p-value < 0.05) between the relative importance and the extent of consideration rank orderings (Appendix 2L).

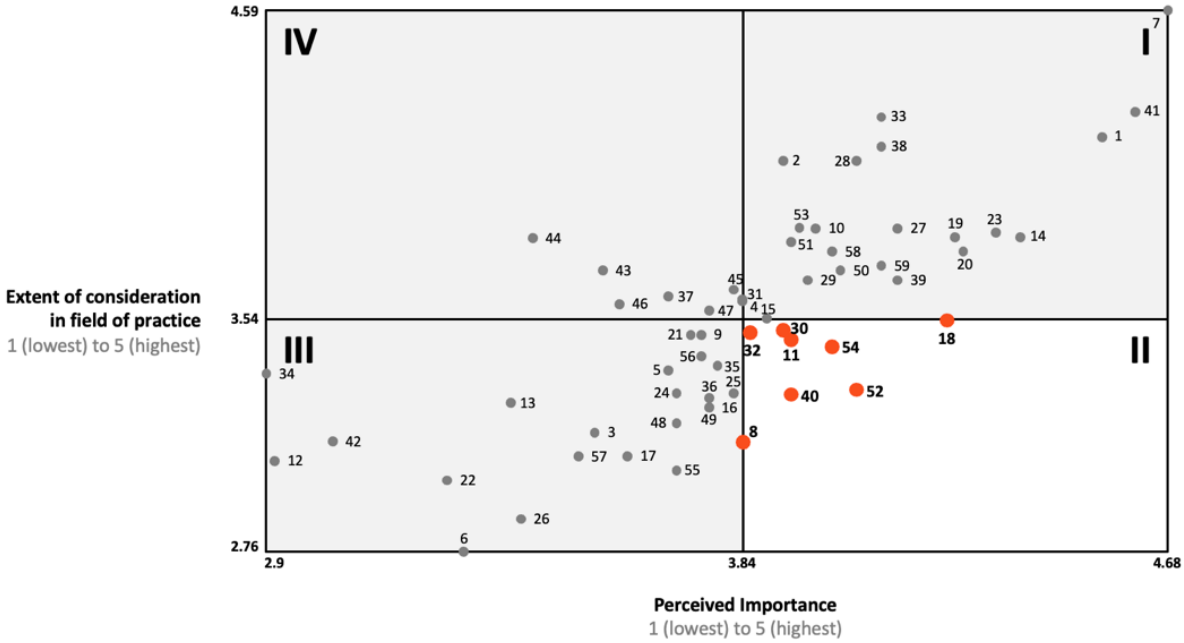
Priority quadrants are delineated based on whether clusters fall above or below the mean ratings for importance (3.84 / 5.00) and extent of consideration (3.53 / 5.00). These quadrants are defined as follows: (1) Quadrant I encompasses clusters of factors perceived as important for a DTx to generate economic value and highly considered by participants in their field of practice throughout the DTx development lifecycle, (2) Quadrant II includes clusters with high importance but low consideration, (3) Quadrant III contains clusters with both low importance and low consideration, and (4) Quadrant IV comprises clusters with low importance but high

consideration. This framework allows for a nuanced analysis of how various clusters of factors are perceived and prioritized in the context of DTx economic value.

The Quadrant II encompasses clusters perceived as highly important in influencing DTx economic value, yet insufficiently considered in participants' daily decision-making processes, thus indicating a potential gap. Three clusters fall within this priority quadrant: *DTx Implementation*, *DTx Monetization Models*, and *DTx Associated Costs*. These clusters are recognized by all stakeholder groups for their critical role in a DTx ability to generate economic value, as evidenced by a low mean SD rating of 0.12 across these three clusters. However, they are simultaneously acknowledged, particularly by Researchers, as potentially receiving inadequate consideration throughout the DTx development lifecycle. This discrepancy underscores a potential area of consideration for the respective stakeholders involved in DTx development and implementation strategies.

With a p-value < 0.05, the difference between the two overall scale rankings for these clusters is statistically different as reported by the non-parametric Wilcoxon rank-order test (Appendix 2L). Nevertheless, these findings should be interpreted within the context of each stakeholder group.

Figure 15. Bivariate go-zone plot of individual factors influencing the economic value of DTx perceived importance and extent of considerations in the field of practice (n=62)

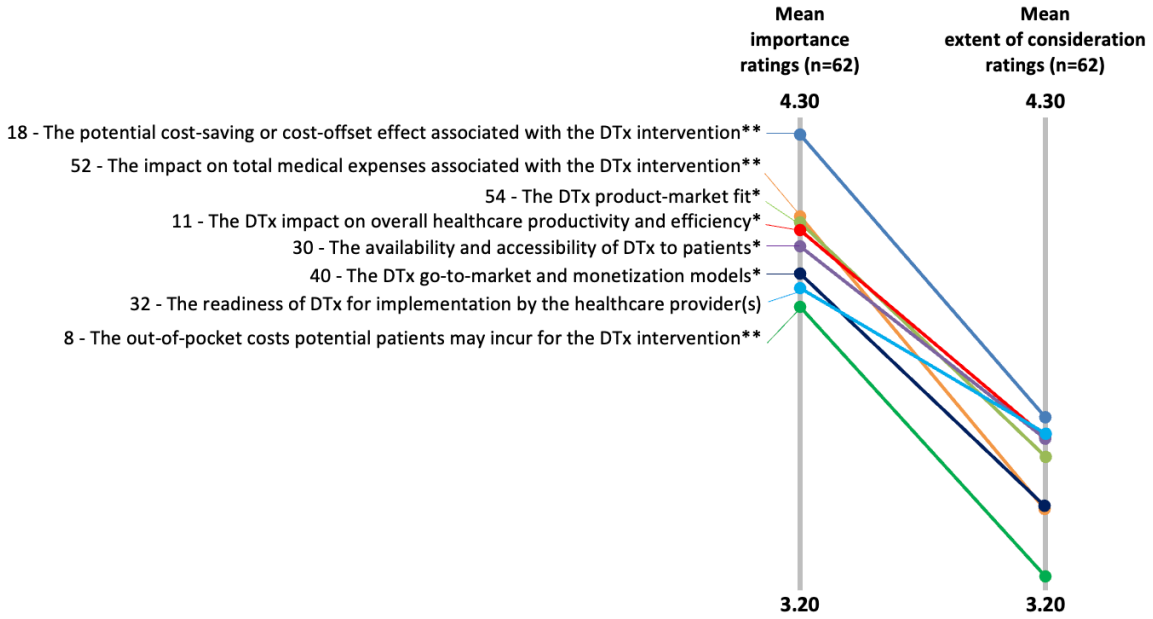


This quadrant analysis plots individual factors based on their importance (x-axis) versus extent of consideration (y-axis). The scattered plot identifies eight specific factors that fall into the priority quadrant (Quadrant II) - meaning they are considered highly important but receive insufficient consideration in practice.

An analysis of the go-zone graph at the factor level reveals eight factors (factors 8, 11, 18, 30, 32, 40, 52 and 54) positioned in Quadrant II, the priority quadrant (Figure 15). These eight factors emerged as crucial for a DTx to generate economic value, with their mean importance ratings surpassing the overall mean across all 59 factors studied. Paradoxically, these same eight factors were reported as less considered by the participants compared to the other factors, with their mean extent of consideration ratings falling below the overall mean.

Figure 16 illustrates the relationship between the mean rating scores for both scales. These pattern matches for the factors identified in Quadrant II are valuable for detecting high-level patterns and offer a visual comparison of how stakeholders rated these factors. The descending diagonal lines indicate that each factor's importance rating is higher than its corresponding extent of consideration rating, confirming a potential lack of consideration of these factors despite their perceived importance in driving DTx economic value.

Figure 16. Pattern match of the relationship between stakeholders mean ratings: importance and extent of consideration (n=62)



A single asterisk (*) indicates a p-value < 0.005, and double asterisks (**) indicate a p-value < 0.001. The non-parametric Wilcoxon Rank-order test for matched pairs indicates a statistical difference (p-value < 0.01) between the relative importance and the relative extent of consideration rank orderings (Appendix 2L).

These eight priority factors (Figure 14 and Figure 15) span five of the eight total clusters. This distribution suggests that, according to participants, no single factor or cluster should be prioritized in isolation. Instead, multiple factors across the entire DTx lifecycle may require consideration or prioritization by the relevant stakeholders at each stage.

5.5. Discussion

5.5.1. Overview

The results of this study illustrate the benefits of GCM methodology as a participatory approach in creating a collective conceptual framework for understanding a specific topic of interest (Laustsen et al., 2021). The approach elucidates stakeholders' shared perspectives, while also revealing how both collective and individual stakeholders contribute to and influence this economic value. This research contributes to the field in three ways.

First, it provides a collective stakeholder approach to identify factors influencing DTx economic value. The research identified 59 such factors, aligning with the emerging literature in this field (Kreuzenbeck et al., 2024; Sapanel et al., 2023; Keogh et al., 2024; van Kessel et al., 2022, 2023; Yan et al., 2021; Kolasa & Kozinski, 2020; Wilkinson et al., 2023; Gomes et al., 2022). Notably, this study highlights several factors that are inconsistently considered in economic evaluations of DTx and are simultaneously recognized as barriers to the widespread adoption of these technologies (Keogh et al., 2024; Kreuzenbeck et al., 2024; Sapanel et al., 2023). These include factors, such as the time and expertise needed for patient education in using DTx technology (factor 5), ongoing maintenance costs (factor 26), direct patient out-of-pocket expenses (factor 8), indirect costs (factor 48), and the local context as a significant source of uncertainty (factor 13).

Second, this study provides a better understanding of the collective conceptualization of factors influencing the economic value of DTx by stakeholders involved in their development, validation, and implementation. It examines the interrelationships between clusters and factors driving DTx economic value from a collective stakeholder perspective. By mapping these connections, it helps gain insight into the intricate ecosystem of factors influencing the economic value of DTx.

Third, the analysis of the stakeholders' perceived relative importance and relative extent of consideration of these factors led to the development of a conceptual framework of priority areas. This framework, illustrated in Figure 12 and Figure 13, and detailed in Table 15, presents a grouped and coherent set of potential priority clusters and factors for driving DTx economic value. It aims to guide stakeholders in comprehensively assessing relevant factors, ensuring a methodical approach to decision-making. It is recommended that each stakeholder group interpret this framework meticulously to comprehensively assess relevant clusters and factors derived from the study findings.

The study revealed both anticipated and unexpected insights, contributing to a more nuanced understanding of individual stakeholder groups' roles within the broader

context of DTx - to influence a DTx ability to generate economic value. Two observations merit particular attention.

The improvement of patients' clinical outcomes emerged as a primary concern across all stakeholder groups (Figure 12). However, despite this broad consensus, this cluster ranked only fourth in importance for Public Stakeholders. This discrepancy may be attributed to the heterogeneous composition of this stakeholder category, encompassing individuals with diverse backgrounds in technology, clinical practice, and payer systems. Also, the complexity of decision-making regarding coverage and reimbursement has intensified, with priority setting and resource allocation posing significant challenges. Public stakeholders are tasked with evaluating not only the clinical and financial impact of individual DTx interventions but also their broader implications for healthcare systems and populations. This evaluation must be conducted in the context of competing alternative treatments and interventions, all vying for limited funding and coverage. Therefore, while the clinical impact of these interventions is crucial, it is not the sole determining factor for final decision.

A second observation relates to Researchers appearing to give less consideration to some factors as compared to other stakeholders groups. This is particularly evident for factors within the *DTx Associated Costs*, *DTx Monetization Models*, and *DTx Healthcare System Impact* clusters, despite Researchers acknowledging the importance of these factors. This divergence potentially reflects the heterogeneous composition of this stakeholder category, as well as Researchers' primary involvement in early stages of DTx development, such as conducting research, knowledge generation, and initial clinical validation. Their priorities or mandates may differ, as they are typically not tasked with examining costs during these initial stages of technology development and clinical validation. However, failing to consider these costs impact early on could negatively impact payment, reimbursement and adoption decisions (Kario et al., 2021). This finding underscores the critical role that all stakeholders, including researchers, play in ensuring DTx demonstrate economic value to potential payers. As innovations from research

institutions often struggle to achieve commercial success (Phillips & Castle, 2017), there exists a significant opportunity to enhance the commercialization of innovative research. A promising starting point could be fostering collaboration among major DTx stakeholder groups, such as through public-private partnerships. These collaborations should aim to integrate commercialization expertise earlier in the DTx lifecycle, ensuring that market viability is considered from the outset of development. By bridging the gap between academic research and commercial application, stakeholders can work together to overcome the challenges that currently hinder the successful translation of DTx innovations into commercially viable products.

5.5.2. Limitations and future research

The mixed methods-based approach, which involved semi-structured interviews (Appendix 2G) and a group discussion with subject matter experts throughout the GCM research steps (Figure 10), particularly for data interpretation, contributed to confirming the external validity of the generated data and results. The external validity of the results is also reinforced by the variety of stakeholders and the wide range of settings involved. The results presented are context-specific, and it is crucial to consider context-specific external validity issues when interpreting them.

The study's sample size (n=62) and participant composition provide valuable insights within the context of the research. While the findings offer a robust and reliable foundation for understanding DTx value generation, certain limitations should be acknowledged. Building on the study’s findings, future research could extend this methodology to explore factors perceived as important by specific subgroups of stakeholders, such as healthcare providers, or new groups like patients. Such investigations could be conducted across various contexts and countries to gain a more comprehensive understanding of the decision-making processes within each stakeholder group. Additionally, exploring the relationship between these perceived factors and actual economic outcomes would provide valuable insights into the real-world impact of DTx interventions.

As the field of DTx continues to evolve, ongoing research will be crucial in refining our understanding of the factors influencing economic value and adoption. By building on the insights gained from this study and expanding the scope of investigation, future research can contribute significantly to the advancement and integration of DTx in healthcare systems. This continued exploration could ultimately help inform the development of more effective, economically viable DTx interventions, benefiting both patients and healthcare systems alike.

5.5.3. Conclusions

The effective deployment of DTx rely on a multi-stakeholder approach throughout their lifecycle, spanning from inception to large-scale deployment. Throughout this journey, various stakeholders and factors influence a DTx ability to generate economic value. This paper aimed to better understand collective representations and perceptions of stakeholders regarding factors driving DTx economic value, and how the diverse stakeholders involved in DTx lifecycle process contribute to and influence their potential economic benefits.

A particularly significant finding was the apparent disconnect between researchers' recognition of economic factors' importance and their actual consideration of these factors in practice. This observation raises important questions about the barriers researchers face in integrating economic considerations during early DTx development. Chapter 6 addresses this critical gap through an in-depth qualitative investigation, exploring researchers' decision-making processes, motivations, and challenges regarding economic considerations in DTx development. By comprehending these perspectives, this final study completes the thesis's progressive journey from identifying economic value drivers to understanding their practical integration throughout the DTx lifecycle.

6

UNDERSTANDING ECONOMIC DECISION-MAKING IN DIGITAL THERAPEUTICS DEVELOPMENT: A QUALITATIVE APPROACH (STUDY 3)

CHAPTER 6. UNDERSTANDING ECONOMIC DECISION-MAKING IN DIGITAL THERAPEUTICS DEVELOPMENT: A QUALITATIVE APPROACH (STUDY 3)

The preceding chapters have progressively built our understanding of economic value in DTx, beginning with a systematic review that mapped the current landscape of economic evaluations and continuing with a GCM study that revealed how diverse stakeholders conceptualize factors influencing DTx economic value. A particularly striking finding from Chapter 5 was the apparent disconnect between researchers' acknowledgment of important economic factors and their limited consideration of these factors in practice. Specifically, researchers consistently assigned lower consideration to economic and implementation factors compared to other stakeholder groups, despite recognizing their significance for successful DTx adoption.

This third and final study responds directly to this identified gap by employing a qualitative research approach grounded in CR to explore the underlying mechanisms that shape researchers' decision-making regarding economic considerations during DTx development and clinical validation phases. Moving beyond merely identifying what factors are underconsidered, this investigation examines why this pattern exists and how it manifests in researchers' approaches to DTx development.

Through in-depth interviews with 17 researchers involved in DTx development—including research-engineers, health systems and social science researchers, clinician-researchers, and practitioner-researchers—this study investigates the complex interplay between institutional structures, professional backgrounds, and implementation uncertainties that influence economic decision-making. The analysis applies both DT and ST frameworks to uncover not just observable decision patterns but also the deeper causal mechanisms that generate them.

By illuminating researchers' decision-making processes and the barriers they face in integrating economic considerations, this final study completes the thesis's comprehensive examination of DTx economic value. The findings provide crucial insights for enhancing alignment between researchers' approaches and the economic considerations necessary for sustainable DTx implementation, ultimately supporting the successful translation of these promising clinical interventions from concept to widespread adoption in healthcare systems.

Publication Status

The manuscript presented in this chapter underwent peer-review evaluation and was subsequently accepted for publication in the Journal of Medical Internet Research (JMIR) on August 21, 2025. The preprint of the article has been published in Research Square, a preprint platform (Appendix 3A).

6.1. Abstract

Background: DTx represent a transformative shift in healthcare delivery, offering software-driven, evidence-based therapeutic interventions. Despite their potential, adoption remains low across healthcare systems, partly due to insufficient economic evidence demonstrating their benefits. Significant knowledge gaps persist regarding stakeholders' approaches to economic decisions in DTx development, with prior studies also indicating limited consideration of economic factors in early DTx development stages, particularly from researchers.

Objective: This study investigates how researchers approach decision-making regarding factors that influence the economic impact of DTx during technological development and clinical validation phases, examining the underlying mechanisms and contextual conditions that shape these processes.

Methods: Using a critical realism epistemological approach, 17 semi-structured interviews were conducted with researchers involved in DTx development, including research-engineers, health systems and social science researchers, clinician-researchers, and practitioner-researchers. The approach combined deductive and inductive coding, followed by abductive and retroductive processes, to identify generative mechanisms underlying observed decision-making patterns. System dynamics modeling was applied to visualize causal relationships through triangulated data sources.

Results: Three interrelated generative mechanisms were identified that shape researchers' decision-making regarding economic considerations: (1) the *Professional Norms*, operating through a reinforcing loop that systematically prioritizes clinical validation while marginalizing economic considerations; (2) the *Researcher Experience*, revealing how professional training and limited economic literacy create cognitive biases that obscure economic factors; and (3) the *Adoption Uncertainties*, demonstrating how implementation concerns influence development decisions through both reinforcing and balancing dynamics. These mechanisms explain why, despite growing recognition of the importance of economic evidence, economic considerations remain peripheral in researchers' decision frameworks.

Conclusions: This study reveals complex interactions between institutional structures, intrapersonal factors, and implementation uncertainties that systematically deprioritize economic considerations in DTx development. The identified mechanisms provide valuable intervention points for strengthening the development process, toward a more comprehensive assessment of clinical, technical, and economic value throughout DTx lifecycle, ultimately enhancing their adoption in healthcare systems.

Keywords: digital health; digital therapeutics; economic evaluation; cost-effectiveness; qualitative study; decision-making; critical realism; decision theory; system dynamics.

6.2. Background

6.2.1. Context

DTx represent a transformative shift in healthcare delivery, offering software-driven, evidence-based therapeutic interventions that prevent, manage, and treat a diverse spectrum of medical conditions (Sverdlov et al., 2018). These digital solutions, ranging from mobile applications to virtual reality environments, are designed to improve patient outcomes through evidence-based therapeutic interventions. The promise of DTx lies in their ability to provide accessible, scalable, and personalized interventions. For instance, mobile applications can deliver cognitive behavioral therapy for mental health conditions, while virtual reality environments may assist in pain management or rehabilitation (Betz et al., 2024; AppliedVR Inc., 2022). This emerging class of medicine can potentially reach underserved populations, provide continuous support between clinical visits, and generate real-time data for healthcare providers to optimize treatment plans.

In the context of global population aging and the concomitant rise in chronic and mental health conditions, DTx offer the opportunity to improve patient outcomes while potentially mitigating the escalating costs associated with traditional healthcare delivery. However, notwithstanding their potential, the literature is unanimous: the adoption of these therapeutics remains low across countries and healthcare systems, with limited integration of DTx into access and care pathways (Cirkel et al., 2024; Johnson et al., 2024; Prodan et al., 2022; Wang et al., 2023; Williams et al., 2020).

The path from concept to market implementation is marked by unique levels of complexity, which differentiate DTx from conventional pharmaceutical drugs and medical devices. These complexities stem from the rapid pace of technological

evolution[2] and the intersection of software development with clinical validation requirements. Additional challenges include the “regulatory gap” in approval and reimbursement processes across countries, and the numerous decision-making processes involving multiple stakeholders from different disciplines (Iqbal & Biller-Andorno, 2022; Williams et al., 2020; Kim et al., 2024).

6.2.2. Determinants of and barriers to DTx adoption

With healthcare systems under pressure to “do more with less”, robust clinical and economic evidence is critical for DTx to be considered for regulatory and reimbursement decisions (Keogh et al., 2024; Labinsky et al., 2023; Lumbreras et al., 2024; Prodan et al., 2022; Kim et al., 2024). Prodan et al. (2022, p. 1) highlighted that to be “*integrated into reimbursement systems, countries require DTx manufacturers to demonstrate clinical value and cost-effectiveness*.”

Recent studies have also underscore that economic factors related to a DTx intervention - such as costs, funding, and resources - have been identified as both barriers and facilitators to adoption and use (Vicki et al., 2020). However, relatively little is known about the capacity of DTx to provide economic value in care (HealthXL, 2021; Kario et al., 2021; Sapanel et al., 2023). Recent recommendations for bridging the gap between digital health tool development and implementation emphasize integrating economic considerations into the early stages of technological development (Keogh et al., 2024).

Recent research has extensively examined decision-making in healthcare innovation (Murray et al., 2016; Nghiem et al., 2023), yet significant knowledge gaps persist regarding stakeholders' approaches to economic decisions in DTx

[2] Three facts illustrate this rapid technological evolution: (1) The number of registered clinical trials worldwide for DTx increased from fewer than 100 in 2016 to over 1,000 in 2023, demonstrating both increased investment in DTx development and a growing emphasis on clinical validation; (2) The number of FDA submissions for digital health products in the USA rose from approximately 40 in 2012 to over 350 in 2023, representing nearly a 900% increase in just over a decade; (3) The DTx global market is projected to grow from $3.4 billion in 2021 to $12.1 billion by 2027, representing a CAGR of 31.4%.

development[3]. Although the literature offers valuable insights into clinical decision-making processes (Keogh et al., 2024; Kim et al., 2024) and technical development frameworks (Carrera et al., 2024; Kim et al., 2024), the intersection of economic considerations with these domains remains understudied.

This gap is particularly significant given the unique characteristics of DTx development. This process is characterized as complex interventions resulting from the intricate interactions of multidisciplinary teams with diverse skills and expertise, and numerous decision-making processes (Murray et al., 2016; Williams et al., 2020; Gomes et al., 2022). A DTx development process often involves software developers, clinicians, regulatory specialists, behavioral experts, and business strategists, each contributing to different aspects of the product lifecycle. The need for interdisciplinarity expertise creates complex stakeholder dynamics and distinct decision-making challenges not fully captured by traditional healthcare innovation frameworks.

6.2.3. Stakeholders' role in driving DTx economic impact

Our previous GCM study has explored further the role of diverse stakeholders involved in DTx development in driving its economic impact (Sapanel et al., 2025). The study identified 59 factors, grouped into eight thematic clusters, that are conceptualized and perceived to influence the economic value of DTx. For each of these factors, healthcare professionals, researchers (including research-engineers, healthcare management and economics researchers, behavioral scientists, and regulatory scientists), industry and public representatives were asked to evaluate (1) their perceived importance in influencing DTx economic value; and (2) the extent to which these factors were considered in day-to-day decision-making throughout the DTx lifecycle.

[3] Throughout this study, the term “DTx development” is used to encompass both the technological development process and subsequent clinical validation through interventional trials.

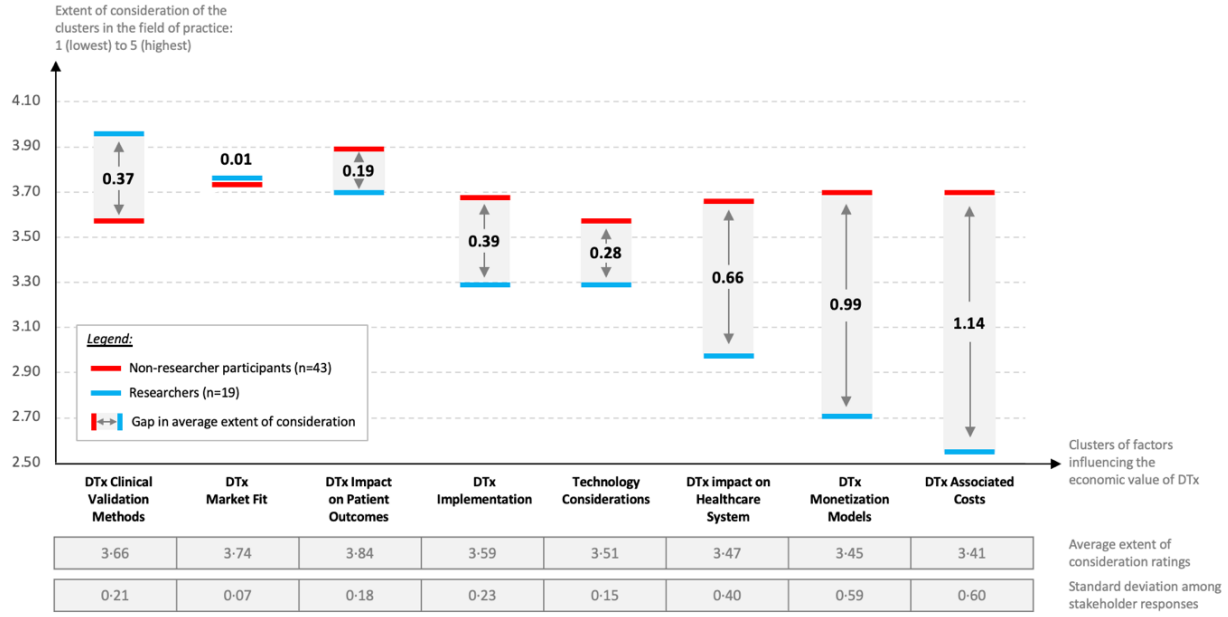
Figure 17 summarizes the study's findings, illustrating the different levels of consideration of factors in the decision-making processes of researchers compared to other study participants during DTx development. Three key findings emerged:

- **Decision-Making Complexity**: The study identified 59 distinct factors that influence the economic value of DTx. This multiplicity of factors demonstrates the intricate nature of decision-making within the DTx ecosystem, raising essential questions regarding stakeholders' awareness of these factors and their approaches to consideration and prioritization;

- **Variance in Factor Consideration**: Researchers displayed greater variability in how they considered different factors (SD=0.50) compared to non-researchers (SD=0.17), suggesting a less uniform approach across the factor spectrum among the research community;

- **Differences in Factor Prioritization**: A clear pattern emerged wherein researchers almost consistently assigned lower average consideration ratings to specific factors and clusters of factors compared to other stakeholder groups. While researchers placed higher emphasis on technical validation in clinical trials, they consistently gave lesser consideration to economic and implementation factors compared to their non-researcher counterparts. Notably, in the "*DTx Associated Costs*" cluster (encompassing direct and indirect expenses) and "*DTx Monetization Models*" cluster (comprising go-to-market and monetization strategies), the differential between researchers and non-researchers approached or exceeded one point on the five-point scale.

Figure 17. The average extent of consideration of clusters of factors influencing the economic value of DTx: researchers vs. non-researcher participants (Sapanel et al., 2025)



This figure depicts the gap in consideration between researchers (n=19, blue lines) and non-researchers (n=43, red lines) across eight clusters of factors influencing DTx economic value. While researchers placed higher emphasis on technical validation in clinical trials, they consistently gave less consideration to economic and implementation factors compared to their non-researcher counterparts.

As Figure 17 demonstrates, researchers consistently prioritize technical validation while giving considerably less consideration to economic and implementation factors, such as costs and monetization models, where the gap between researchers and non-researchers is most pronounced (approaching or exceeding one full point on the five-point scale). These findings highlight the divergent perspectives among stakeholders throughout the DTx development cycle regarding factors that influence economic value creation. The observed disparity between researchers and other DTx stakeholders raises questions about underlying causes. One potential explanation lies in researchers' primary focus on early-stage DTx development—specifically research, knowledge generation, and initial clinical validation—rather than implementation. This pattern suggests that researchers' emphasis on foundational development phases may influence their consideration of economic factors.

6.2.4. Knowledge gap and research objective

While researchers play a crucial role in establishing the scientific foundation and clinical efficacy of DTx solutions (Wang et al., 2023), their limited consideration of economic factors could potentially impact downstream commercial viability and healthcare system integration. Despite economic evidence being critical for adoption, there remains limited understanding of how stakeholders approach economic decisions in DTx development, particularly how researchers' early-stage decision-making impacts downstream value creation. Existing research has examined healthcare innovation decision-making broadly, but significant gaps persist regarding DTx specifically, with their unique interdisciplinary nature and complex stakeholder dynamics.

Thus, the following initial research question is raised: **How do researchers approach decision-making regarding factors that influence the economic impact of a DTx during its technological development and clinical validation phases?**

The knowledge gap motivated us to investigate how researchers approach decisions that influence the economic value of DTx interventions. For this reason, this study examines researchers' decision-making processes throughout the DTx development through qualitative research and through the lens of decision theory (DT). DT serves as what Fletcher (2017) terms an “initial theory” - providing a framework for understanding how researchers navigate complex choices, particularly when balancing economic value against technical and clinical requirements. Such initial theoretical frameworks are invaluable starting points that, as Fletcher notes, help us get “closer to reality” (2017).

The study has theoretical and practical revelatory contributions, meaning that the “*contribution arises when theory reveals what we otherwise had not seen, known, or conceived”* (Nicholson et al., 2018, p. 208). First, it contributes to developing new insights about healthcare innovation decision-making research, understanding the decision-making process of researchers involved in a DTx development, and how

they approach economic considerations. Second, it investigates causality and generative mechanisms influencing researchers' decision-making. Third, this leads to a series of practical recommendations for adapting DTx development practices toward a more iterative and integrated process, incorporating considerations that will enable DTx to generate economic value. As noted earlier, this is fundamental as DTx need to deliver economic value to decision-makers (e.g., public and private payers, regulators, and care providers). Such evidence is important to facilitate decisions around market access, pricing, and reimbursement for these technologies (Kolasa & Kozinski, 2020; Yan et al., 2021).

The remainder of this research paper is organized as follows: The next section establishes Critical Realism (CR) as an epistemological framework for examining both observable decision-making practices and their underlying mechanisms. Following this, the literature review synthesizes healthcare innovation decision-making frameworks. The methodology section outlines the qualitative approach used to analyze 17 in-depth researcher interviews. These interviews reveal the mechanisms influencing researchers' decision-making processes, which are presented in the Results section. The paper concludes by discussing theoretical implications and suggesting directions for future research.

6.3. Epistemological Framework: Critical Realism

The qualitative research is informed by CR, which emerged as an alternative, or "Third Way" (Wainwright & Forbes, 2000) between the two dominant second-half 20th-century social science philosophies: post-positivism and interpretivism (Bhaskar, 2008; Groff & Morgan, 2023; Monaghan, 2024). While post-positivism focuses on empirically observable facts, and interpretivism emphasizes subjective meanings through idealism, CR offers a middle path between them, as it distinguishes between reality and the "observable" world, acknowledging what scholars term the ontological depth of reality (Putri et al., 2023).

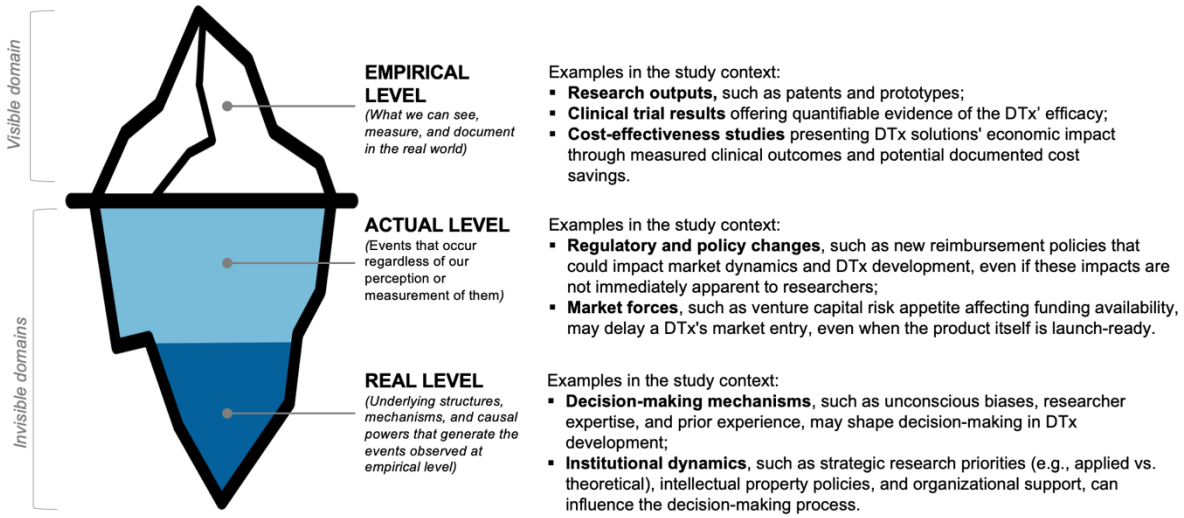
Drawing on Fletcher's iceberg analogy (2017), CR views reality as an iceberg, where most of reality remains invisible to the observer (Figure 18). In CR's foundational text, Bhaskar (2008) established three interconnected domains of reality that help us understand this depth:

- **Empirical**: This domain captures the perceptions, feelings and experiences of the researchers as they navigate the DTx development process. It represents only the most surface level of the observable reality.

- **Actual**: This domain refers to events or phenomena that occur, independently of the researchers' awareness or interpretation. While these events are concrete occurrences, they emerge from deeper causal powers.

- **Real**: This domain contains the causal mechanisms that generate observable events (also known as outcomes) in the "actual" and shape experiences. These mechanisms operate whether they are activated or perceived, such as institutional pressures for commercialization manifested through performance metrics, underlying power dynamics between academic and commercial interests, or structural economic constraints that influence priorities. These mechanisms, while not directly observable, can be theoretically identified through their manifestation in events and experiences.

Figure 18. Fletcher's three-layered "iceberg" of critical realism applied to the research study context



The figure illustrates the three levels of reality in CR: the visible "Empirical" level showing observable outcomes like clinical trial results, the "Actual" level representing events occurring independently of observation, such as policy changes, and the submerged "Real" level containing underlying causal mechanisms like institutional dynamics and unconscious biases that generate all observable events.

Recent research has demonstrated CR particular relevance for social studies of health, illness, and medical settings (Khanna et al., 2023; Monaghan, 2024), as well as in information systems research (Oseni et al., 2023; Stohr et al., 2024).

Theory plays a central role in CR research as Mercier et al. (2023, p. 2) emphasized, because "*theories represent our explanations of what occurs at the real level.*" While Fletcher (2017) notes that CR investigations necessarily begin with theory-guided problems or questions, Bhaskar (2008) wisely cautions against overly rigid commitment to the content of specific theories.

These theoretical foundations guided the refinement of the initial research question: **What are the underlying mechanisms and contextual conditions that shape researchers' decision-making processes regarding economic factors perceived to influence a DTx economic value in its technological development and clinical validation, and how do these manifest in practices?** This question captures more specifically decision-making under uncertainty - a core focus of DT - while reflecting CR's three levels of reality: underlying mechanisms in decision-

making (real domain), contextual conditions (actual level), and manifestation in practices (empirical level).

Having established CR as the research study's epistemological framework, we can now examine more in-depth how researchers navigate the complexities of DTx development.

6.4. Literature Review

6.4.1. Decision theory

DT provides a comprehensive foundation for analyzing complex choice-making processes under uncertainty – a central challenge in healthcare innovation. DT helps us understand both the observable patterns in researchers' choices and the underlying mechanisms generating them by drawing on principles from economics (Danermark et al., 2005), psychology (Tversky & Kahneman, 1974), statistics (Raiffa, 1968), and medicine (Bleichrodt & Pinto, 2000).

In healthcare innovation, DT encompasses both normative and descriptive approaches (Rhodes & Lancaster, 2019). The normative perspective outlines how decisions should ideally be made to optimize outcomes, while the descriptive perspective explains how decisions actually occur made in practice, often influenced by biases and limitations (Rapoport, 1989). The theory bridges two major frameworks: Expected Utility Theory (EUT) and Behavioral Decision Theory (BDT). Together, these complementary perspectives offer a holistic view of decision-making, capturing both the idealized rational process and real-world challenges researchers face in healthcare environments.

The normative component: Expected utility theory

EUT is a major theory of decision-making under risk (Takemura, 2021) developed by von Neumann and Morgenstern (1944). It offers valuable insights into optimal decision-making under uncertainty—a persistent challenge in healthcare (Ruger,

2007; Watkins, 2020). EUT posits that individuals make decisions by evaluating the probability and utility (satisfaction or value) of each possible outcome. The theory expresses rational choice mathematically as the maximization of expected utility, calculated by multiplying the utility of each outcome by its probability, providing a weighted average of utility outcomes while accounting for inherent risks and uncertainties of DTx development.

In healthcare, this theoretical framework takes on practical significance, as patient outcomes are aimed to be maximized. In DTx development, researchers must weigh multiple factors: potential for improved health outcomes against various risks, including possible clinical trial failures, regulatory hurdles, and market acceptance challenges. The process of developing and validating DTx thus exemplifies how EUT's principles manifest in real-world healthcare innovation, particularly through structured evaluation frameworks like HTA.

HTA framework in healthcare decision-making

HTA provides a systematic approach to evaluating new pharmaceutical treatments, medical devices, and digital health technologies, such as DTx, weighing potential benefits—typically measured in QALYs—against associated costs (Tummers et al., 2020). It helps decision-makers balance benefits against risks while considering their broader implications. This evaluation systematically considers multiple components: (1) direct costs (e.g., software development, clinical validation, regulatory compliance), (2) indirect costs (e.g., infrastructure requirements, training needs, implementation support), and (3) intangible factors (e.g., user acceptance, healthcare system integration, data privacy considerations).

While EUT provides a theoretical foundation for decision-making under uncertainty, HTA translates these principles into a practical methodology for evaluating healthcare technologies. It provides a structured approach to systematically evaluate alternatives, quantify outcomes, and assess probabilities—key elements of utility maximization in healthcare—while accounting for the multi-stakeholder complexity. HTA effectively operationalizes EUT’s theoretical principles while

offering practical guidance for technology assessment (2018). Consequently, many countries, including Germany and the UK, mandate HTA evaluations for DTx market access.

EUT limitations in real-world healthcare decision-making

Despite providing a structured methodology for evaluating complex healthcare decisions, EUT faces several practical limitations (Buchak, 2017). The theory's assumption of rationality conflicts with bounded rationality, where decision-makers operate under cognitive constraints, time pressure, and biases (McCaughey & Bruning, 2010). Healthcare professionals, including researchers, often work with incomplete or ambiguous information, making it difficult to accurately assess probabilities and expected outcomes. This challenge becomes particularly acute in early DTx development stages, where researchers may only have initial concepts or prototypes, and historical data may be limited or not directly applicable to novel digital interventions. The theory's requirement for precise utility quantification becomes therefore particularly challenging in healthcare settings, where outcomes can be multidimensional and difficult to reduce to a single utility measure, and fraught with many uncertainties (Plsek & Greenhalgh, 2001).

The complexity of healthcare decisions, involving multiple stakeholders with diverse interests, further challenges the theory's assumption of unified utility maximization. The theory also struggles to account for the heuristic decision-making that often characterizes healthcare practice, as well as organizational constraints and influences (Kozlowski et al., 2017). These limitations suggest that while EUT provides valuable theoretical insights and a structured framework for decision analysis, especially through HTA frameworks, its practical application must be complemented by approaches that account for healthcare decision-making complexities.

The descriptive component: Behavioral decision theory

Grounded in BDT, the descriptive approach examines how researchers make decisions, acknowledging inherent human biases and limitations. It enriches understanding by incorporating psychological insights into the decision-making process.

BDT reveals several key phenomena that influence healthcare decision-making. Bounded rationality is central to BDT (Hernandez & Ortega, 2019; Takemura, 2021). It acknowledges that rationality is limited when researchers make decisions, under cognitive and resource constraints, researchers tend to select satisfactory rather than optimal solutions. Researchers' judgment can be influenced by cognitive biases - referred to as the rationalist paradigm for decision-making (Croskerry, 2003). These include optimism bias (underestimating the technical complexity of integrating clinical requirements) (Weinstein, 1980), pro-innovation or technology-first bias (prioritizing technical performance over user accessibility) (Greenhalgh, 2013) and selection bias (designing inclusion criteria that fail to represent real-world patients) (Tripepi et al., 2010). These biases are shaped by researchers' backgrounds and experience, such as differences between those with engineering backgrounds versus practicing physicians (Saposnik et al., 2016).

The bounded rationality of decision-makers within organizations can be further influenced by contextual factors that shape decisions. These contextual elements—organizational structures defining authority and communication, stakeholder relationships creating political pressures, and environmental constraints limiting options—interact with cognitive limitations and behavioral biases to produce decisions inconsistent with rational models (Camerer & Malmendier, 2012).

BDT also explains how researchers use heuristics – mental shortcuts – to navigate decisions under uncertainty and time pressure (Kahneman, 2011; Desmond et al., 2013). The representativeness heuristic, for example, suggests that researchers might base judgments on similarity to experiences or stereotypical scenarios (e.g., if previous DTx showed a 30% dropout, similar rates might be expected for future

DTx). Understanding these heuristics is crucial in healthcare innovation, where decisions must often be made with incomplete information and significant time constraints.

BDT limitations in healthcare decision-making

The theory's emphasis on individual cognitive processes and biases may not fully capture the complexity of healthcare decision-making, where institutional and systemic factors play crucial roles. Indeed, Torbica et al. (2020) emphasized that institutional contexts and social values significantly shape how economic evaluations are used in healthcare decisions, suggesting a need for more comprehensive analytical frameworks.

The theory's limitations become particularly apparent when considering the complex regulatory frameworks and established clinical practices within which healthcare organizations operate. These systemic constraints often override or reshape individual behavioral tendencies. In DTx development, for instance, regulatory requirements and reimbursement policies frequently dictate decision pathways regardless of individual or group behavioral patterns.

Finally, BDT's treatment of expertise and professional judgment presents another limitation. While the theory excels at identifying cognitive biases, it may underestimate the value of accumulated professional experience and domain expertise in healthcare settings (Ozer et al., 2019). Healthcare researchers often develop sophisticated mental models and decision-making frameworks that, although appearing to deviate from rational choice principles, may represent highly effective adaptations to healthcare environments.

Decision theory framework synthesis

As Desmond et al. (2013) note, decision-making in healthcare innovation encompasses various strategies employed under different circumstances. The integration of normative and descriptive components creates a robust theoretical foundation that captures such complexity by defining optimal decision-making

approaches while accounting for human tendencies and real-world complexities in healthcare innovation. This dual perspective is particularly relevant when examining how researchers navigate economic considerations in DTx development, where decisions emerge from an intricate balance between rational analytical approaches (EUT) and the inevitable influence of behavioral and contextual factors (BDT).

The intersection of these theoretical frameworks, however, also reveals important tensions that warrant careful consideration in healthcare innovation contexts. EUT foundational assumption of utility maximization often conflicts with BDT recognition of bounded rationality. This tension may manifest distinctly in early-stage DTx development, where researchers face multiple challenges: incomplete information about potential outcomes, unclear utility functions that challenge EUT relevance, and organizational pressures that align more closely with BDT descriptive approach. For example, when evaluating potential clinical endpoints for a DTx intervention, researchers must balance the theoretical optimum against practical constraints, such as measurement feasibility and user engagement.

The synthesis of these theoretical frameworks informs the research approach by highlighting areas for investigation, as outlined in Table 16. This theoretical foundation supports analysis through multiple lenses: evaluating theoretically optimal decisions suggested by EUT, considering the behavioral influences highlighted by BDT, and exploring how these perspectives manifest in real-world DTx development settings.

Table 16. Relevance of decision theory in the context of the research question

Theoretical Foundation	Core principles	Relevance to the Research Question
Expected Utility Theory (EUT)	• Rational decision-making based on utility maximization; • Systematic quantification of utility (e.g., health outcomes) through HTA; • Evaluation of risk and uncertainty.	• Provides a framework for rational decision-making under uncertainty, offering standardized approaches for generating and evaluating evidence; • Guides the evaluation of technological and clinical factors using economic models (such as HTA) to maximize utility and optimize health outcomes; • Informs decision-makers in resource allocation during technology development and validation.
Behavioral Decision Theory (BDT)	• Cognitive biases and decision heuristics; • Bounded rationality; • Contextual dependence of decisions.	• Cognitive biases may lead researchers to overestimate benefits or underestimate risks, skewing development decisions; • Affects how economic risks and clinical uncertainties are perceived, potentially influencing technology development and prioritization; • Highlights the importance of understanding the decision context and available information to distinguish between rational and satisfactory decision-making.

While DT provides valuable insights into how researchers approach complex choices in DTx development, it primarily focuses on individual decision-making and cognitive processes, and how rational "agents" should make optimal choices. However, DTx development involves multiple stakeholders, organizational structures, and environmental constraints within complex dynamic systems (Crosland et al., 2024), where researchers' decisions emerge from dynamic interactions rather than linear cause-effect relationships (Plsek & Greenhalgh, 2001). To fully understand these complex dynamics and interrelations and how they shape researchers' decision making, the theoretical foundation must extend beyond DT.

In a "*dynamic, evolving, and interconnected world"* Sterman (2006) invites scholars to adopt a more "*holistic, broad, long-term, dynamic view*" using systems thinking (ST) to understand such dynamic complexity. ST offers a complementary framework to DT that situates individual decision-making within broader systemic contexts, helping to comprehend how decisions emerge from and contribute to complex, non-linear interactions between stakeholders, technologies, and institutions (Peters, 2014). This perspective allows an examination of how

researchers' economic decisions both shape and are shaped by broader systemic structures and feedback loops, providing a more comprehensive understanding of the DTx development ecosystem. The following section explores how ST enhances the theoretical framework to comprehensively capture the complex dynamics underlying economic decision-making in DTx development.

6.4.2. Systems thinking: A framework for understanding complex healthcare decisions

ST provides a robust framework for understanding complex, multi-level systems where technological, individual, organizational, and broader contextual factors interact dynamically, influencing researchers' decision-making processes and ultimately DTx development trajectories (Plsek & Greenhalgh, 2001). These interactions over time create emergent properties that cannot be understood by examining components in isolation, making ST particularly valuable for comprehending the complexity of researchers' decision-making processes in DTx development.

In recent years, ST has increasingly been applied in healthcare innovation contexts to understand complex challenges that resist traditional linear analysis (Allahi et al., 2018; Carey et al., 2015; Chang et al., 2017; Crosland et al., 2024; Jadeja et al., 2022; Langellier et al., 2019; Lounsbury et al., 2015; Peters, 2014; Sterman, 2006). These applications include but are not limited to explanations of high-level problems in complex healthcare systems (Allahi et al., 2018), digital health technology implementation and adoption (Greenhalgh et al., 2017), and the effects of policy decisions on health outcomes (Jadeja et al., 2022; Langellier et al., 2019).

Among its contributions, ST introduces several essential concepts that enrich the understanding of DTx development beyond what DT alone can provide. First, emergence—the principle that system behaviors arise from interactions between components rather than from the components themselves—helps explain why DTx development outcomes often differ from those predicted by rational choice models. Second, non-linearity in system behavior reveals why seemingly minor decisions in

early DTx development stages can produce disproportionately large effects on clinical validation outcomes and economic viability. These systems concepts provide analytical tools to examine how researchers' economic decisions ripple through the complex DTx development ecosystem, producing both intended and unintended consequences that feedback to influence subsequent decisions.

Furthermore, ST provides valuable analytical tools for examining power dynamics in DTx decision-making—an important dimension that traditional DT often neglects. In the complex ecosystem of DTx development, power asymmetries between stakeholders significantly influence which economic considerations receive priority and how they are operationalized in development decisions. For instance, power imbalances between researchers and their funders, regulators, and healthcare payers can constrain research priorities by favoring certain metrics over others. The integrated theoretical framework incorporates these power dynamics by examining how system structures allocate decision authority, control resource flows, and establish legitimacy hierarchies that constrain or enable certain economic considerations.

As an analytical approach, ST significantly enhances analysis of how diverse stakeholders influence researchers' economic decision-making in DTx development. Moving beyond traditional stakeholder analyses that treat entities as having fixed, independent interests, ST examines the dynamic interdependencies among researchers, patients, clinicians, regulatory bodies, payers, and investors. These stakeholders form a complex network where changes in one entity's requirements ripple throughout the system. For example, when payers demand specific economic evidence, researchers may reshape their clinical validation strategies, which can alter patient enrollment criteria, potentially affecting result generalizability and ultimate market adoption. By mapping these stakeholder interdependencies through systems models, the study identifies bidirectional economic considerations between stakeholders, revealing feedback loops that either reinforce or counteract researchers' initial decision premises.

An advantage of integrating ST into the theoretical framework is its capacity to address the temporal dynamics of DTx development—an aspect often overlooked in traditional DT approaches. Langley (2013, p. 4) emphasized the "centrality of time" in process studies, noting that "*process conceptualizations offer an essential contribution to organization and management knowledge that is not available from most variance-based generalizations*." This temporal dimension is particularly relevant for DTx development, which represents a "temporally evolving phenomenon" (Langley et al., 2013). The development of DTx unfolds across multiple time horizons, from short-term tactical decisions to long-term strategic positioning, with economic considerations manifesting differently throughout these timeframes. ST, particularly through system dynamics (SD) modeling, allows us to identify and analyze the varying temporal scales of feedback loops in DTx development. By incorporating temporal dynamics into the analysis, how the tension between short-term economic pressures and long-term value creation is navigated by researchers can be better understood.

SD, developed by Forrester in the 1950s, is a methodology within ST that offers a structured approach for understanding complex systems through the identification of feedback loops, time delays, and non-linear relationships (Sterman, 2000). It uses simulation modeling to represent and quantify the impact of causal interrelationships between variables within a system, with the ultimate goal of understanding explaining their behaviors over time (Jadeja et al., 2022; Marshall et al., 2015).

SD studies can be carried out qualitatively or quantitatively (Carey et al., 2015; Peters, 2014). When data are limited, unreliable, or difficult to quantify, or if the study focuses more on understanding general system behavior patterns, such as explaining "*the problem in a better way*", a qualitative participatory approach is particularly well suited (Allahi et al., 2018). This approach "*engages stakeholders throughout the process ensuring that real-world circumstances are taken into account*" (Jadeja et al., 2022, p. 2). If a benefit of SD is to convert qualitative understanding into a quantitative approach, scholars tend to study SD and effects only qualitatively, a potential limitation of SD (Allahi et al., 2018).

SD tools, such as causal loop diagrams (CLDs), which are visual tools that map the relationships and feedback loops between different elements in a system, help capture the non-linear mechanisms and interactions of a complex system. Sterman (2000) argued that CLDs help capture hypotheses about the dynamic causes, represent the mental models of individuals, and communicate the important feedback loops that might lead to economic considerations being taken into account throughout the DTx development process. As Renmans et al. (2020) suggest, integrating ST through CLDs strengthens this research study approach by helping to comprehend the interdependencies between mechanisms and their operation through complex, interdependent variables.

Importantly, CLDs can enable the identification of intervention or leverage points, with potential "what if" scenarios, where interventions might produce substantial system change (Peters, 2014; Sterman, 2000). CLDs are of particular importance, as the complexity in systems, such as DTx development systems "*hinders our ability to discover the delayed and distal impacts of interventions, generating unintended side effects*" (Sterman, 2006, p. 1).

Connection to critical realism and decision theory

ST aligns naturally with the CR ontological depth (Mingers, 2014). While CR distinguishes between empirical, actual, and real domains, ST provides methodological tools to explore the mechanisms generating observable patterns. The feedback loops and structural relationships identified through SD, such as in a CLD correspond to what Bhaskar (2008) terms the "generative mechanisms" at the real level of reality. Mingers (2014) argues how both CR and ST can complement each other. He notes that CR can provide a more rigorous philosophical underpinning that ST lacks, while ST can provide clearer articulations of CR's stratified ontology, such as circular causality through positive and negative feedback loops (Mingers, 2014).

ST also complements and extends DT by situating individual decision-making within broader contextual structures, as noted earlier. While EUT provides normative

frameworks for optimizing decisions and BDT explains cognitive limitations, ST illuminates how these decision processes are embedded within and influenced by larger organizational and environmental systems (Sterman, 2006). This integration creates a more comprehensive framework for understanding how researchers navigate complex decision environments when developing DTx.

The integration of DT and ST creates productive theoretical intersections that enhance analytical capabilities beyond what either framework could provide independently. For instance, the heuristics that BDT identifies as shaping economic decisions can be understood as adaptive responses to system complexity rather than simple cognitive shortcuts. By explicitly cross-referencing concepts between DT and ST throughout the analysis, more nuanced interpretations of empirical findings can be developed, by which both individual agency in decision-making and the structural constraints and enablers that shape decision possibilities are acknowledged.

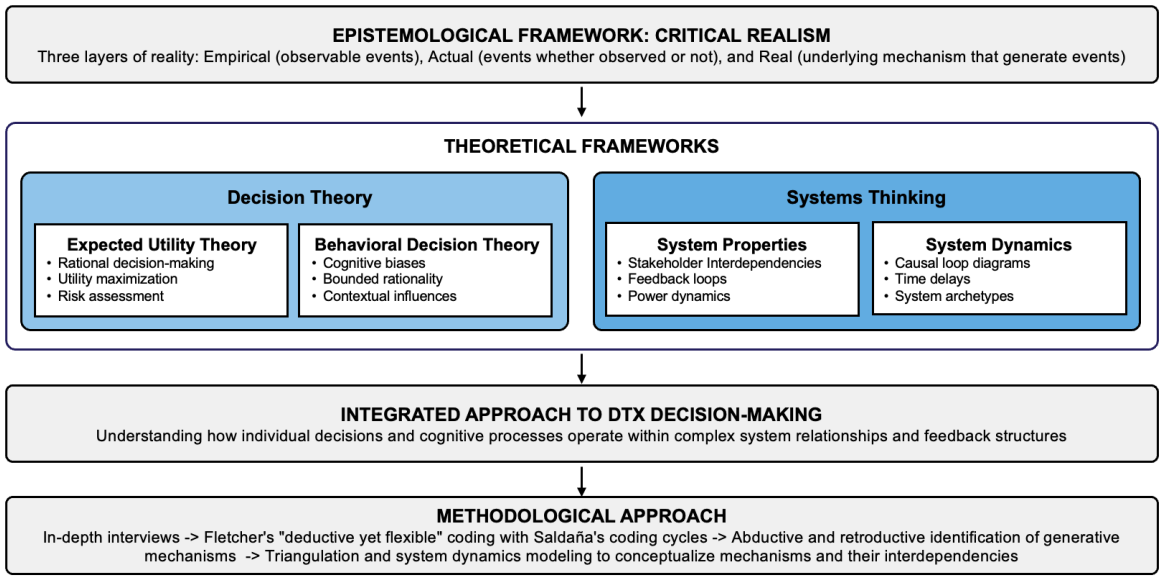
Theoretical framework synthesis

To conclude, the complex, multi-stakeholder nature of DTx development requires robust theoretical grounding to understand researchers' decision-making processes. DT, through its dual components of EUT and BDT, provides a comprehensive framework for analyzing both the underlying mechanisms and contextual conditions that influence researchers' decision-making. ST offers a natural extension to DT by providing conceptual tools to understand how individual decisions both influence and are influenced by broader system structures.

As illustrated in Figure 19, this study's integrated theoretical framework combines DT with ST within a CR ontology to comprehend researchers' decision-making processes. This integrated approach enables us to identify not just what economic decisions are made, but how they emerge from complex interactions between individual cognitive processes, organizational structures, and environmental contexts. Such understanding is crucial for identifying potential intervention points and developing more effective strategies for economically sustainable DTx

innovations that successfully navigate the complex pathway from concept to clinical implementation.

Figure 19. Integrated theoretical framework for researchers' decision-making in DTx development



This figure outlines an integrated theoretical framework for studying researchers' economic decision-making in DTx development. It illustrates how the CR's three layers of reality provide the epistemological framework for combining DT and ST to understand how researchers' decisions operate within complex system relationships, ultimately informing a methodological approach.

The theoretical frameworks have profound implications for the research study methodology. Rather than examining decision outcomes in isolation, the approach necessitates methods that can capture both the individual decision-making processes and the system properties that influence them. Practically, this means employing multi-level data collection strategies that document not only researchers' explicit decision criteria and frameworks but also the organizational structures, resource allocations, and environmental constraints within which these decisions occur. The adoption of SD tools like CLDs enables us to map these complex interrelationships and identify key feedback mechanisms that drive system behavior.

6.5. Methods

A qualitative, exploratory methodological framework was designed to examine how researchers understand and consider factors deemed to influence DTx economic value, as well as to uncover underlying generative mechanisms for such consideration and their operationalization at the DTx development phase.

6.5.1. Participant selection and recruitment

The decision-making processes of 17 researchers were investigated, including five (5) research-engineers, six (6) health systems and social science researchers, four (4) clinician-researchers, and two (2) practitioner-researchers (Table 17). A nonprobabilistic purposeful sampling procedure was used to identify and select participants based on their relevant experience within specific contexts (Palinkas et al., 2015), to facilitate comparative analysis, and to meet the following inclusion criteria: (1) a minimum of five years of experience in DTx development or clinical validation, (2) current involvement in the technological development or clinical validation of a DTx, (3) fluency in English or French. Initial recruitment occurred through the research team's professional network, with participants encouraged to refer qualified colleagues through snowball sampling.

The study was approved by the Ethics Boards of the National University of Singapore (certificate number: NUS-IRB-2023-399) and the University of Quebec at Montreal (certificate number: UQAM-CIEREH-2024-6028). Written informed consent was obtained from participants to engage either in-person or in web-based interviews. No compensation or incentive was provided. All interviews were audio-recorded and transcribed in their entirety. Interview data were securely stored on protected servers with access restricted to the research team. To ensure participant privacy and confidentiality, data were labeled with participant codes, and a separate secure list of code-to-name matchups was maintained. The study was conducted according to the Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines (Tong et al., 2007), as detailed in Appendix 3C.

Table 17. Demographic data of study participants

Pseudonym[a] *(participant number)*	**Field of practice**	**Experience across the DTx lifecycle**[b]			**Years of experience**	**Setting** *(country)*	**Gender**	**Education**
		1	2	3				
RESEARCH-ENGINEERS								
Emma *(P1)*	Biomedical engineering	x	x	x	> 10	Public academic institution *(Singapore)*	F	Ph.D.
Eva *(P2)*	Biomedical engineering	x	x	x	> 10	Public academic institution *(USA)*	F	Ph.D.
Ezra *(P3)*	Biomedical engineering	x	x		> 5	Public academic institution *(Singapore)*	M	Ph.D.
Eisa *(P4)*	Biomedical engineering	x	x		> 5	Public academic institution *(Singapore)*	M	Ph.D.
Elisabeth *(P5)*	Neuroengineering	x	x	x	> 10	Private healthcare organization *(Switzerland)*	F	Ph.D.
HEALTH SYSTEMS AND SOCIAL SCIENCE RESEARCHERS								
Sasha *(P6)*	Behavioral sciences			x	> 10	Public academic institution *(Singapore)*	M	Ph.D.
Sara *(P7)*	Healthcare management			x	> 10	Public academic institution *(Germany)*	F	Ph.D.
Senna *(P8)*	Health policy		x	x	> 5	Public academic institution *(United Kingdom)*	M	Ph.D.
Shiva *(P9)*	Health policy	x	x		> 5	Public academic institution *(Singapore)*	M	Ph.D.
Surya *(P10)*	Health economics	x	x	x	> 20	Public academic institution *(United Kingdom)*	M	Ph.D.
Santana *(P11)*	Health economics		x	x	> 10	Public academic institution *(Germany)*	M	Ph.D.
CLINICIAN-RESEARCHERS								
Christoph *(P12)*	Neuropsychology		x	x	> 20	Private healthcare provider *(Australia)*	M	Ph.D.
Cheah *(P13)*	Ophthalmology	x	x		> 10	Public healthcare provider *(Singapore)*	M	Ph.D.
Chevannah *(P14)*	Cardiology	x		x	> 10	Private healthcare organization *(Germany)*	F	Ph.D.
Camirah *(P15)*	Nursing	x	x		> 5	Public healthcare provider *(Singapore)*	F	Ph.D.
PRACTITIONER-RESEARCHERS								
Priscillah *(P16)*	Technology implementation	x	x	x	> 20	Public healthcare provider *(Canada)*	F	M.Sc.
Priyah *(P17)*	Technology implementation	x	x	x	> 15	Public healthcare provider *(Singapore)*	F	Ph.D.

[a] The pseudonyms are designed to convey key information about each participant. The first letter indicates their role: 'E' for research-engineers, 'S' for health systems and social science researchers, 'C' for clinician-researchers, and 'P' for practitioner-researchers. The last letter denotes their current work setting: 'A' for academic organization, and 'H' for healthcare providers or organizations (either private or public). The gender of the pseudonym corresponds to the participant's sex. For instance, the pseudonym "Christoph" (P12) signifies a male clinician-researcher working in a healthcare organization or provider.

[b] Phase 1 encompasses the technological development of the DTx intervention, followed by phase 2, the clinical validation of the DTx intervention through clinical trials, and finally phase 3 corresponds to the implementation of the DTx intervention in a real-world environment.

6.5.2. Data collection

Semi-structured interviews between April and September 2024 were conducted, either in-person or via video conferencing, lasting 30-60 minutes. This interview format balanced an exploration of existing literature on researchers' decision-making processes while allowing the emergence of novel insights. The interview guide (Table 18) covered topics including: (1) the participants' roles as DTx researchers, (2) their priorities and key considerations throughout the DTx lifecycle, and (3) their day-to-day prioritization and decision-making processes.

The interview questions evolved iteratively both within and between interviews throughout the data collection process. Early interviews revealed the importance of implementation considerations, leading to additional questions about how researchers anticipated and addressed implementation challenges. Similarly, emerging themes around professional training prompted new questions about how researchers' educational backgrounds influenced their approach to economic considerations.

Table 18. Interview topic guide

Topics	Guiding topics for discussion
Background and Opening Topics	• Professional background and role in DTx development • Current DTx project(s) context and stage • Professional training influences on economic decision-making approaches
Understanding of Economic Value *(Real to Actual Domain)*	• Personal understanding of DTx economic value • Experience with economic decision-making in DTx projects • Key considerations, priorities and decision-making drivers that guide DTx development • Organizational context and constraints
Contextual Conditions *(Actual Domain)*	• Market and regulatory environment • Resource availability and limitations • Stakeholder collaboration, influences and pressures • Organizational incentives and their influence • How uncertainty affects decision-making processes
Practical Implementation *(Empirical Domain)*	• Specific examples of economic decisions made • Implementation challenges and solutions • Success metrics and evaluation methods • Lessons learned from past decisions • Trade-offs between competing priorities • Balancing clinical versus economic considerations • Role of experience in decision-making • Group decision-making dynamics
Reflection on Practice	• Perceived effectiveness of current decision-making approaches • Challenges in translating economic considerations into practice • Tools or support needed for better decision-making • Recognition of potential biases or limitations • Evolution of the decision-making approach over time
Closing	• Additional thoughts on economic value considerations • Recommendations for other researchers • Reflections on ideal versus actual decision-making processes

Detailed field notes were taken during and immediately after each interview to capture non-verbal cues and emerging insights. Data collection continued until theoretical saturation, when additional interviews yielded no substantial new themes or insights and resulted in "*little or no change to the codebook*" (Guest et al., 2006, p.65; Saunders et al., 2018).

6.5.3. Data analysis

The data analysis followed a structured three-step analytical framework grounded in CR principles, as developed by Fletcher (2017). This approach progressed through coding and identification of demi-regularities, abduction, and retroduction—with each phase building upon the previous one. Throughout each analytical step, bi-weekly member checking with the research team and regular peer debriefing sessions were conducted to minimize potential bias and ensure analytical rigor. Table 19 outlines these key analytical steps, which uncovered the underlying mechanisms driving decision-making in DTx development.

Table 19. Data analysis methodology summary

Step	Description	Results
1. Coding and Identification of Demi-Regularities	• Creation of a "deductive yet flexible" (2017) coding framework combining DT concepts with DTx literature, while effectively capturing CR's stratified ontology. • Application of both deductive and inductive coding using ATLAS.ti software. • Implementation of Saldaña's cycles of coding methodology for systematic data analysis (Saldaña, 2021). • Adoption of Fletcher's approach to identify recurring patterns (demi-regularities) at the CR real level (2017).	• Expansion of the initial codebook from 58 to 78 distinct codes, as detailed in Appendix 3B. • Identification of three core themes as illustrated in Appendix 3D: (1) centrality of clinical evidence, (2) importance of considerations in implementation, and (3) absence of economic value consideration.
2. Abduction	• Implementation of Sætre and Van de Ven four-step abductive reasoning approach (2021): (1) observing puzzling facts in researchers' decision-making patterns, (2) confirming these anomalies with empirical evidence, (3) formulating explanatory hypotheses, and (4) evaluating alternative explanations.	• Iterative analysis of empirical data and theoretical literature revealed two puzzling patterns in researchers' decision-making: (1) strong prioritization of clinical evidence while consistently deprioritizing economic considerations (despite acknowledging their importance), and (2) significant focus on implementation factors that actually align with economic value domains in HTA frameworks, despite researchers' claims of neglecting economic considerations.

3. Retroduction	• Investigation of causal mechanisms using Danermark's framework (2005). • Analysis of dependencies and interactions between the identified mechanisms, validated via three complementary triangulation methods (data, iterative, and investigators) (Farquhar et al., 2020). • Visualization of complex relationships through SD and CLDs.	• Recognition of three primary generative mechanisms: (1) the *Professional Norms*, (2) the *Researcher Experience*, and (3) the *Adoption Uncertainties*. • Developed CLDs for each mechanism (Figures 22 to 24), mapping the variables and potential causal links, which ultimately converged into an integrated single model (Figure 24) explaining the interactions between identified mechanisms and their influence on DTx decision-making.

Step 1: Coding and identification of demi-regularities

A "*deductive yet flexible*" (Fletcher, 2017) coding process was implemented that synthesized theoretical foundations and existing literature, while also capturing CR's stratified ontology to develop the initial coding framework. This approach began with the creation of a theoretically informed codebook derived from multiple complementary sources.

First, key concepts from DT were extracted, specifically BDT and EUT, to develop foundational codes. These included "Bias > Availability heuristic" (capturing researchers' tendency to overestimate the likelihood of events based on recall ease) and "Probability > Probability calculations" (documenting objective and subjective probability assessments in DTx development decision-making). HTA principles from EUT were further incorporated, generating codes, such as "Economic Considerations > Economic evaluation methods" to document approaches for assessing DTx cost-effectiveness, including cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis.

Second, the theoretical framework was enriched by integrating findings from recent DTx development literature (Cirkel et al., 2024; Fassbender et al., 2024; Prodan et al., 2022; Sapanel et al., 2023, 2025; van Kessel et al., 2023; Williams et al., 2020; Kim et al., 2024). For example, "Economic Considerations > Funding sources" captured available financial resources and funding options that van Kessel et al. (2023) described as "vital" during and post-research DTx phases. Similarly,

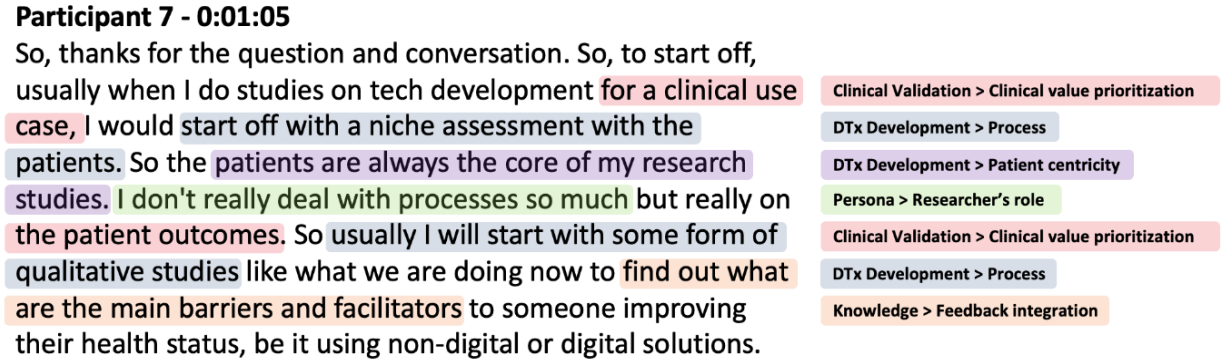
“Economic Considerations > Implementation related” documented researchers' awareness of practical deployment considerations, such as clinical workflow integration and provider training needs, which Cirkel et al. (2024) identified as primary barriers to DTx adoption.

To ensure philosophical alignment with the research approach, codes derived from CR tenets were integrated. These included “Knowledge Integration > Patient feedback integration” to document attempts to incorporate patient perspectives into the DTx development process, and “DTx Development > Patterns” to identify recurring approaches in development processes and decision-making.

Most codes appeared across multiple sources: theoretical literature, empirical research, and CR principles. For instance, “Bias > Overconfidence,” addressing the tendency to overestimate one's abilities and prediction accuracy, appears both in CR as a cognitive constraint and in BDT as a fundamental decision-making bias.

The initial codebook comprised 58 theoretically derived codes (Appendix 3B). This framework was applied to transcripts using ATLAS.ti software (ATLAS.ti Scientific Software Development GmbH). Throughout this iterative coding process, a comprehensive audit trail was maintained to document all coding decisions, rationale for code modifications, and the systematic evolution of the codebook from its initial 58 codes to the final framework of 78 codes. These memos served to support the validity of every stage of data collection and analysis (Sarah J., 2013). Figure 20 illustrates a representative sample of the coded transcript analysis.

Figure 20. Sample coded transcript



The above figure provides a sample coded transcript showing qualitative data analysis with color-coded thematic categories applied to a participant interview.

In alignment with CR principles, while the deductive approach provided theoretical foundations, an inductive process was incorporated to ensure an authentic representation of participants' perspectives (Roberts et al., 2019). To systematically analyze the data, Saldaña's cycles of coding methodology were applied throughout the coding process (2021).

The first coding cycle employed descriptive and in vivo coding methods to identify first-order codes that preserved participants' original language and captured basic descriptive elements of the data. This process led to the development of new codes, while some existing codes were combined or refined to better reflect participants' experiences. For example, "Knowledge > Patient Feedback Integration" was broadened to "Knowledge > Feedback Integration" to reflect participants' frequent reports of consulting physicians, nurses, and specialists. The notion of DTx adoption emerged early as a potentially important factor throughout the DTx process, leading to the creation of the "Implementation > Adoption" code. Through this iterative coding process, the framework expanded from 58 provisional codes to 78 distinct codes (Appendix 3B), demonstrating the iterative nature of the coding process (Fletcher, 2017). Throughout this process, detailed notes for each interview transcript were maintained, documenting key discussion points, interpretations, potential participant quotes and changes to the codebook.

These first-order codes were then aggregated during the second coding cycle using pattern coding and focused coding techniques to develop more conceptual second-order categories that represented broader analytical groupings. For example, several first-order codes, such as “Economic value awareness,” “Business model,” and “Clinical validation costs” were synthesized into the second-order category, “Economic considerations.”

This progression from participant verbatim, through concrete first-order codes, to abstract themes followed Saldaña's principle of “code weaving,” as illustrated in Appendix 3D, where codes were integrated into a coherent analytical narrative that connected empirical observations with theoretical constructs, thereby facilitating the identification of tendencies in empirical data (Fletcher, 2017) - what CR practitioners term “demi-regularities”, searching for recurring patterns in participants’ experiences and perspectives within the developed codes.

Through subsequent cycles of axial coding, enhanced by ATLAS.ti software's visualization tools—including word clouds and treemaps where code size dynamically reflects application frequency—commonly coded elements and their intricate relationships were systematically explored and mapped. This analytical approach enabled the establishment of connections between second-order categories, progressively distilling the data into eight third-order subcategories (Appendix 3D). These were ultimately consolidated into three overarching core themes discussed in the Results section: (1) the centrality of clinical evidence, (2) the importance of implementation considerations, and (3) the notable absence of economic value consideration.

Step 2: Abduction

Following CR principles, the analysis proceeded through complementary abductive (Step 2) and retroductive processes (Step 3) (Fletcher, 2017). Abductive reasoning is a process of forming explanatory hypotheses for less understood phenomena. Dunne and Dougherty (2016, p. 131) defined abduction or ‘retroduction’ as a form of “*reasoning that generates and evaluates hypotheses in order to make sense of*

puzzling facts." Sætre and Van de Ven (2021, p. 684) highlighted that abduction "*begins with observing and confirming an anomaly, and generating and evaluating hunches that may explain the anomaly, for subsequent deductive constructing and inductive testing.*" A concrete example illustrates abductive reasoning in a clinical trial of a new DTx for diabetes management. Initially hypothesized, based on a clinical trial, to improve glycemic control for all consistently engaged patients, the implementation revealed a nuanced reality: while 90% of patients demonstrated expected improved glycemic levels, 10% experienced worsening glycemic control despite high app engagement. This unexpected finding prompts abductive reasoning, with a series of exploratory hypotheses: Could these patients have a different pathophysiological subtype of diabetes? Might the app's algorithm recommendations be inappropriate for certain dietary patterns? Are these patients experiencing alert fatigue leading to decision paralysis? Or could the interface design create cognitive barriers for users with specific cognitive styles or health literacy levels? Critically, abductive reasoning does not produce definitive answers but suggests plausible explanations that warrant further investigation.

Sætre and Van de Ven (2021) four-step approach was adopted for the abductive reasoning process, which they note, "*may overlap, iterate, and unfold in stochastic ways over time*." The first step involves observing anomalies or puzzling facts in the empirical data that might not align with initial assumptions or existing models and thus remain unexplained. The second step confirms that such anomalies exist and are grounded in evidence, defining what is known or unknown about them. The third step involves formulating hypotheses or generating hunches that may provide plausible explanations for the anomalies. The final step consists of evaluating these hunches and alternative explanations.

Through this process, the iterative movement between empirical data and theoretical literature identified potential puzzling facts and initial patterns in researchers' decision-making processes. The Results section reconceptualizes and redescribes these puzzling facts and provides plausible explanations for these observations.

Step 3: Retroduction

Through retroduction, the final stage of CR analysis, the causal mechanisms and conditions underlying the observed patterns in researchers' decision-making (Oseni et al., 2023; Sayer, 1992) were investigated. Retroduction involves reasoning from observed demi-regularities to the underlying structures and causal powers that make them possible (Bhaskar, 2008). These mechanisms, defined by Bhaskar (2008) as the causal structures that trigger events or outcomes, represent the layer of the "actual". This investigation revealed deeper causal powers and structures producing observable phenomena, moving beyond surface-level correlations or patterns. The analysis specifically examined interrelated mechanisms that either stimulate or constrain the consideration of economic factors in DTx development.

Following Danermark et al.'s framework (2005), three fundamental questions were explored: How were these patterns in researchers' decision-making possible? What properties were essential to their existence? And what causal mechanisms drove them? This investigation involved iterative analysis of data from steps 1 and 2.

To illustrate the retroduction process, we examined the "absence of economic value consideration" demi-regularity - a robust observable pattern identified across 17 researchers from diverse backgrounds and contexts, with only one exception (Cheah, P13). Through retroduction, the following questions were raised: What underlying structures and causal powers make this absence not merely possible, but systematically reproduced across different researchers, institutions, and DTx projects? Why is this pattern so robust that it persists even when researchers acknowledge the importance of economic factors for implementation success?

The first alternative explanation examined was the knowledge deficit hypothesis, which predicted that economic training would eliminate the absence pattern. However, this was found to be insufficient as the sole explanation. Despite their expertise as health economists Surya (P10) and Santana (P11) were found to operate within institutional frameworks that marginalized economic considerations in DTx projects. The second alternative explanation tested was the individual

preference hypothesis, which predicted that some researchers naturally gravitate toward clinical/technical domains, while others prefer economic analysis. This explanation was also found to be insufficient, given the pattern's consistency across personality types, career stages, and disciplinary backgrounds. Even business-oriented researchers like Priscillah (P16) exhibited the same pattern of marginalizing economic considerations. The third alternative explanation was the rational temporal sequencing hypothesis, which predicted that researchers deliberately postpone economic considerations because early-stage technical uncertainty makes economic evaluation premature. This was falsified by data showing that strategic temporal decisions about when to introduce economic factors were not being made. Instead, satisficing behavior was exhibited, with researchers defaulting to familiar domains rather than systematically planning economic integration points.

This systematic explanation testing process revealed that no single-level explanation could account for the pattern's robustness. For each demi-regularity, such systematic and iterative questioning processes were implemented. Working backward from observed effects to theorize underlying causes was then undertaken, with mechanism propositions being iteratively tested against the data.

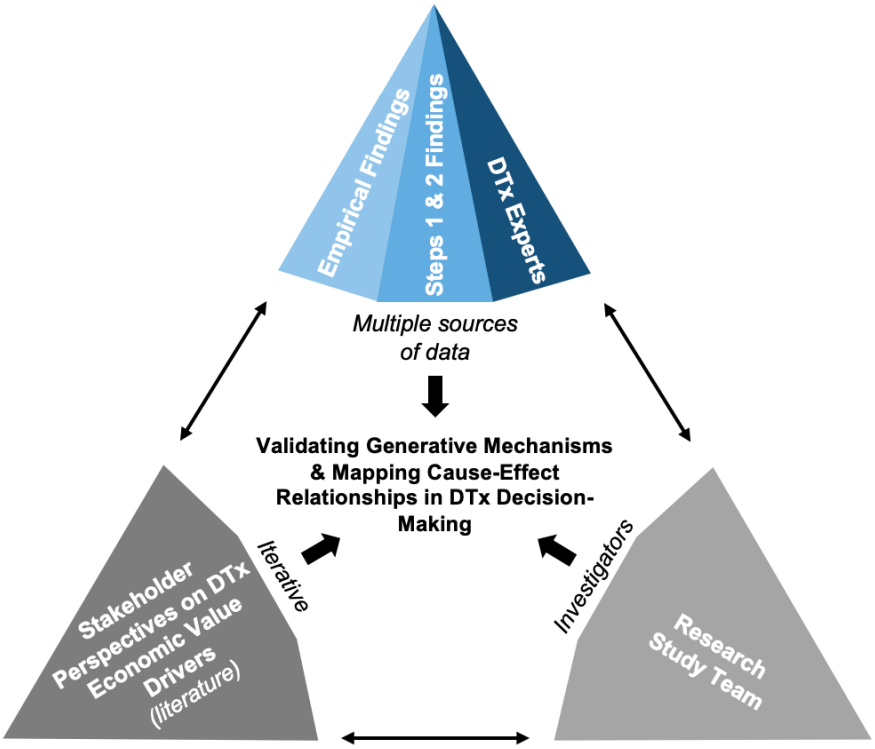
This process ultimately led to the identification of three primary generative mechanisms that best explain the observed patterns in researchers' decision-making practices: 1) the *Professional Norms*, 2) the *Researcher Experience*, and 3) the *Adoption Uncertainties*. These mechanisms are discussed in detail in the Results section.

Drawing on the methodological approaches of Lawani (2020), Stohr et al. (2024), and Nguyen et al. (2025), SD was applied to enhance understanding, visualize, and to articulate how these mechanisms and their components manifest and influence each other through causal relationships via a CLD. SD modeling has been used extensively in healthcare to better understand complex behaviors and interconnected challenges in healthcare technology development (Allahi et al.,

2018; Fernandez de Canete et al., 2019, 2019; Homer & Hirsch, 2006; Lounsbury et al., 2015).

To conceptualize these mechanisms and elucidate their interdependencies through a CLD, an iterative three-step process was implemented to: (1) identify influencing variables, (2) map relationships and assign polarity, and (3) validate and refine the model. Throughout each phase, three distinct categories of unit triangulation were incorporated (Farquhar et al., 2020), as illustrated in Figure 21.

Figure 21. Triangulation approach to validating mechanisms and mapping cause-effect relationships in DTx decision-making



This figure illustrates the approach combining multiple sources of data, iterative, and investigator triangulation to systematically validate the generative mechanisms and their relationships throughout the three-phase CLD construction process.

Step 1: Variable identification

The data triangulation involved comparing **multiple sources of data**, including the study's empirical findings from both steps 1 and 2, to identify potential variables and their relationships influencing researchers' decision-making processes. The

extraction of variables and their relationships from the research data incorporated both explicit participant statements about causal relationships and pattern analysis across interviews to ensure comprehensive relationship mapping. Each potential relationship was systematically evaluated against three evidence criteria: (1) explicit mention in participant interviews, (2) support in existing literature, and (3) logical consistency with decision-making theory. Relationships meeting at least two criteria were included in the model.

Step 2: Relationship mapping and polarity assignment

In parallel with variable identification, **iterative triangulation** included systematic comparisons with insights from the foundational study described in the Background section that shaped this paper's research question (Sapanel et al., 2025). This foundational study had previously identified variables, but also causalities of eight clusters of factors perceived to influence DTx economic value. This process allowed to compare literature findings and refine variables influencing researchers' decision-making process, and their interdependencies, leading to a CLD for each of the three generative mechanisms (Figures 22 to 24).

Relationship polarities (positive or negative) were established by analyzing directional influence between variables, supported by literature citations and participant quotes. Positive relationships indicate that variables move in the same direction—both increasing or both decreasing together. Negative relationships indicate opposite movements. Relationship strength (strong or weak) was determined by analyzing the frequency and emphasis of these connections within the data.[4]

[4] Weak versus strong causal links, or the "importance" of a relationship, is evaluated by both the frequency and intensity of identified connections. Causal links were categorized as "weak" when mentioned by only a minority of stakeholders (i.e., 1-2 researchers) or described by respondents using qualifying language such as having "somewhat" of an influence or being "emerging," "nascent," or "weak" in nature. Conversely, strong causal links met two critical criteria: broader stakeholder recognition (acknowledged by at least 3 researchers) and substantial supporting evidence (frequently emphasized in interview transcripts as having direct, significant impact on core system behavior).

Feedback loops were identified through manual loop tracing—specifically by tracing paths through the causal network diagram and identifying where variables connect back to themselves through a series of relationships. Common system archetypes that appear frequently across different domains were also sought, such as “limits to growth” or “fixes that fail,” with consideration given to the characteristics of their feedback structures (Clancy, 2018; Sánchez, 2024; Senge, 2006). Each loop was categorized as either reinforcing (R) or balancing (B) based on the product of polarities along the loop. Reinforcing loops amplify change in a consistent direction, creating exponential growth or decline patterns, while balancing loops counteract change and tend toward stability or equilibrium. Each loop was named according to its primary function within the system, with documentation of its constituent variables and potential impact on system behavior.

Step 3: Model validation and refinement

To validate and refine the model, as new versions of the CLDs emerged, they were discussed with the research study team through **investigator triangulation** to analyze and interpret findings, including reviewing codes when needed to ensure convergence. As part of the iterative process, discussions with three DTx experts who met the study inclusion criteria but were outside the original sample were scheduled at different time intervals to interpret, validate, and refine emerging versions of the individual mechanisms CLD (Figures 22 to 24), which over time converged into a single integrated refined CLD (Figure 24), illustrating the generative mechanisms and their manifestations shaping economic considerations in DTx development.

These three categories of triangulation served CR aims in developing deeper explanatory accounts while acknowledging knowledge limitations, ultimately capturing the complexity involved in the system of interrelated variables shaping researchers' decision-making and their considerations of economic aspects. This process facilitated the refinement and validation of identified generative mechanisms while visually mapping the cause-effect relationships underlying DTx decision-making processes (Stohr et al., 2024). Ultimately, this triangulation

approach aimed to achieve a higher degree of internal and external validity, strengthening confidence in the findings (Farquhar et al., 2020).

Methodological Safeguards

Multiple methodological safeguards were implemented to ensure the validity, reliability, and trustworthiness of the study findings.

Internal reliability was ensured through several analytical procedures (Sarah J., 2013): 1) biweekly peer debriefing sessions were conducted between research team members to review coded transcripts and establish consensus on emerging themes; 2) a comprehensive audit trail was maintained to document all coding decisions, modifications, and the systematic evolution of the codebook; and 3) iterative retroduction process was employed to test hypothesized generative mechanisms against empirical patterns.

External validity was established through triangulation approaches (Miles et al., 2019), whereby the analysis was grounded in established theoretical frameworks (CR, DT, ST) and findings were systematically compared with existing literature. The theoretical soundness of emerging CLDs was validated by three external DTx experts meeting study inclusion criteria at different analytical intervals, providing preliminary evidence of pattern recognition and transferability within the field.

These combined methodological approaches collectively establish the credibility and transferability of findings to similar research contexts.

6.6. Results

This section presents the results from the data analysis outlined in the Method section, including the emerging themes from step 1, puzzling facts and their plausible explanations from step 2, and three primary generative mechanisms retroduced at step 3.

6.6.1. Emerging themes (step 1)

The data analysis, conducted during the first step of *“Coding and Identification of Demi-Regularities,”* revealed three core aggregated themes, as illustrated in Appendix 3D.

First, the centrality of clinical evidence emerged as the most prominent demi-regularity, quantitatively corroborated by the highest coding frequency for the “Clinical Validation > Clinical value prioritization” code across the transcript corpus. Despite EUT's prediction that researchers would systematically evaluate all value components, participants consistently steered discussions toward clinical considerations. The predominance of clinical considerations became particularly evident through researchers' implicit interpretations of key terminology. When participants employed terms, such as “validation” and “generating evidence,” these consistently referenced clinical trials and clinical evidence generation rather than other forms of validation (technical or economic).

This clinically driven perspective extended to researchers' conceptualization of “value” of a DTx, which they predominantly viewed through the lens of clinical needs and safety/efficacy evidence. This pattern, which emerged consistently across clinician-researchers, was exhibited by most health systems and social science researchers and was frequently observed by practitioner-researchers. Notably, interviews with research-engineers revealed a more nuanced pattern. Within this group, technological “performance” of the DTx, and what one participant termed 'shiny engineering innovations' emerged as equally significant factors in their

decision-making frameworks. This variation suggests a potential disciplinary influence on value assessment approaches within DTx research and development.

Second, the importance of implementation considerations emerged as another major theme, revealing an interesting interplay between rational planning and behavioral responses to uncertainty. Participants consistently emphasized factors like “manpower utilization”, “workflow integration,” “care pathway changes”, clinical team “productivity” impacts, and “acceptability” from both patients and care teams. As Cheah (P13) explained, “*when you implement a [DTx] solution in a clinical setup, most likely it's not going to work out. Implementation is an issue, such as adherence and adoption of a technology*”. Emma (P1) elaborated on this perspective: “*There's obviously the medical value of the DTx, but it's also the workflow fit, and the human factors more broadly considered. What is the patient journey, where the solution is going to fit, understand the physician's decision making, their involvement, are the nurses involved?*”

Uncertainties surrounding implementation and adoption may foster risk-averse decision-making, potentially limiting innovation in traditionally conservative healthcare settings. Elisabeth (P5) emphasized the importance of balancing internal constraints to avoid “*overburdening some of the early thinking point*” while maintaining an innovative culture. She highlighted the critical role of the timing and innovation stage when incorporating various DTx components (clinical, technical, and economic).

This risk-aware approach could also drive more rigorous pre-implementation planning during early DTx development, including new frameworks for risk assessment and controlled experiments. The study findings revealed that researchers typically employ multiple validation approaches to address implementation uncertainties, including pilot studies, usability testing, and structured physician and patient consultations to comprehensively evaluate needs and perspectives.

Third, the absence of economic value considerations in early development stages emerged as a consistent pattern, reflecting the BDT's concept of bounded rationality in complex environments. With a single exception (Cheah, P13), both clinician-researchers and research-engineers consistently indicated that economic factors fell outside their priorities or perceived responsibilities. Researchers also expressed uncertainty about incorporating economic considerations into their DTx development processes. This pattern aligns with previous findings, where researchers reported giving lower consideration to economic-related factors compared to other stakeholder groups (Sapanel et al., 2025). Cheah (P13) stood as the sole exception, noting: "*In our ongoing study, the cost effectiveness of our model of care is the primary endpoint, and obviously, the secondary endpoints are actually the efficacy and safety to supplement prior evidence we have on those aspects*." This systematic de-prioritization of economic considerations in the sample deviates from the EUT's prediction of comprehensive utility maximization, creating potential blind spots in decision-making.

These demi-regularities suggest a complex interplay between rational decision-making frameworks and behavioral influences, with interesting tensions between EUT predictions and BDT observations, shaping how researchers approach DTx development decisions.

6.6.2. Puzzling facts and plausible explanations (step 2)

The second step of the abductive reasoning process identified puzzling facts and provided plausible explanations for them. A key empirical finding was researchers' predominant focus on clinical evidence, either as a single priority or combined with technological performance considerations in DTx development. Surprisingly, researchers focused almost exclusively on clinical benefits, leaving little room for other forms of value evidence, particularly economic considerations or process-oriented categories (e.g., DTx that enhance self-management capabilities, support informed decision-making, or reduce healthcare access barriers). This finding contrasts with researchers' acknowledged importance of such factors for successful

implementation (Sapanel et al., 2025), as well as with healthcare systems' evolution since 2008—from the “triple aim” of improving care, health, and cost (Berwick et al., 2008) to the “Quadruple Aim” framework that adds meaning at work. Modern healthcare frameworks recognize that, given limited resources, the economic aspects of healthcare delivery cannot be separated from clinical considerations. Germany's Digital Health Applications (DiGA) framework exemplifies this integrated approach, legitimizing “*patient-relevant improvements in structure and process*” alongside direct medical benefits when evaluating DTx for market approval (Goeldner & Gehder, 2024, p. 2).

The dominance of clinical evidence permits multiple theoretical interpretations. At its core, it likely reflects a deeply embedded institutional logics within healthcare, where clinical outcomes (such as mortality rates, complication rates, and treatment success) have historically served as the foundation of medical decision-making. Organizational structures and research priorities—whether oriented toward pure or translational research[5]—may influence researchers’ decision-making patterns.

Participants viewed economic considerations as outside their domain of expertise, expressing uncertainty regarding economic evaluations and their inherent complexity for DTx. This represents a form of constrained utility maximization where researchers optimize within familiar domains rather than across all value dimensions (clinical, technical, and economic). This selective optimization contrasts with EUT's prediction of comprehensive value assessment and maximization but aligns with BDT's concept of bounded rationality. While researchers wanted “their” DTx to be of use, their tendency toward “familiarity” was observed—defaulting to clinical metrics rather than pursuing comprehensive value assessments—and “satisficing behavior,” choosing the first option that meets minimum acceptability levels. As articulated by Camirah (P15): “*We tried doing some form of costing*

[5] An institution with a translational focus can be characterized as one that systematically transforms digital health innovations from conceptual research into evidence-based, regulatory-approved therapeutic interventions, with infrastructure and expertise spanning the entire development pipeline from early scientific discovery to real-world implementation. The degree of “translational” focus ultimately depends on the institute's balance between later-stage development activities (clinical validation, regulatory approval, implementation science) and earlier-stage research efforts (mechanism discovery, prototype development).

analysis, but we're having difficulties; we are not sure whether we are holistic enough in presenting the costings of this project to higher management. So that's something we are still struggling with. At this point, we may be throwing money into the ocean…"

The systematic deprioritization, or absence, of economic considerations throughout DTx development may be attributed to a lack of awareness of their importance at individual and/or institutional levels, particularly regarding later stages of the DTx process, including regulatory approval, implementation, and adoption. It can also be hypothesized that researchers were led back to more familiar domains by a certain level of economic literacy limitations in the interview sample. Moreover, most researchers conceptualized the DTx process as linear and chronological or sequential, though Senna (P8) characterized it as "iterative." They outlined a stepwise approach, beginning with ideation and problem identification, followed by technology fit assessment, workflow integration, and feasibility studies prior to clinical validation and implementation. This sequential decision-making framework may explain the deferral of economic considerations to later stages, further supporting the use of heuristic decision-making strategies outlined in the BDT framework.

Researchers consistently reported uncertainty surrounding DTx implementation and adoption as a potential "barrier" or "complexity," which led to the second major theme discussed above: the importance of implementation considerations and how they shape researchers' early decision-making. Their acknowledgment of these aspects as significant threats to DTx success was surprising (to the research study team). Although researchers reported that economic elements did not enter their decision-making process, many of the implementation-related aspects they did consider correspond to direct and indirect medical and non-medical costs associated with DTx in HTA terminology.

Indeed, the pattern of implementation prioritization aligns with important domains in HTA frameworks (Haverinen et al., 2024; Sapanel et al., 2023; Segur-Ferrer et al.,

2023). Although researchers reported limited consideration of economic factors throughout DTx development, the findings suggest, therefore, that certain aspects of DTx economic value may be more thoroughly integrated throughout DTx development than either articulated by the researchers or previously evidenced. Indeed, in prior research, the "*DTx Associated Costs*" cluster, focusing on various expenses associated with DTx intervention, was reported by researchers as the least considered cluster influencing DTx economic value (Sapanel et al., 2025). While this aligned with the empirical data of this study, the reinterpretation of these findings and contextualization within existing theoretical frameworks supports a more nuanced understanding.

In conclusion, the abductive analysis revealed key puzzling facts in DTx researchers' decision-making processes. They suggest a complex interplay between institutional logics, individual expertise boundaries, and conceptual frameworks regarding the DTx development process. This abductive step provided plausible explanations for these phenomena, which are further examined in the retroductive step (step 3) of the analysis to develop a deeper understanding of the underlying mechanisms and structures influencing DTx researchers' decision-making patterns.

6.6.3. Generative mechanisms (step 3)

As noted earlier, three primary generative mechanisms were retroduced to explain how researchers' approach to DTx development and their consideration of economic factors: (1) the *Professional Norms*, (2) the *Researcher Experience* and (3) the *Adoption Uncertainties*.

In this section, each mechanism is examined individually through CLDs, identifying respective variables (the measurable factors that can change within each mechanism) and their primary balancing (B) or reinforcing (R) loops. Primary loops are feedback loops that operate entirely within a single mechanism. These loops contain strong causal relationships between closely related variables and represent the essential dynamics within a distinct part of the system. Primary loops typically

demonstrate immediate and direct impacts on key system variables. Secondary loops, by contrast, connect across different mechanisms within the system, creating bridges between primary loops. These loops often contain at least one weak causal link and exert less direct influence than primary loops. Secondary loops reveal how effects propagate throughout the entire system, showing cross-mechanism interactions that create more complex emergent behaviors than would be visible from primary loops alone.

Building on each mechanism's CLD (Figures 22 to 24), an integrated model is presented in Figure 24, combining the three mechanisms into a comprehensive system. Based on this systems analysis, theoretical propositions are developed for each mechanism to explain how causal relationships influence researchers' decision frameworks. It should be noted that the term “causal” as used in this qualitative study does not imply statistical causation as established through experimental design or quantitative methods. Rather, it refers to theorized causal mechanisms and relationships that emerge from participants' lived experiences and narratives. This understanding of causality aligns with critical realist approaches that seek to identify underlying generative mechanisms while acknowledging the contextual, complex, and often non-linear nature of social phenomena (Fletcher, 2017). Also, weak versus strong causal links, or the “importance” of a relationship, is evaluated by both the frequency and intensity of identified connections. Causal links were categorized as “weak” when mentioned by only a minority of stakeholders (ie, 1-2 researchers) or described by respondents using qualifying language, such as having “somewhat” of an influence or being “emerging,” “nascent,” or “weak” in nature. Conversely, strong causal links met two critical criteria: broader stakeholder recognition (acknowledged by at least 3 researchers) and substantial supporting evidence (frequently emphasized in interview transcripts as having a direct, significant impact on core system behavior).

After examining each mechanism individually, cross-mechanism relationships and secondary loops (i.e., cross-mechanism loops) will be explored. For enhanced readability, mechanism names and variables appear in italics throughout the text.

The Professional Norms mechanism

The first mechanism, *Professional Norms*, refers how embedded healthcare norms and practices fundamentally influence the development trajectories of DTx. This mechanism operates through a reinforcing loop (R1) alongside an exogenous variable—the *comprehensiveness of funding requirements*—which influences the system but is not itself affected by other variables within the system diagram. These *Professional Norms* create self-perpetuating patterns that systematically prioritize clinical validation while obscuring other forms of complementary evidence or value dimensions.

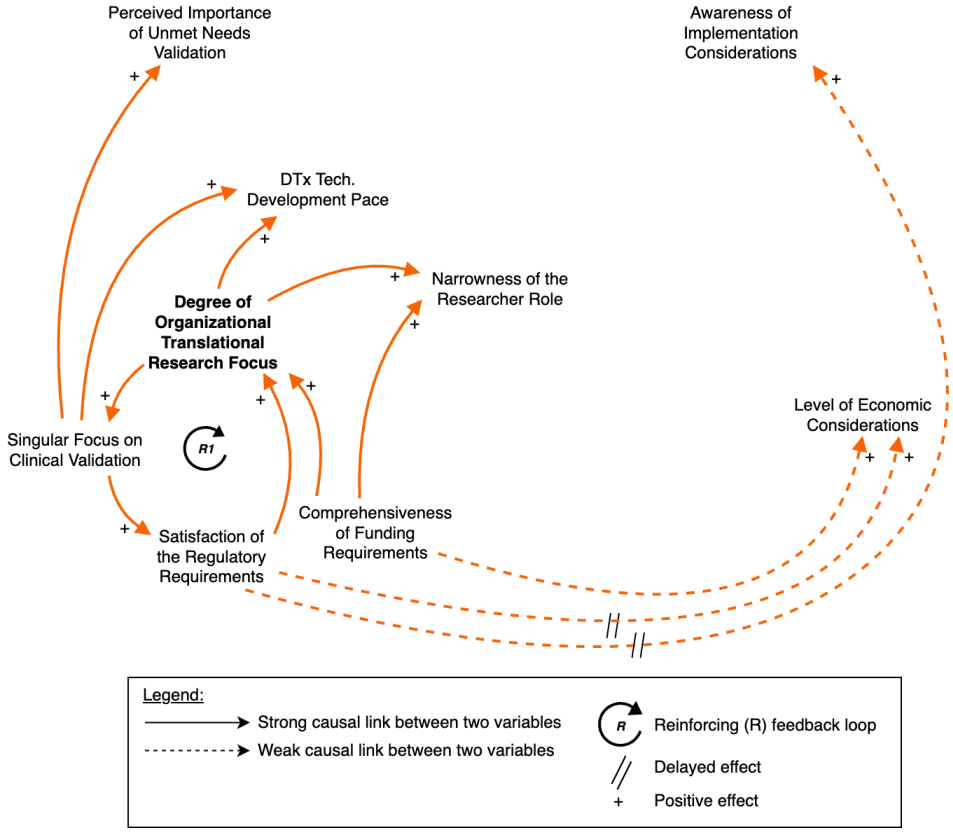
Sarah's (P7) reflections provide initial insight into how this mechanism operates in practice: "*DTx products must first demonstrate robust clinical benefits before gaining market access, and undergo rigorous evaluation to determine whether they are clinically efficacious to warrant market authorization. Pricing discussions with manufacturers occur only after this clinical validation has been established. [...] In Germany, manufacturers can pursue one of two pathways: either demonstrating their DTx's clinical value, or proving process or structural improvements for the health system. However, in practice, approximately 95% or more utilize the clinical value pathway rather than focusing on process improvements*."

This clinical prioritization is further reinforced by funding structures. Camirah (P15) observed that grant and funding requirements have historically focused exclusively on clinical impact, with only recent initiatives beginning to incorporate economic dimensions into the grant review process.

As illustrated in Figure 22, the *Professional Norms* mechanism functions through an interconnected set of causal relationships—represented by solid lines (representing strong influences) and dashed lines (indicating weak or emerging influences)—that collectively prioritize clinical evidence while marginalizing economic considerations. This pattern, while unsurprising within healthcare contexts, significantly constrains the development process and highlights the persistent tension between rational

decision-making frameworks and behavioral influences that drive researcher choices.

Figure 22. The *Professional Norms* and its manifestations shaping economic considerations in DTx development



The figure introduces the Professional Norms mechanism that illustrates how healthcare norms, institutional settings, and regulatory requirements, which are reinforced by funding requirements, create a reinforcing loop (R1: Clinical Value Loop) that prioritizes clinical validation while marginalizing economic considerations in DTx development (emerging connection indicated in dashed line).

Reinforcing loop 1 (R1): Clinical value loop

In R1, the *degree of organizational translational research focus* emerges as a primary influence, bolded in Figure 22 to express the centrality of this node of the causal model. The findings reveal two important aspects that influence researcher decision frameworks: the translational nature of the research institution, as hypothesized during step 2 of abduction.

Researchers in our sample worked across institutes. Their roles covers varying orientations, from basic scientific and technological development to clinically focused or translational research bridging academia and healthcare practice. These institutional visions exist along a continuum from basic science to translational approaches oriented toward commercialization. A key aspect of the translational dimension would be how early in the development process, economic considerations, implementation science, and stakeholder engagement are integrated. Such positions influence both institutional and individual research agendas, creating predetermined key focus areas and performance metrics for researchers. This effect is exemplified in how Ezra (P3) described the relationship between his lab's vision and their output: "*The aim of our lab, or of our institute, is to do something that could potentially impact society. We consider multiple aspects, such as implementation or translation. We're not just doing research for the sake of publishing, nor are we focused solely on basic science. We want to do something impactful that could potentially be translated into real-life benefits for the general public."*

Team composition and multidisciplinary expertise within research organizations, directly impacted by the translational nature of these organizations and shapes researchers' mindsets and priorities. Engineer-researcher Eva's (P2) experience working alongside behavioral scientists illustrates this dynamic: "*Researchers like me, we are too focused on numbers, like how effective is the solution, and our expertise domain. When I joined [Bioengineering Research Institute Name], I was surprised about the behavioral component. I didn't appreciate it at first, but now I see its importance. It opened my mind and perspective, especially for improving DTx usability and engagement*." This excerpt demonstrates how diversifying team composition can potentially disrupt the reinforcing loop (R1) by introducing alternative perspectives, although the data suggest such disruptions rarely extend to economic considerations.

Simultaneously in R1, the imperative to satisfy regulatory requirements—which emphasize DTx safety and efficacy demonstrations for market approval—reinforces

research organizations' singular focus on clinical validation. This creates a self-reinforcing cycle that perpetuates the almost exclusive prioritization of clinical validation in institutional evaluation frameworks, despite growing literature recognition of economic evidence importance. While clinical validation represents a necessary milestone, it constitutes a short-term endpoint relative to the ultimate goal of successful DTx implementation in clinical practice.

Two additional observations merit attention. First, while EUT would predict comprehensive integration of regulatory requirements throughout development, the findings reveal these considerations often emerge much later. As Cheah (P13) noted: *“A lot of times, the solution solves a problem, but it doesn’t end up somewhere because considerations of regulatory and reimbursement with the actual greater landscape, are not in our minds.”* The *satisfaction of the regulatory requirements* tends to be considered more as a chronological endpoint of clinical validation, rather than serving as guidance throughout the DTx development process.

Second, participants noted a “regulatory gap” for DTx—an absence of specific regulatory requirements defaulting to current software-as-medical-device regulations—which may explain the limited consideration given to regulatory aspects by researchers early in the DTx process. For these reasons, the relationship between the *satisfaction of the regulatory requirements* and the *level of economic consideration* is depicted as a dashed line in Figure 22, indicating a weak causal link as well as a temporal delay which, even when regulatory considerations are addressed, would not necessarily lead to greater attention to the economic value a DTx might need to demonstrate for wider adoption as discussed in the Background section.

The positioning of research organizations on this translational spectrum is also largely influenced by the available funding sources, such as research grants, subsidies, donations or investor capital. This influence is particularly significant regarding the comprehensiveness of their requirements (i.e., how extensive the

elements required in a grant proposal are, whether they include the clinical, technological and economic impact of a potential DTx). As Emma (P1) noted: "*Some grants now require us to think about commercialization pathways, which forces us to consider the economics earlier on*." Similarly, Camirah (P15) observed: "*More and more, I find that these grant application forms require you to justify the economics of your innovation... So to justify that, we always have to tell them how much economic benefit our solution would provide, which is hard to find*." While some funding bodies require cost impact assessments for DTx solutions, participants described this as an emerging rather than established practice. For this reason, the relationship between the "*comprehensiveness of funding requirements*" and the *degree of organizational translational research focus* is depicted as a weak or emerging negative causal link in Figure 22.

These funding sources through their requirements can either enable or constrain action, influencing researchers' consideration of various aspects in DTx development. In the causal model, *the comprehensiveness of funding requirements* represents a potential intervention point that could disrupt the R1 loop by introducing economic considerations into performance metrics, though this effect appears limited in current practice.

System implications and propositions

R1 and the impact of current requirements of funding mechanisms create persistent patterns that institutionalize clinical outcome prioritization while marginalizing complementary value dimensions necessary for sustainable implementation. Hence, it is posited:

- Current organizational settings, funding and regulatory requirements in healthcare research collectively establish a rigid evaluative framework that systematically and exclusively prioritizes clinical evidence, effectively precluding the integration of alternative value dimensions, particularly economic considerations, throughout the DTx development process.

- The temporal delay between *satisfying the regulatory requirements* and the *level of economic considerations* (shown by the parallel lines in the diagram) creates a structural barrier that persists even when funding bodies begin to incorporate implementation-related factors into their awarding processes.

- Organizational settings, toward more translational aspects, that diversify team composition beyond clinical expertise will demonstrate greater integration of economic considerations throughout the DTx development lifecycle.

- Interventions targeting the weak causal links (dashed lines) between both the regulatory and funding environments to the *level of economic considerations* offer potential leverage points for system change.

The *Professional Norms* mechanism functions primarily as a situational mechanism (Gebre-Mariam & Bygstad, 2019), describing how macro-level contextual conditions and institutional power dynamics, which reflect embedded healthcare norms influence DTx development approaches, predominantly driven by clinical considerations. The power of this mechanism lies in its ability to shape the decision space available to researchers before individual factors come into play, effectively defining the range of considerations perceived as legitimate or necessary. The subsequent mechanism reveals how intrapersonal factors and cognitive constraints further shape the way they make decisions in this predefined space.

The Researcher Experience mechanism

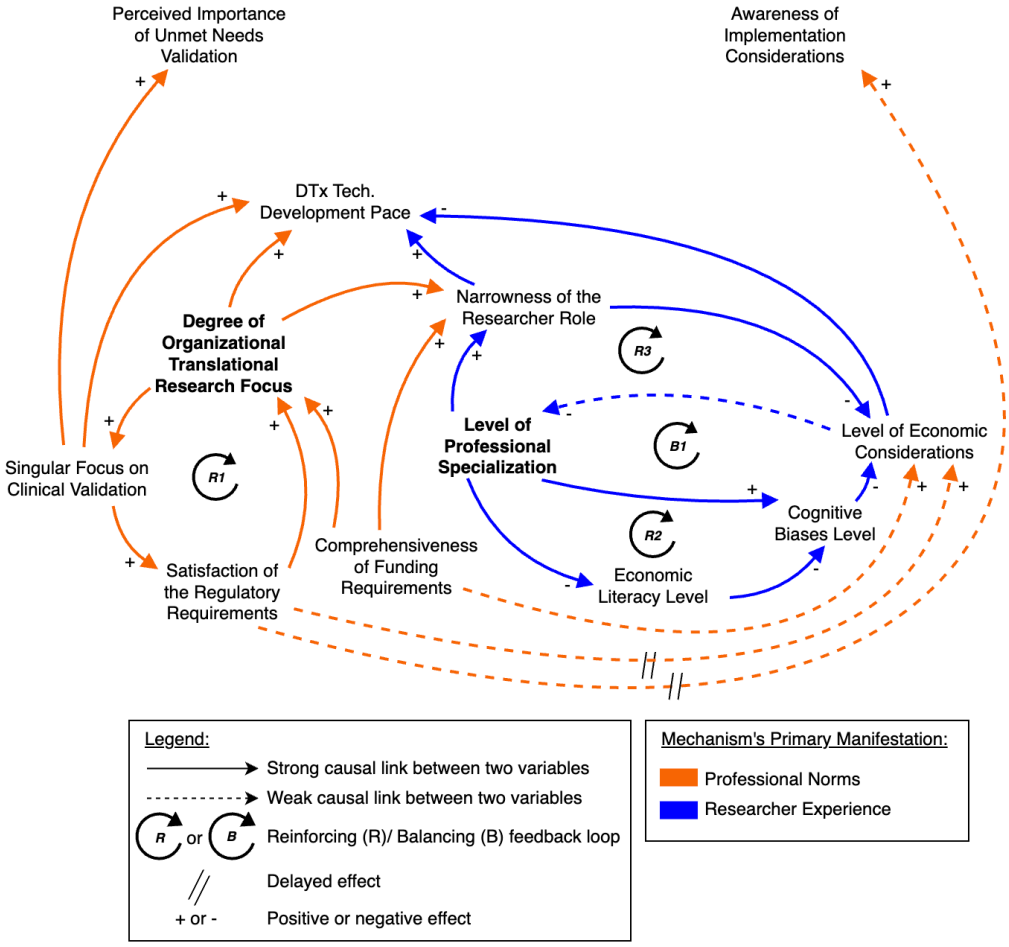
The second mechanism demonstrates how researchers' professional background, including their training, experience and expertise, alongside cognitive patterns, influences their DTx development decisions, particularly regarding economic considerations.

The participant interviews revealed how researchers' professional backgrounds systematically shape their approach to DTx development in ways that often exclude economic considerations, with researchers across different disciplines consistently

acknowledging that their specialized training created blind spots regarding health economics perspectives. Ezra (P3), who has a science-heavy educational background, noted the absence of economic concepts in their formal training. These knowledge gaps are further compounded by cognitive biases shaped by professional training that influence decision-making throughout the DTx development process. Engineering-trained researchers like Eisa (P4) recognized their tendency to prioritize technical optimization over economic feasibility and broader health system integration requirements, while Sasha (P6) candidly summarized "*this is how it works [referring to the DTx development process], what you do, and your choices are partially driven by your past experiences*."

This mechanism manifests through two reinforcing loops (R2 and R3) and one balancing loop (B1), as illustrated in Figure 23 and detailed in Appendix 3G. It reveals how individual characteristics systematically shape development approaches through complex interactions between professional background and established decision-making frameworks.

Figure 23. The *Researcher Experience* mechanism and its manifestations shaping economic considerations in DTx development



This figure introduces the Researchers' Experience mechanism that demonstrates how researchers' professional background, training, and cognitive biases create two reinforcing loops (R2: Literacy Loop and R3: Role Boundary Loop) and one balancing loop (B1: Bias Loop) that systematically channel focus toward familiar domains and away from economic considerations.

The researcher's *level of professional specialization* serves as a fundamental determinant that shapes how narrowly focused their roles become (positive relationship in R3), influences their *economic literacy level* (negative relationship in R2), and contributes to the formation of cognitive biases (positive relationship in B1). This variable, bolded in Figure 23, indicates the centrality of this node, being in each of the three loops that constitute this mechanism.

Reinforcing loops R2 and R3: Literacy and Role boundary loops

The study revealed indeed that researchers' training and educational backgrounds - whether in engineering, clinical, or social sciences - created distinct mental models for approaching DTx development. Rather than optimizing utility or outcomes across all value dimensions, researchers demonstrated strong domain-specific thinking patterns. Eisa (P4) candidly acknowledged that it might create a tunnel vision: "*because from my engineering background, I will not see things from a health economics point of view*." This domain-specific focus was reinforced by Ezra (P3): "*maybe it's just me, like most of the classes I took, they were more like tech or science heavy. I don't think they ever mention anything regarding a translational type of work*." While Cheah (P13) noted some exposure to economic concepts during his specialization training, this proved to be an exception rather than the norm.

These statements illustrate how R2 and R3 loop begin with the *level of professional specialization* and creates path dependencies that shape decision frameworks. Professional training creates expertise in narrow fields, often accompanied by pressures to publish in specialized journals and/or secure domain-specific funding. This leads researchers to prioritize familiar domains (clinical or technical), thereby reinforcing the tendency to specialize further in those same domains. This creates a reinforcing loop where specialized expertise further narrows focus, decreasing the likelihood of acquiring broader economic competencies.

Within the R2 loop, the observed limited *level of economic literacy* among researchers, created or reinforced by the *level of professional specialization*, represents a key intermediate variable that creates persistent knowledge gaps in DTx development. It establishes a self-reinforcing cycle where researchers gravitate toward familiar domains and methodologies, whether clinical or technological. As noted earlier, while EUT suggests that researchers aim to complement their expertise by incorporating economic considerations, observations instead reveal satisficing behavior when faced with unfamiliar economic aspects. This behavior further strengthens the tendency to stay within familiar areas and exhibits a

negative relationship with the *level of cognitive biases*: the higher the researcher's *level of economic literacy*, the less likely they are to engage in satisficing behavior and the fewer cognitive biases they exhibit in this domain.

Within the R3 loop, the *level of professional specialization* strongly influences the *narrowness of the researcher's role* as discussed above*,* which is further shaped by the *degree of organizational translational research focus* and the *comprehensiveness of funding requirements*.

As noted earlier, research institutions evaluate research-related performance metrics and incentives around publications and clinical validation. These metrics serve as visible manifestations of underlying *Professional N*orms, and effectively constrain researchers' roles and foci. They systematically exclude consideration of translational aspects or alternative value forms, such as economic utility, and they marginalize the implementation-oriented knowledge generation that could facilitate broader DTx adoption. Such metrics, while creating what EUT would consider a rational framework for maximizing utility within institutional constraints, potentially introduce what behavioral economists term "reward substitution" (Ariely & Wertenbroch, 2002; Garza et al., 2016). This phenomenon occurs when proximate goals substitute for ultimate goals. In this context, researchers focus on publications and clinical validation (proximate goals) rather than successful broad DTx implementation for improved clinical outcomes beyond limited trial participants (ultimate goals).

Consequently, two tensions emerge. First, academic publication and patenting can conflict due to their opposing requirements regarding public disclosure. Public disclosure can directly impact a researcher's ability to patent an invention because most patent systems require "novelty" - meaning the invention must not have been disclosed publicly before filing the patent application. Second, a potential and interesting tension exists where rational responses to institutional incentives may produce suboptimal outcomes from a broader utility perspective. As engineer-researcher Emma (P1) explained: "*As a researcher, my KPIs are that I need to*

develop something, I need to publish something... the time that I have to implement it is not even in my area of KPIs." This statement illustrates how the R3 loop operates in practice, with performance metrics directly shaping researcher priorities in ways that exclude *economic considerations*.

Balancing loop B1: Bias loop

The B1 loop in the causal model demonstrates how the *level of cognitive biases level***,** reinforced by researchers' specialized expertise and a gap in economic literacy, systematically influences development decisions. Surya (P10) attributed these biases also to the consequences of professional training (*déformation professionnelle* in BDT terms), which offered limited to no exposure to economic principles, which further reinforces these biases. Sasha's (P6) earlier statement about "*This is how it works, what you do, and your choices are partially driven by your past experiences*" captures how the B1 loop operates in practice, with past experiences shaping current perceptions and decisions. From the interviews, these biases manifested in various forms in DTx development decision-making, ranging from optimism bias regarding technical solutions, confirmation bias in clinical efficacy assessments, and status quo bias favoring existing healthcare delivery models: "*Engineers often have unrealistic expectations about adoption rates because they underestimate institutional resistance to new technologies*" as Surya (P10) observed. Also, Sasha (P6) mentioned: "*I know from my professional experience...that potential end-users, such as patients,* [in a feedback session] *don't tell the truth, might not care, or pay attention. The data will be seriously tainted if you just ask them straightforward questions*." This statement—based on professional experience—reveals the preconceived notion that participants are unreliable, a cognitive bias. Such beliefs may "seriously taint" (to use Sasha's own terminology) the interpretation of future patient interactions, potentially leading to confirmation bias in data interpretation.

While these cognitive patterns are expected and appear throughout the DTx development process, they seem to systematically obscure economic considerations. They represent domain-specific expertise that shapes how

researchers evaluate evidence and approach decision-making throughout the DTx lifecycle.They are identified in Figure 23 as negative influences on the *level of economic considerations*. The power of the balancing loop B1 lies in its largely unconscious operation, with researchers often unaware of how cognitive biases shape their perception of what constitutes relevant considerations. Emma (P1) illustrated this phenomenon: "*Engineers think this is the problem and they work on a solution for it and then after they finish the solution when they're trying to implement it, they realize that that's actually not the problem; there's something else*."

System implications and propositions

The interaction between loops R2, R3 and B1 and their set of interdependent variables creates a particularly robust system resistant to change, one that maintains the observed gap in economic consideration throughout the DTx lifecycle. As Figure 23 demonstrates, when domain-specific training combines with cognitive biases, the effect is not merely additive but multiplicative, creating what SD identifies as a "success to the successful" archetype (Sánchez, 2024; Senge, 2006). This dynamic generates momentum through reinforcing success loops, establishing patterns where initial specialization becomes increasingly strengthened over time. This self-reinforcing mechanism can be moderated through the balancing loop B1, with carefully designed interventions that target these causal relationships - interventions that would require further research to define and implement effectively.

These interdependent variables create a robust *Researcher Experience* mechanism influencing the timing and depth of economic considerations in DTx development. While the *Professional Norms* mechanism operates at the institutional level to constrain the decision space, this second mechanism operates at the individual level to shape how researchers navigate within that space. While researchers demonstrate rational decision-making within their domain expertise, they exhibit satisficing behavior when encountering unfamiliar economic considerations. The implications of this mechanism for DTx development are important, hence it is posited:

- The more specialized a researcher's training in clinical or technical domains, the greater the likelihood they will exhibit satisficing behavior when confronted with economic considerations in DTx development.

- Researchers' cognitive biases, particularly domain-specific thinking patterns, will systematically influence their perception of what constitutes relevant evidence in DTx development, with economic evidence being reported as being systematically obscured.

The *Researcher Experience* mechanism represents an “action formation mechanism” (Gebre-Mariam & Bygstad, 2019), explaining how researchers' characteristics generate specific actions and decisions in DTx development. Unlike the first mechanism, which shapes the broader decision context, this mechanism explains how individual researchers process information and make decisions within that context. The analysis demonstrates how these individual-level factors lead researchers to prioritize familiar domains, creating systematic patterns in DTx development approaches.

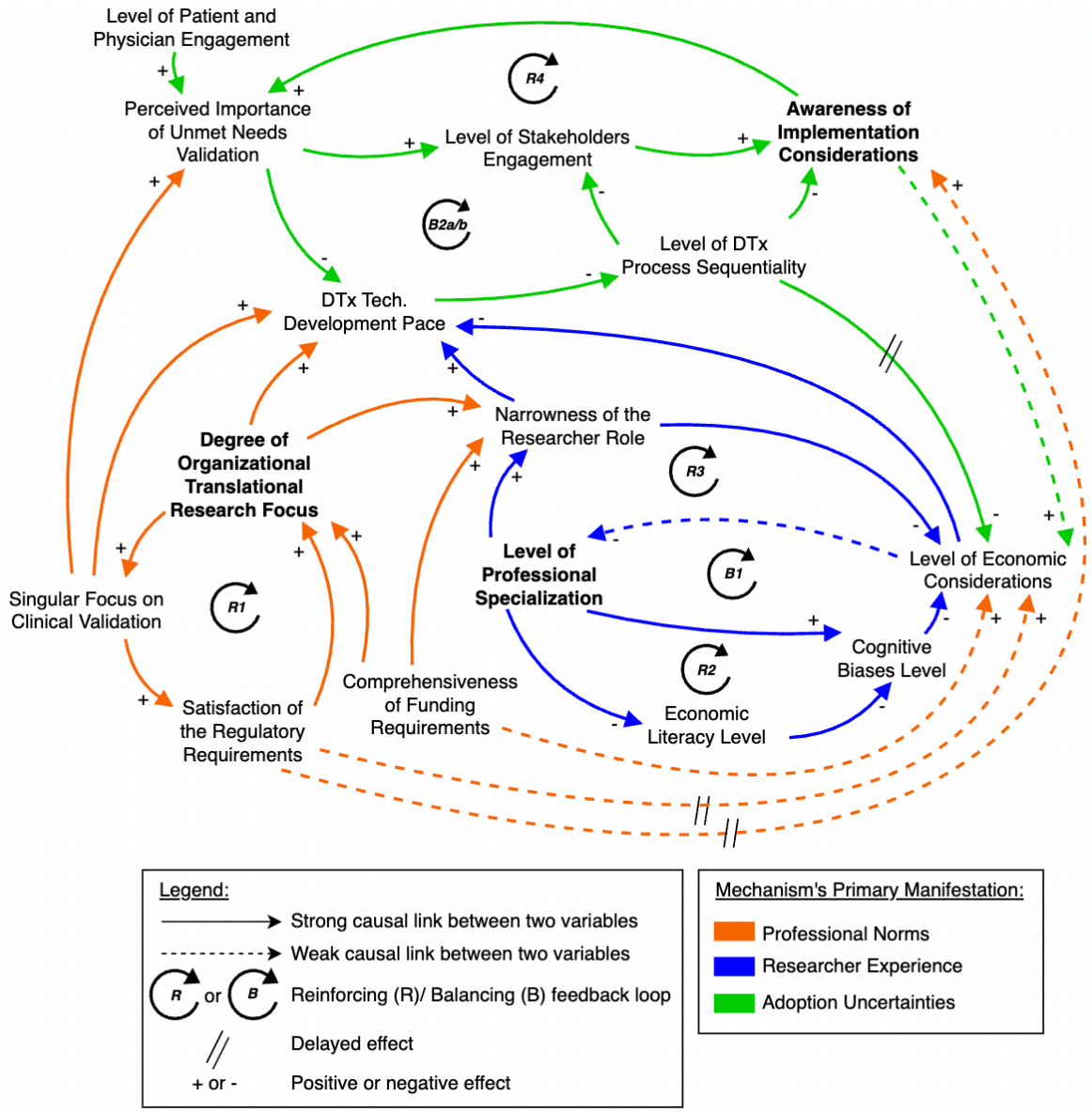
The investigation revealed a third critical mechanism related to the uncertainties of DTx adoption within healthcare systems. This *Adoption Uncertainties* mechanism addresses how researchers navigate the complex landscape of implementation challenges and stakeholder engagement throughout the DTx lifecycle, revealing a different dimension of barriers to economic consideration in DTx development. This third mechanism operates in conjunction with the previous two, as illustrated by the cross-mechanism relationships in Figure 24, where elements from each mechanism ultimately influence economic considerations through various direct and indirect pathways.

The Adoption Uncertainties mechanism

Implementation uncertainties surrounding DTx adoption within healthcare systems indeed emerge as a third critical mechanism shaping researchers' development decisions. This mechanism, illustrated in Figure 24, reveals how researchers' awareness of adoption challenges drives increased focus on clinical needs, while

stakeholder engagement simultaneously influences development approaches. Sarah (P7) articulated this dynamic: “*The big hurdle we see is that clinicians are the main influences on product acceptance. To have a product accepted by health professionals, you must address a real problem and consider workflow integration. If a physician has only seven minutes per patient but needs ten minutes to explain app installation, with weekly follow-ups and no additional payment, it won't work. This must be considered from day one throughout development stages*.” Sarah's (P7) insights suggest that DTx development processes should more systematically integrate real-world implementation constraints, recognizing that successful adoption ultimately depends on addressing genuine clinical problems within practical healthcare delivery contexts. Similar to the *Researcher Experience* mechanism, this mechanism emerges from the interplay between balancing and reinforcing forces, creating a complex system of development influences.

Figure 24. Generative mechanisms and their manifestations shaping economic considerations in DTx development



This figure introduces the Adoption Uncertainties mechanism that illustrates how implementation challenges create dynamic interactions between two balancing loops (B2a: Implementation-Driven Development and B2b: Stakeholder-Driven Development) and one reinforcing loop (R4: Collaboration). This mechanism reveals how researchers' awareness of adoption challenges drives increased focus on clinical needs, while stakeholder engagement simultaneously influences development approaches. Additionally, the figure presents an integrated model that combines all three generative mechanisms (Professional Norms, Researcher Experience, and Adoption Uncertainties) with their respective primary loops, demonstrating how institutional forces, researcher intrapersonal factors, and implementation uncertainties collectively influence economic considerations throughout the DTx development lifecycle.

Balancing loops B2a and B2b: Implementation-Driven Development and Stakeholder-Driven Development loops

The *awareness of implementation considerations* serves as a central imperative throughout the DTx development process, functioning as the primary driver in both the B2a/b and R4 loops in the causal model. In the interviews, researchers consistently emphasized workflow integration, resource requirements, and organizational readiness. Practitioner-researchers particularly confirmed implementation considerations as critical determinants of DTx success, reflecting both rational planning and practical responses to uncertainty in complex healthcare environments: "*Focus [during implementation]] should be on widespread adoption rather than profit maximization*" as mentioned Cheah (P13). This fundamental reshaping of development priorities due to adoption uncertainties was so prominent in the content analysis that it led to the creation of a dedicated code (*Implementation cost > Adoption*) in the initial codebook to highlight the profound influence of these considerations on development decisions.

The findings reveal that greater researcher awareness of implementation adoption challenges positively associates with an increased *perceived importance of unmet needs validation* (positive relationship), ensuring future DTx interventions address specific unmet needs and reduce instances of having a "*solution looking for a problem*."

Participants reported conducting consultation focus groups with patients and physicians (an exogenous variable in the CLD), but revealed these sessions often narrowly target clinical unmet needs rather than broader implementation challenges: "*We should also consider complex approval processes, challenges with pilot projects and sustainable funding, or yet the resistance to change from healthcare professionals..."* (Priscillah, P16). Although literature frames this step as "problem-specification" for identifying real-world needs (Kim et al., 2024), the participants' narrower interpretation represents another manifestation of bounded rationality, where clinical validation takes precedence over comprehensive value assessment.

This focus on clinical unmet needs, while important, often fails to incorporate broader economic dimensions necessary for successful implementation.

As the *perceived importance of unmet needs validation* grows, it reshapes research priorities and considerations beyond simple technological requirements, ultimately slowing the *DTx technological development pace* (negative feedback dynamic). Researchers respond by breaking the DTx development process into more manageable sequential DTx processes as a step-by-step approach. They spend more time ensuring their technology can address the unmet need – despite growing recognition of the need for more integrated approaches.

This sequential approach temporarily reduces uncertainty by emphasizing short-term, step-by-step linear progression rather than iterative development. However, this creates potential long-term integration challenges. While some researchers like Santana (P11) advocated for a DTx implementation-aware development, where adoption considerations actively shape early decisions, most researchers reported having a more linear and sequential approach, which contributes to the persistent gap between clinical validation and economic consideration. This is visualized as a green line in Figure 24, where the *level of DTx process sequentiality* tends to delay *the level of economic considerations* to later stages, beyond the “responsibilities” of the interviewed researchers, to use their own words. This temporal disconnect represents a critical barrier to integrated DTx development.

This sequential approach further delays implementation considerations (negative relationship). It creates a balancing effect in the system, counteracting the reinforcing dynamic of loop R4, and contributes to the system’s stability.

Reinforcing loop 4 (R4): Collaboration loop

In R4, the importance placed on addressing clinical needs creates a positive feedback dynamic, driving the *level of stakeholder engagement*, with a more multidisciplinary and interdisciplinary approach, acknowledged as crucial by the participants for successful DTx development. The interviews identified a complex network of stakeholders potentially engaged throughout the DTx lifecycle, including

engineers, data scientists, behavioral scientists, economists, healthcare providers, clinicians, hospital administrators, regulatory bodies, and commercial stakeholders.

These collaborations enhance the *awareness of implementation considerations*, which ultimately reinforce the *perceived importance of unmet needs validation* (positive relationship, completing the R4 loop). However, rather than following EUT's prediction of comprehensive stakeholder integration, the interviews show that stakeholder engagement patterns typically follow a more sequential approach. This results in what participants characterize as *delayed stakeholder engagement*, which is reinforced by the negative influence of the *level of DTx process sequentiality*. This challenge is illustrated by Camirah's (P15) reflection: "*I initially did not involve hospital administrators in my solution development, which created later challenges in the implementation process.*" When the R4 loop functions sub-optimally due to limited stakeholder engagement—as in Camirah's (P15) example—it may fail to address the full complexity of implementation, including economic considerations.

System implications and propositions

The dynamic tension between loops B2a/b and R4 creates what is called in SD a "fixes that fail" archetype (Sánchez, 2024; Senge, 2006). Short-term solutions, such as sequential development to address a clinical unmet need, create longer-term consequences like fragmentation and delayed stakeholder engagement. While ensuring a DTx addresses clinical needs is important, this approach produces an ongoing tension between immediate development priorities and long-term implementation success. Researchers increasingly recognize the need for early stakeholder collaboration to address adoption uncertainties. However, translating this recognition into systematic practice remains a key challenge in DTx development. Hence, it is posited:

- The greater the perceived implementation uncertainty surrounding a DTx, the higher the likelihood researchers will seek a more multidisciplinary approach, integrating various stakeholder feedback throughout the DTx development process.

- DTx development projects with formalized processes for early stakeholder feedback across diverse stakeholder groups will demonstrate higher levels of economic consideration throughout the development process.

- The temporal disconnect between the *level of DTx process sequentiality* and the *level of economic considerations* creates structural barriers that persist even when researchers recognize the importance of implementation factors.

Following Gebre-Mariam and Bygstad's framework (Gebre-Mariam & Bygstad, 2019), this mechanism represents a “transformational mechanism”, showing how researchers' responses to implementation uncertainties and their decisions about stakeholder engagement collectively transform into broader patterns in DTx development practices, ultimately aggregating into systematic patterns of sequential development processes and delayed stakeholder engagement.

While the first two mechanisms primarily explain why economic considerations are marginalized in DTx development, the *Adoption Uncertainties* mechanism helps explain why implementation concerns (which often have economic dimensions), even when recognized, tend to be addressed in ways that are clinical as one priority while further fragmenting the development process rather than promoting integrated approaches.

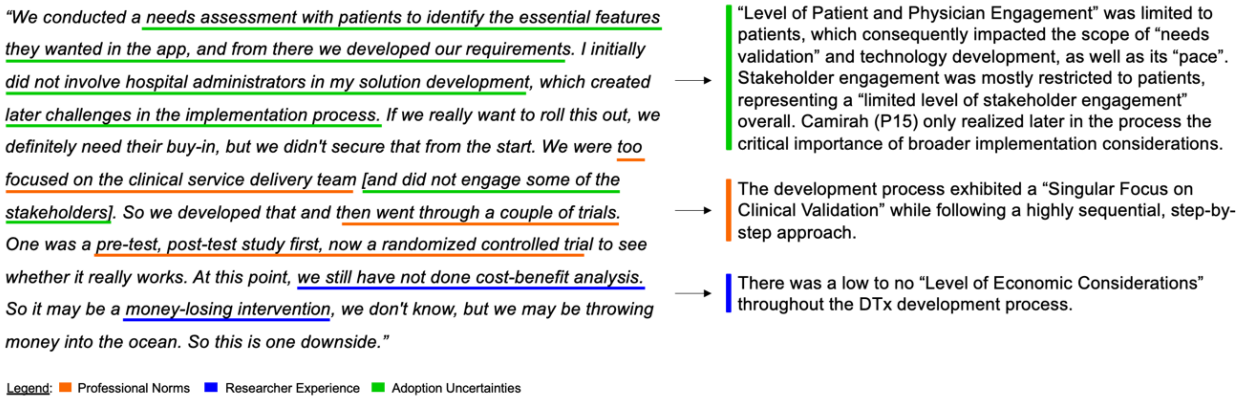
Cross-mechanism relationships and secondary loops

These three interrelated mechanisms - *Professional Norms*, *Researcher Experience*, and *Adoption Uncertainties* - function as an integrated system shaping researchers' decision frameworks in DTx development. These mechanisms are not merely theoretical constructs but manifest directly in researchers' experiences and decision-making processes, as evidenced by representative quotes in Appendix 3E.

They also demonstrate the interplay between rational decision-making approaches (as predicted by EUT) and behavioral influences (as described by BDT).

The mechanisms interact through multiple interconnected pathways (Figure 24), operating through “contingent causality,” where outcomes may vary based on interactions with other mechanisms' prior effects (Stohr et al., 2024). Figure 25 illustrates these cross-mechanism interactions and demonstrates how this integrated system ultimately shapes economic considerations throughout the DTx development lifecycle.

Figure 25. Cross-mechanism interactions illustrated through Camirah (P15)'s quote.



Beyond the seven primary balancing and reinforcing loops introduced above to comprehend each of the three mechanisms, our analysis reveals six additional secondary loops operating across mechanisms.

These secondary loops (B3a/b/c, B4 and B5a/b) – resulting in 13 total loops in the CLD as illustrated in Appendices 3E, 3F and 3G - serve as critical connective elements between mechanisms. Though exerting less direct influence than primary loops, these secondary loops play a vital integrative role in interconnecting the identified mechanisms. They demonstrate how effects propagate between mechanisms, offering deeper insights into system functionality.

The Specialization-Technology Loop (B3a) bridges *Researcher Experience* and *Adoption Uncertainties* mechanisms. It illustrates how professional specialization directly influences DTx development processes and, ultimately, economic considerations. The Implementation-to-Specialization Loop (B3b) and Stakeholder-Guided Implementation-to-Specialization Loop (B3c) extend this mechanims integration by connecting two critical system variables: the *level of professional specialization* and *awareness of implementation considerations*.

The Development Efficiency Loop (B4), comprising strong causal links between three key variables, demonstrates how DTx development processes - particularly regarding efficiency and sequential approach - directly influence economic considerations (negatively and with time delay). The Implementation-Economic Development Loop (B5a) and Stakeholder-Informed Implementation-Economic Loop (B5b) reveal how DTx processes—with or without stakeholder engagement—create balancing effects that typically also introduce temporal delays in economic considerations.

These complex relationships are represented through primary and secondary feedback loops, demonstrating several key insights:

- The analysis extends beyond pattern recognition in empirical data to reveal underlying generative mechanisms operating at the real level of CR ontology, which produce the observed patterns in researchers' decision-making practices;
- The visualization highlights the complexity of the decision-making process and the diverse variables that influence researchers' decision frameworks, demonstrating the intricate causal pathways that shape economic considerations in DTx development;
- Understanding these underlying mechanisms and their manifestations reveals potential intervention points where DTx development processes might be modified to better integrate economic considerations.

These insights provide valuable practical implications for adapting development practices and influencing events and actions at both actual and empirical levels, as it will be discussed in the following section.

6.7. Discussion

6.7.1. Summary of main findings

This study identified three interdependent generative mechanisms that shape researchers' economic decision-making in DTx development through the lens of CR. The *Professional Norms* mechanism reveals how institutional structures create self-reinforcing patterns that systematically privilege clinical validation while marginalizing economic considerations. This operates through a reinforcing loop where organizational settings, regulatory requirements, and funding requirements establish evaluative frameworks that constrain the consideration of alternative value dimensions.

The *Researcher Experience* mechanism demonstrates how professional training and cognitive biases create domain-specific thinking patterns that lead researchers to prioritize familiar frameworks and exhibit satisficing behavior when confronted with unfamiliar economic considerations.

The *Adoption Uncertainties* mechanism elucidates how implementation challenges are addressed through both reinforcing and balancing feedback loops, where greater perceived implementation uncertainty correlates with more multidisciplinary approaches but often creates temporal disconnects between sequential development processes and economic considerations.

These mechanisms, operating at the real level of CR ontology, help explain the empirically observed systematic deprioritization of economic factors in early DTx development, despite their acknowledged importance for successful implementation. By integrating insights from both EUT and BDT, the findings demonstrate how researchers navigate complex decision environments, and seek

to optimize outcomes within their domain of expertise, while exhibiting satisficing behavior when they encounter economic considerations outside their professional training. Rather than reflecting a simple absence of economic thinking, our analysis reveals a more nuanced reality: formal economic considerations remain peripheral, while substantive economic decision-making occurs implicitly throughout DTx development.

This apparent paradox emerges because economic considerations in DTx development operate on two distinct levels: 1) Explicit economic considerations—direct cost-effectiveness analyses, budget impact assessments, and formal economic evaluations that researchers consciously recognize as “economic”—and 2) Implicit economic considerations—implementation-related factors that have economic implications but are not conceptualized by researchers as economic decisions.

These three mechanisms collectively reveal what could be termed as an “economic awareness gap”: a systematic disconnect between researchers' actions and their conceptual frameworks. This gap manifests in three important ways: 1) Terminological disconnection—researchers employ economic reasoning without economic vocabulary; 2) Disciplinary boundaries—implementation concerns are viewed as separate from economic considerations; and 3) Temporal fragmentation—economic implications are recognized but not integrated across development phases. Understanding this gap provides crucial insights for developing more effective strategies to bridge the divide between technical innovation and economic sustainability in DTx development.

The findings both validate and expand upon existing literature on healthcare innovation decision-making, especially about decision frameworks tendency in early development phases to prioritize technical feasibility and clinical applicability, with economic considerations often introduced later in the development cycle (Mathews et al., 2019). As Davahli et al. (2018) highlighted, several studies analyzed decision-making in healthcare and emphasized a tendency toward focusing on short-term

results and using a single-performance measure for problems in the decision-making process. This observation echoes the current research findings regarding researchers who prioritize more short-term endpoints, such as clinical validation. As noted earlier, short-term solutions, such as sequential DTx development aimed at addressing short-term needs and research metrics, can create longer-term problems, such as a lack of comprehensive evidence required for large-scale deployment and adoption. The literature highlights how well-intentioned interventions and inherent trade-offs might generate ripple effects throughout the system, extending far beyond the isolated and more short-term consequences that stakeholders might initially anticipate (Nguyen et al., 2025). The integrated CLD in Figure 24 and the findings from this study help to visualize and understand complex system behavior leading to the inclusion or exclusion of economic considerations in DTx development, offering decision-makers both a conceptual tool and potential intervention points for improvement.

The predominance of clinical considerations in this study aligns with previous research on DTx technology development (Sapanel et al., 2025; Wang et al., 2023), while the identification of specific mechanisms through which economic considerations become systematically deprioritized advances the understanding of researcher decision-making processes. The findings on the influence of professional training on decision frameworks corroborate earlier research about educational background's role in innovation development (Gayathri, 2018; Li & Yu, 2018; Saposnik et al., 2016). Additionally, the analysis of adoption uncertainties provides novel insights into how implementation concerns shape early DTx development decisions. The significance found regarding adoption considerations is consistent with existing literature documenting implementation challenges in digital health interventions (Fassbender et al., 2024; Johnson et al., 2024; Prodan et al., 2022). Notably, this aligns with the research study team’s previous findings where the “*DTx Implementation*” cluster of factors received the highest importance rating (3.97 out of 5) among stakeholders, marginally exceeding even the “*DTx Impact on Patient Outcomes*” (3.96 out of 5) (Sapanel et al., 2025). This consistency across

studies reinforces the critical importance of implementation considerations in DTx development, despite their frequent disconnect from economic assessments.

6.7.2. Theoretical contributions

This study makes several significant theoretical contributions to understanding decision-making in healthcare innovation contexts.

First, it demonstrates how EUT and BDT manifest in complementary ways throughout DTx development, revealing patterns specific to DTx development. The findings show a complex dynamic where researchers navigate rational decision-making frameworks and behavioral influences within institutional constraints. While EUT provides valuable insights into how researchers attempt to optimize clinical and technical outcomes, BDT explains the cognitive constraints and biases that lead to systematic deprioritization of economic considerations. This integration of normative and descriptive decision theories creates a more comprehensive framework for understanding the complex dynamics of healthcare innovation decision-making.

Second, the application of CR, coupled with ST, offers a novel methodological approach for examining the causal mechanisms underlying observable patterns in healthcare innovation processes. While CR has been applied to healthcare systems analysis (Angus & Clark, 2012; Dugle et al., 2020; Koopmans & Schiller, 2022) and ST has been employed in health innovation contexts (Linnéusson et al., 2022; Morgan et al., 2024; Thelen et al., 2023), their systematic integration for investigating DTx development mechanisms—particularly researchers' decision-making patterns—represents a methodological advancement that appears absent from the extant literature. This integrated approach addresses a documented gap whereby existing DTx research predominantly employs descriptive methodologies that examine observable outcomes rather than the underlying causal mechanisms that generate these patterns.

By identifying mechanisms operating at the real level of CR ontology, the analysis moves beyond superficial correlations to reveal the deeper structural forces that shape DTx development trajectories. As Renmans et al. (2020) suggest, integrating ST through CLDs strengthens the analytical approach by enabling a deeper understanding of the interdependencies between mechanisms and their operation through complex, interdependent variables. The CLDs enabled the identification of feedback mechanisms and leverage points within the system that might otherwise remain obscure in traditional linear analyses. This systems approach revealed how seemingly minor decisions early in DTx development can create amplifying effects through feedback loops, ultimately influencing economic consideration throughout the development process. This approach therefore provides a more nuanced understanding of how various factors influence researcher decision-making in DTx development and may prove valuable for future studies seeking to understand complex, multi-stakeholder healthcare innovation processes.

Third, the findings contribute to the growing literature on digital health implementation by highlighting the interconnected nature of technical, clinical, and economic decision-making throughout the DTx lifecycle. By empirically documenting the mapping of the causal feedback loops through which these decisions influence each other, the research demonstrates how early-stage development choices can have significant downstream implications for economic viability and implementation success. This systems perspective extends current implementation frameworks by emphasizing the temporal dynamics and causal interdependencies that shape DTx development outcomes.

In summary, the application of CR, combined with DT and ST, offers a robust framework for understanding how different levels of reality interact to produce observed outcomes in complex healthcare innovation processes. This approach moves beyond surface-level insights to reveal deeper structural mechanisms and provides a more nuanced understanding of how various factors influence researcher decision-making in DTx development.

6.7.3. Practical implications

The complex interplay between three generative mechanisms - *Professional Norms, Researcher Experience,* and *Adoption Uncertainties* - identified in this study has significant practical implications for enhancing economic consideration integration in DTx development.

For research organizations, the findings suggest several actionable approaches to better integrate economic considerations throughout DTx development, and, broadly speaking, to integrate translational considerations into day-to-day operations rather than treating translation to clinical practice as a distant endpoint.

Research organizations should adopt structured development frameworks that explicitly incorporate economic assessments at multiple stages rather than treating economic evaluation as a final checkpoint. Considering “implementation checkpoints” that parallel clinical validation milestones can encourage researchers to collect real-world feasibility data and proactively consider implementation barriers, including economic aspects and adoption uncertainties. This approach will ensure continuous attention to economic factors throughout the development process. Systematically diversifying research team composition to include experts, such as health economists and implementation scientists from project inception, is also crucial, as the findings suggest that diverse teams can disrupt the self-reinforcing patterns that marginalize economic considerations, particularly when economic expertise is integrated early rather than consulted ad hoc. Additionally, research organizations should consider revising researcher evaluation metrics to include indicators of implementation feasibility and economic assessment quality alongside traditional clinical and technical outcomes, potentially using balanced scorecards that weigh these dimensions according to the project stage.

Individual researchers can enhance their approach to economic considerations in several ways. It is recommended that researchers adopt structured decision-making frameworks that systematically consider economic factors alongside clinical and technical aspects. Existing frameworks, such as the NASSS (Nonadoption,

Abandonment, Scale-up, Spread, and Sustainability) could be adapted to incorporate economic considerations more explicitly (Greenhalgh et al., 2017). More specific frameworks, such as the "*Economic Evaluation of Digital Health Interventions*" framework by the World Bank Group (Wilkinson et al., 2023), or the "*The DTx Real-World Evidence Framework*" by Kim et al. (2024) could also be considered. Furthermore, implementing simplified economic assessment tools, such as mini-HTA or "rapid review" approaches, would balance comprehensiveness with practicality for researchers with limited economic expertise (Haverinen et al., 2024).

Pursuing targeted training in basic health economic principles and evaluation methodologies relevant to digital health is also important, as the findings suggest that even foundational economic literacy can help researchers overcome satisficing behavior when confronted with economic considerations. Researchers should also begin implementation planning from project inception, with particular attention to identifying cost drivers, potential monetization models, and resource requirements for sustainable deployment. Early stakeholder engagement across the implementation spectrum can help identify economic considerations that might otherwise remain invisible until later development stages.

For policymakers and funding agencies, the findings suggest several approaches to promote economic consideration in DTx development. The development of standardized but pragmatic economic evaluation guidelines and the creation of incentives for early economic consideration through policy or funding mechanisms would systematically enhance integration of economic factors and create systemic pressure for comprehensive value assessment. Such guidelines would need to be specifically tailored to DTx, acknowledging their unique characteristics and development processes. These guidelines should provide actionable frameworks and practical economic assessment methodologies appropriate for researchers without extensive economic training. Creating funding mechanisms that explicitly reward early consideration of economic factors, perhaps through milestone-based funding that includes economic assessment requirements at each stage, directly addresses the reinforcing feedback loops identified in the *Professional Norms*

mechanism. Additionally, increasing funding for implementation research that explicitly examines economic aspects of DTx deployment can help create an evidence base to guide future development efforts and address the concerns identified in the *Adoption Uncertainties* mechanism.

These recommendations directly address the identified mechanisms, offering intervention points to enhance economic consideration throughout DTx development and creating a foundation for more integrated approaches to value assessment in digital health innovation.

6.7.4. Study limitations

When interpreting these research findings, it's important to acknowledge certain limitations. Methodologically, while the sample included experienced researchers from diverse backgrounds, participants were predominantly, at the time of the study, evolving in academic and public healthcare contexts. This sampling approach enabled detailed examination of mechanisms within publicly funded research environments, which constitute a significant proportion of global DTx development activities and serve as foundational sites for innovation translation (Miao et al., 2024). Moreover, commercially oriented DTx development environments, characterized by profit-driven objectives and investor accountability requirements, may operate under different institutional logics that could alter the identified mechanisms. However, these findings maintain practical relevance for commercial settings through the prevalent academic-commercial collaborations that characterize DTx development (Miao et al., 2024), particularly during clinical validation phases where academic expertise remains paramount. Future research should validate mechanism generalizability across these diverse institutional contexts.

From a geographic perspective, the sample, while international, had greater representation from specific regions, which may not fully capture contextual factors unique to specific healthcare systems. Additionally, the recruitment approach may have introduced selection bias, attracting participants with a greater interest in

economic considerations, although the findings of limited economic integration suggest this was not a genuine concern.

From a theoretical perspective, CR emphasizes that generative mechanisms often are “context-sensitive” and operate contingently (Jagosh et al., 2015; Renmans et al., 2020). This implies that the mechanisms identified in this study could, but not necessarily, produce analogous structures, but inevitably exhibit different behavioral outcomes in varied organizational, regulatory, or funding contexts, as discussed above.

The CLDs, while systematically developed through a triangulation process both of data and of methods, does represent the available evidence, but perhaps not fully the nuanced and textured complexity of real-world decision processes. The exploratory qualitative approach employed, is valuable for identifying key relationships, but it does limit the ability to assign quantitively the weighted importance of different causal relationships or the strength of feedback mechanisms.

Even with these limitations, the rigorous methodological approach employed, theoretical grounding, and consistent findings across diverse set of experienced participants suggest that the identified mechanisms represent robust explanatory frameworks structured for understanding economic consideration in DTx development.

6.7.5. Future research

This study opens several promising avenues for future investigation that would build upon the identified mechanisms and further advance understanding of economic decision-making in DTx development.

From a methodological perspective, conducting longitudinal research following multiple DTx innovations from conception through implementation would allow examination of how economic considerations evolve throughout the lifecycle. Such

studies could identify critical junctures where economic factors become more salient and explore how early economic decisions impact later implementation outcomes. Additionally, complementary downstream research should examine DTx implementation and adoption in real-world clinical environments, as understanding actual adoption patterns and barriers in practice settings is essential for validating the economic assumptions made during development phases.

As noted by Allahi et al. (2018), if a benefit of SD is to convert qualitative understanding into a quantitative approach, scholars tend to study SD and its effect qualitatively, a potential limitation of SD. Therefore, to address this potential limitation, we could develop and validate quantitative instruments for measuring the strength of the three identified mechanisms across different organizational contexts. This would allow us to determine which one has the greatest influence on economic considerations in various settings. Designing intervention studies that target specific aspects of the identified mechanisms could determine which approaches most effectively enhance economic consideration integration, such as testing different team composition models or economic training programs.

Theoretically, future research should investigate potential boundary conditions for the identified mechanisms, examining whether they operate similarly across different healthcare contexts, funding models, or regulatory environments. This would help refine theory and enhance its applicability across contexts. Further exploration of the integration of ST, implementation science, and economic theory could develop more comprehensive models of healthcare innovation decision-making that explicitly account for economic considerations. Conducting comparative studies examining how the identified mechanisms manifest differently in various organizational contexts (academic, commercial, healthcare provider-based) would enhance understanding of contextual influences on economic decision-making.

In terms of applied research, developing and evaluating targeted educational interventions designed to enhance economic literacy among DTx researchers could test whether increased knowledge translates to a more comprehensive economic

consideration in decision-making. Evaluating the effectiveness of integrated development frameworks that explicitly incorporate economic considerations throughout the DTx lifecycle would measure their impact on both development efficiency and implementation outcomes. Investigating how different policies and regulatory environments influence researchers' economic decision-making could for example identify which policy approaches most effectively promote comprehensive value assessment in DTx development

Finally, a critical priority for subsequent studies should be examining downstream DTx adoption and implementation in real-world clinical settings. While this research has focused on early-stage economic decision-making, complementary research is needed to understand how DTx interventions perform economically when deployed in actual healthcare environments. Such studies should investigate implementation barriers, clinician adoption patterns, patient engagement rates, and actual cost-effectiveness outcomes in practice, as these real-world factors often differ significantly from development-phase assumptions and directly impact the economic viability of DTx solutions.

6.7.6. Conclusions

This study advances our understanding of researchers' economic decision-making in DTx development through the lens of CR, revealing complex interactions between institutional structures, researchers' intrapersonal factors, and implementation uncertainties. By identifying three interrelated generative mechanisms—*Professional Norms, Researcher Experience, and Adoption Uncertainties*—the research provides a comprehensive explanatory framework for the systematic deprioritization of economic considerations observed in DTx development.

The findings demonstrate that economic considerations are not merely overlooked due to individual researcher preferences but are systematically marginalized through self-reinforcing institutional structures, domain-specific professional training, and sequential development approaches that create temporal disconnects between

clinical validation and economic assessment. Effectively integrating economic considerations throughout the DTx development process requires multi-level interventions addressing both structural factors and individual decision-making processes.

The persistent tension between rational optimization and behavioral influences creates complex decision landscapes that researchers must navigate. Understanding these dynamics is essential for developing more integrated approaches to DTx development that balance clinical, technical, and economic considerations from inception through implementation. The uncovered mechanisms provide valuable intervention points for strengthening the DTx development process and fostering more comprehensive value assessment.

As DTx continue transforming healthcare delivery, understanding and optimizing economic decision-making processes become increasingly crucial for realizing their potential to improve patient outcomes while creating sustainable value for healthcare systems. By revealing the underlying mechanisms that shape economic consideration in DTx development, this study provides a foundation for future research and practice aimed at enhancing the integration of economic factors throughout the digital health innovation lifecycle.

This qualitative investigation of researchers' perspectives has provided crucial insights into the practical challenges and opportunities for integrating economic considerations in early DTx development. Together with the systematic review's identification of economic value drivers (Chapter 4) and the group concept mapping study's stakeholder conceptualizations (Chapter 5), this final empirical component completes the thesis's comprehensive examination of the DTx economic value landscape. Building upon these complementary methodological approaches, Chapter 7 synthesizes the accumulated evidence into an integrated discussion, developing evidence-based methodological recommendations that address the primary objective of this thesis: guiding stakeholders toward more effective consideration of economic value drivers throughout the DTx lifecycle.

DISCUSSION AND IMPLICATIONS

7

CHAPTER 7. DISCUSSION AND IMPLICATIONS

This chapter synthesizes key findings from the thesis to address central questions regarding the complex relationship between DTx and economic value. It examines how findings from three cascading studies reveal the intricate interplay between stakeholder perspectives, development processes, and economic considerations throughout the DTx lifecycle.

The chapter begins by contextualizing the research within current healthcare challenges. This section summarizes the three interconnected research objectives of this thesis, which are to: (1) examine the economic value creation of DTx as a new class of medicine, (2) analyze how different stakeholders conceptualize and prioritize different factors of economic value across the DTx lifecycle, and (3) explore the underlying conditions that influence how economic considerations are integrated into DTx development processes.

The core of the chapter (Section 7.2) is organized around research outputs according to their theoretical contributions, practical contributions, and managerial recommendations. The theoretical contributions advance conceptual frameworks for understanding DTx economic value beyond traditional metrics, while practical contributions translate these insights into actionable approaches for relevant stakeholders. Five managerial recommendation sets that constitute a comprehensive framework for enhancing the economic viability of DTx interventions are proposed.

The chapter concludes by acknowledging research limitations and suggests future research directions (Section 7.3), followed by a synthesis of the thesis' contributions to the field of digital health (Section 7.4).

7.1. Taking a Step Back

As outlined in Chapter 1, the integration of DTx into healthcare systems remains limited despite their potential to address the unprecedented rise in chronic and mental health conditions. In a context of healthcare resource optimization, economic impacts serve as critical decision elements in allocating health budgets for novel interventions within healthcare systems (Kario et al., 2021; Gomes et al., 2022). However, the economic value of DTx, especially from the perspectives of governments, payers and care providers, remains underexplored, which contribute to the slow adoption of these interventions (Keogh et al., 2024; Kreuzenbeck et al., 2024).

Characterized as complex interventions (Murray et al., 2016), DTx present unique challenges in assessing their economic impact (Gomes et al., 2022). The drivers of DTx economic value have not been thoroughly investigated (Piera-Jiménez et al., 2021), and there is a paucity of knowledge regarding the influence of various stakeholders involved throughout a DTx lifecycle on the potential economic value generation and subsequent commercialization and deployment of these emerging technological interventions. The interplay between stakeholder involvement and DTx economic value creation has yet to be fully elucidated, leaving gaps in how to optimize their development and deployment for maximum benefit within healthcare ecosystems.

To address the research gaps discussed in Chapter 2, this thesis and its associated research work were aimed at three objectives:

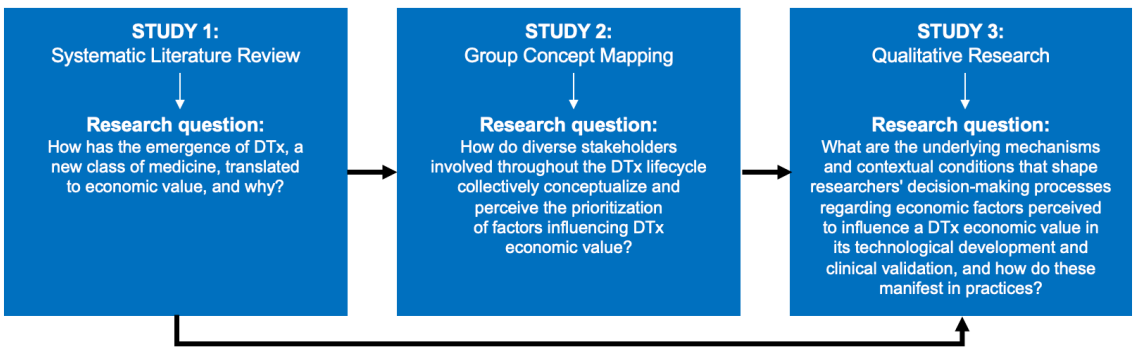
1. **Sub-objective #1: Understand and characterize the concept of economic value in the context of DTx, as well as factors that might influence the DTx and economic value relationship.** This objective seeks to establish a foundational understanding of how economic value is conceptualized and manifested within the DTx landscape.

2. **Sub-objective #2: Gain deeper insights into how economic value and its drivers are considered by diverse stakeholders during the early stages of DTx technological development and clinical validation.** This objective seeks to uncover how diverse stakeholders consider economic value and its drivers during the initial stages of DTx development and clinical validation. By exploring current practices and day-to-day realities, insights were generated to inform methodological recommendations for integrating economic considerations throughout the DTx lifecycle. This understanding helps bridge the gap between theoretical economic value and practical implementation in the DTx lifecycle.

3. **Main objective: Develop methodological recommendations to guide stakeholders involved in DTx development and clinical validation, and implementation to maximize the capacity of DTx to generate economic value.** These recommendations are intended to move toward an evidence-based decision-making process when it comes to potentially considering economic value drivers throughout the DTx lifecycle.

From a methodological perspective, this thesis builds upon three core research questions that were sequentially conducted to meet the study's objectives, as illustrated in Figure 26. Each study builds on the findings of the preceding one to uncover new insights that contribute to the body of knowledge. This interconnected approach ensures a cohesive progression of research throughout the thesis.

Figure 26. Three core research questions examined in the thesis



Systematic Literature Review (Chapter 4, Paper 1)

In the first study, a systematic literature review was conducted and revealed that DTx can be cost-effective and offer economic value in certain use cases and local contexts, while simultaneously improving patient care.

This review, encompassed 18 studies, also identified methodological shortcomings in DTx economic evaluations that warrant attention in future assessments. Through a comprehensive analysis of the included studies, several key factors associated with the economic impact of DTx interventions were identified. Specifically, *Healthcare Resource Use*, *Pharmaceutical Treatment*, *Participants' Baseline Characteristics*, and *Attrition Rates* emerged as “economic drivers” of DTx interventions. These findings establish a crucial foundation for understanding the economic landscape of DTx. It underscores areas needing further investigation and methodological refinement in future evaluations of these innovative technologies.

Group Concept Mapping Study (Chapter 5, Paper 2)

The second study, using a GCM approach, identified 59 factors which influence the economic value of DTx, based on factors identified in the systematic review (chapter 4, paper 1). These factors were subsequently grouped into eight distinct clusters (n=37). Four stakeholder groups—healthcare professionals, researchers, industry stakeholders, and public sector representatives (n=62)—assessed the importance of these clusters and factors in generating economic value for DTx. Additionally, participants evaluated the extent to which each of the 59 factors is considered in their respective fields or practices (n=62).

The analysis revealed a high degree of consensus among respondents by identifying *DTx Impact on Patient Outcomes* and *DTx Implementation* as the most influential clusters of factors affecting DTx economic value. Concurrently, the study found that the *DTx Associated Costs* and *DTx Monetization Models* clusters potentially receive insufficient consideration, particularly among researchers.

The GCM methodological approach facilitated a comprehensive understanding of how stakeholders conceptualize, perceive, and consider factors impacting DTx economic value throughout their lifecycle. The study highlighted potential discrepancies between the perceived importance of certain clusters and their actual consideration by specific stakeholder groups. Furthermore, it revealed divergent views among stakeholder groups regarding the consideration of factors affecting DTx economic value, particularly between researchers and non-researcher participants (Table 15).

The GCM study unveiled the complex interplay of multiple stakeholders in shaping DTx economic value, as well as the multifaceted factors influencing such value. Based on these findings, a conceptual framework delineating priority clusters and factors driving DTx economic value was proposed to offer a structured approach for future research and development in this field.

Qualitative Research Study (Chapter 6, Paper 3)

The third study employed qualitative methods and used in-depth semi-structured interviews to further investigate, from CR epistemological positioning, the findings of the GCM study (chapter 5, paper 2), with a particular emphasis on the specific researchers' decision-making processes and underlying generative mechanisms influencing researchers' approach to economic considerations in DTx development.

This qualitative investigation corroborated the complex interplay of factors influencing economic considerations throughout the DTx lifecycle, as highlighted in the first two studies. Notably, the research revealed that economic integration remains limited, particularly in the early phases of the DTx lifecycle. The study identified three interrelated generative mechanisms that shape researchers' decision-making regarding economic considerations: (1) the *Professional Norms*, (2) the *Researcher Experience*, and (3) the *Adoption Uncertainties*. These mechanisms support an explanation as to why, despite growing recognition of the importance of economic evidence, economic considerations remain peripheral in researchers' decision frameworks. The study proposes specific recommendations,

or intervention points, to strengthen the DTx development process toward a more comprehensive assessment of clinical, technical, and economic value throughout technological development and clinical validation, ultimately enhancing their deployment within healthcare systems.

In the subsequent section, a deeper exploration of the research contributions is presented to elucidate how the findings from each research study address the research questions and objectives, as their relate to the existing literature.

7.2. Research Outputs and Meeting Research Objectives

This thesis aimed to identify and understand the economic value drivers of DTx and their consideration throughout the product development lifecycle through the execution of three research studies. Through systematic literature review, GCM, and qualitative investigation, this research has generated significant theoretical and practical contributions, along with evidence-based managerial recommendations, as summarized in Table 20 and elaborated in subsequent sections. These contributions collectively advancing our understanding of DTx economic value relationships and generation while providing actionable insights for stakeholders across the DTx ecosystem.

Table 20. Overall summary of key thesis contributions

Category	Key Contributions	Significance
Theoretical Contributions	• Expanded conceptualization of DTx economic value • Collective stakeholder conceptual framework for DTx economic value • Generative mechanisms of economic decision-Making in DTx Development • Temporal framework for economic value integration • Systems-based framework for DTx value generation	Provides conceptual foundations for understanding how economic value is considered, created, and assessed throughout the DTx lifecycle.
Practical Contributions	• Expanded the concept of DTx economic value • Identified of 59 economic value factors • Standardization approach for economic evaluations • Guidance for addressing stakeholder perception gaps • Framework for early economic integration	Translates theoretical insights into actionable approaches for all stakeholders across the DTx ecosystem.
Managerial Recommendations	1. Foster interdisciplinary collaboration 2. Embed economic considerations early 3. Establish economic integration guidelines 4. Integrate economic dimensions in training 5. Enhance methodological rigor	Provides stakeholder-specific intervention points where targeted action can enhance economic viability of DTx.

This section therefore synthesizes the research outputs in relation to the thesis objectives, addressing how each objective has been met and the specific contributions achieved.

7.2.1. Theoretical contributions

This thesis offers five main theoretical contributions to understanding DTx economic value creation, assessment, and consideration throughout the product development lifecycle, as detailed below.

Expanded Conceptualization of Economic Value in DTx

The research advances theoretical understanding by expanding the conceptualization of economic value in DTx beyond traditional cost-effectiveness metrics. Building upon Lakdawalla et al.'s (2018) expanded concept of value in healthcare, this thesis demonstrates that DTx economic value encompasses

multiple dimensions extending beyond conventional health economic outcomes. The systematic literature review identified 18 drivers impacting DTx economic value, while the GCM study expanded this understanding to 59 factors. These factors reveal that the DTx economic value includes elements, such as productivity improvements, adherence-enhancing features, and real option value—factors often overlooked in traditional economic evaluations.

This expanded conceptualization is particularly significant, as it demonstrates that DTx economic value emerges from complex interactions between technological characteristics, implementation requirements, clinical impacts, and market factors. The results establish that these value elements operate dynamically across the DTx lifecycle, with different elements assuming prominence at different development stages. This nuanced understanding provides a more comprehensive theoretical framework for comprehending the full spectrum of economic value in DTx, and broadly speaking, digital health interventions.

Collective Stakeholder Conceptual Framework for DTx Economic Value

The thesis introduces a novel collective and co-constructed stakeholder framework for understanding how economic value is conceptualized and prioritized by diverse stakeholders throughout the DTx lifecycle. The GCM study demonstrates that stakeholders consistently identify clinical impact and implementation considerations as the most influential factors affecting economic value, while it reveals significant variance regarding how different stakeholder groups prioritize and consider economic factors.

This framework makes an important theoretical contribution by elucidating how researchers, healthcare professionals, industry representatives, and public stakeholders develop distinct mental models of DTx value, leading to systematic differences in factor prioritization and consideration. By mapping these conceptual differences across stakeholder groups, the research provides a theoretical foundation for understanding how divergent stakeholder perspectives can create implementation gaps in DTx development and deployment. The finding that

researchers systematically gave lesser considerations to economic factors, compared to other stakeholders, represents a significant theoretical insight into potential barriers in translating DTx from research to practice.

Generative Mechanisms of Economic Decision-Making in DTx Development

The qualitative study advances theory by identifying three primary generative mechanisms that shape researchers' decision-making regarding economic considerations in DTx development: *Professional Norms*, *Researcher Experience*, and *Adoption Uncertainties*. These mechanisms, operating through systemic reinforcing and balancing feedback loops, explain why economic considerations remain peripheral in researchers' decision frameworks despite growing recognition of their importance in the literature (Gomes et al., 2022; Keogh et al., 2024; Kreuzenbeck et al., 2024).

This theoretical contribution is important, as it moves beyond descriptive accounts of decision-making to identify the underlying causal structures that generate observable patterns in DTx development. The research demonstrates how *Professional Norms* systematically prioritize clinical validation while marginalizing economic considerations, how researchers' professional training and cognitive biases create path dependencies that influence development decisions, and how implementation uncertainties drive both fragmentation and stakeholder engagement in complex ways. By visualizing these mechanisms through CLDs, the research provides a theoretical foundation for understanding how institutional structures, interpersonal and intrapersonal factors, as well as implementation dynamics collectively shape DTx development trajectories.

Temporal Framework for Economic Value Integration

The research contributes to a temporal theoretical framework that helps comprehend when and how economic considerations should be integrated throughout the DTx lifecycle. Previous literature has predominantly focused on end-stage economic evaluation, whereas this research demonstrates the critical importance of early-stage economic integration in DTx lifecycle.

For example, the qualitative study develops this temporal framework by revealing how researchers' conceptualization of the DTx process as linear and chronological contributes to the deferral of economic considerations to later stages. This theoretical insight explains a fundamental tension in DTx development: despite growing awareness of implementation challenges, researchers continue to follow sequential development processes that systematically delay economic considerations. The research identifies how this temporal disconnect creates structural barriers that persist even when researchers recognize the importance of implementation factors, given that it provides a theoretical foundation for understanding how economic value is created and sustained throughout the DTx development lifecycle.

Systems-Based Framework for DTx Value Generation

The research introduces a systems-based theoretical framework for understanding how economic value is generated in DTx interventions. By employing CLDs to map the complex interrelations between variables which influence DTx economic value, the research moves beyond linear models of value creation to capture the dynamic and interconnected nature of the DTx development ecosystem.

This systems perspective aligns with Greenhalgh et al.'s (2017, p. 2) assertion that "(…) *it is not individual factors that make or break a technology implementation effort but the dynamic interaction between them*." The CLD developed in this thesis (Figure 24) provides a theoretical foundation for understanding how early-stage decisions propagate throughout the system to influence ultimate economic outcomes. This systems-based framework is particularly insightful for explaining how apparently minor decisions in early DTx development stages can produce disproportionately large effects on clinical validation outcomes and economic viability through feedback mechanisms and non-linear interactions among key factors.

These above theoretical contributions collectively advance the understanding of DTx economic value by providing conceptual frameworks that bridge the gap between theoretical knowledge and practical applications. By offering more complex theoretical models for understanding the causal interplay of factors influencing DTx economic value, this research lays the groundwork for more effective approaches to developing, evaluating, and implementing economically viable DTx interventions in healthcare systems.

7.2.2. Practical contributions

While the theoretical contributions presented contribute to advances in the conceptual understanding of the relationship between DTx and economic value, their significance lies equally in their practical applicability. Translating these theoretical insights into actionable approaches is useful to address pressing challenges faced by healthcare stakeholders throughout the DTx ecosystem. The following practical contributions demonstrate how abstract frameworks can be operationalized into concrete recommendations for stakeholders involved in DTx lifecycle, enhancing economic value consideration throughout development and implementation.

To effectively synthesize these contributions, it is beneficial to revisit the thesis' objectives and address each one systematically. The practical contributions outlined below translate research findings into actionable insights that can enhance the economic viability and successful implementation of DTx interventions in real-world healthcare settings. These contributions directly address the research objectives by providing tangible frameworks, tools, and approaches that can be applied by researchers, engineers, clinicians, HTA specialists, payers, and policymakers to overcome identified barriers in DTx development and implementation.

Sub-objective #1:
Understand and characterize the concept of economic value in the context of DTx, as well as factors that might influence the DTx and economic value relationship.

The complexity of defining and assessing economic value in the context of DTx implementation in healthcare systems was highlighted through a multifaceted research approach. This approach encompassed a literature review (Chapter 2), systematic literature review (Chapter 4), GCM study (Chapter 5), and a qualitative study (Chapter 6). As discussed earlier, the research revealed that the concept of economic value for DTx extends beyond traditional health outcomes and net costs, aligning with Lakdawalla et al.'s (2018) expanded concept of value in healthcare. In an inventory of “value elements”, Lakdawalla et al. (2018) proposed new elements, such as “productivity” (impact of treatment on productivity), “adherence-improving factors” (features of the treatment that enhance adherence), and “real option value” (technology extending patient life). These value elements were also identified in the first two studies as important, although they are inconsistently included in economic evaluations of DTx.

The systematic literature review provided critical insights into the methodological approaches used to assess the economic value of DTx interventions and their potential cost-effectiveness. This comprehensive analysis highlighted both the strengths and limitations of current DTx economic evaluation methods, leading to important considerations and recommendations for strengthening and standardizing such evaluations. While revealing the potential economic benefits of DTx interventions, the review simultaneously underscored their context-specific nature, proposing recommendations to address significant methodological challenges in current DTx economic evaluations.

These findings and subsequent recommendations align closely with those of other scholars in the field, especially the need for more robust evidence demonstrating the value proposition of DTx (Rahimi, 2019). Furthermore, the recommendations address the complexities inherent in DTx interventions, as emphasized by Gomes et al. (2022) and Kolasa and Kozinski (2020), who stressed the importance of

integrating these complexities into economic assessments. The general call for strengthening current economic evaluations of these emerging interventions, as proposed by Yan et al. (2021) is also reflected in the findings.

The GCM study (Chapter 5) along with the qualitative study (Chapter 6) further enriched the understanding of the concept of economic value in the context of DTx, revealing that its definition varies among diverse stakeholders involved throughout the DTx development lifecycle. This finding corroborates Greenhalgh et al.'s assertion that "value" means different things to different stakeholders (2017).

In the initial phases of DTx development, the concept of economic value is frequently, albeit implicitly, characterized or articulated in terms of the intervention's potential effects on patient flow, resource utilization, and treatment adherence. These factors have been identified as crucial determinants of DTx economic value, often superseding traditional measures of cost-effectiveness – the technical standard by HTA experts and regulatory authorities for market approval and reimbursement.

Beyond understanding and defining the concept of economic value in the context of DTx, the first sub-objective also aimed to identify the specific economic value drivers relevant for DTx. Through the systematic literature review, 18 factors impacting a DTx economic value were identified, characterized as having an "important" or "significant" impact or were deemed "decisive" to the cost-effectiveness of DTx. The GCM study expanded this understanding by facilitating the identification of 59 factors critically influencing the economic value of DTx, including the 18 initial factors. These factors were determined to be important and influential to a DTx economic value by an international expert panel of participants (n=62).

Finally, another critical insight derived from each study is the causal relationship between early-stage economic considerations and a DTx's capacity to generate economic value. As evidenced in the systematic review, and corroborated by participants in the GCM study, the economic value of a DTx is influenced by the

early incorporation of economic factors in its development and clinical validation processes. This finding underscores the necessity of considering these economic elements from the outset of the DTx lifecycle. Such an approach may enhance the overall economic impact and viability of the DTx intervention.

While this recommendation represents a novel approach in the DTx landscape, it aligns with recent research advocating for the incorporation of economic factors into the initial phases of technological design and development. Keogh et al. (2024) and Michie et al. (2017) have indeed emphasized the importance of this integrated approach, highlighting its potential to enhance the overall value and economic viability of DTx solutions.

By considering clinical, technological and economic aspects concurrently, stakeholders can create more robust and commercially viable products that are better positioned to meet the needs of patients, healthcare providers, and payers alike. This approach may ultimately increase the likelihood of successful market access, implementation and long-term viability of DTx interventions.

In conclusion, through a mixed methods-based approach, combining three research studies, this thesis provided both breadth and depth to a systemic, yet nuanced and detailed understanding of the complex interplay between various factors that shape DTx economic value. It is suggested that by anticipating and integrating economic factors during the initial phases of DTx development, the chances of regulatory approval, reimbursement and ultimately adoption can be optimized.

The identification of these factors also serves as a foundation for future research and practical applications in the field of DTx economic evaluation.

Sub-objective #2:
Gain a deeper understanding of how the DTx economic value and its drivers are considered early in the DTx technological development and clinical validation

The GCM study and the qualitative study contributed significant new insights to this sub-objective. The GCM study provided a better understanding of how stakeholders involved in the development, validation, and implementation of DTx collectively conceptualize factors influencing their economic value. This methodological approach was instrumental in elucidating how both collective and individual stakeholders, including specific groups (e.g., researchers), contribute to and influence DTx economic value. Furthermore, it facilitated a deeper understanding of the interrelationships among the eight clusters and 59 factors driving DTx economic value.

Notably, the study revealed that researchers, as a stakeholder group, considered factors related to *DTx Clinical Impact* cluster to be of paramount importance in driving economic value, while assigning low priority to *DTx Associated Costs* in their day-to-day activities and decision-making processes. This analysis uncovered a significant perception gap between researchers and other participant groups, extending beyond this cluster of cost considerations to others as well (Table 15).

The subsequent qualitative investigation (Chapter 6) explored this perception gap, and it elucidated that the way researchers execute their early DTx engagement, development, and clinical validation can influence the conditions that drive economic value—a critical determinant for market access and reimbursement (Kario et al., 2021). The analysis revealed three core themes, several puzzling decision-making patterns, and three primary generative mechanisms: *Professional Norms*, *Researcher Experience*, and *Adoption Uncertainties*. SD methodology facilitated the development of CLDs for each mechanism, mapping variables and causal relationships that ultimately converged into an integrated model that explains the interplay between these mechanisms and their collective influence on researchers' DTx decision-making processes.

These findings highlight the pivotal role of researchers during early DTx development phases and emphasize the necessity of incorporating economic value drivers from inception, as articulated by Keogh et al. (2024) and Michie et al. (2017). By recognizing and addressing barriers, such as limited awareness of economic considerations, researchers can strengthen the economic viability of DTx interventions throughout their lifecycle. This proactive approach to economic value generation may create more efficient development pathways and enhance the probability of successful market access, deployment and clinical adoption of DTx.

Main objective:
Develop methodological recommendations to guide stakeholders involved in the DTx development, clinical validation and implementation consider potential economic value drivers.

The two aforementioned sub-objectives of this thesis research culminated in the development of a set of methodological recommendations designed to guide stakeholders throughout the DTx lifecycle, elucidating what constitutes economic value drivers for DTx, and how such drivers are and might be considered. They acknowledge the multifaceted nature of DTx development, clinical validation and implementation by recognizing that decisions made at various stages of the lifecycle can significantly impact the overall economic viability of these interventions. These recommendations also provide a structured approach for stakeholders to evaluate and prioritize various factors which contribute to the economic value of DTx, potentially leading to more economically viable solutions.

The thesis' recommendations are presented in detail in the subsequent section. They bridge the gap between theoretical understanding and practical application, often characterized as the transition "*from bench to bedside.*"

7.2.3. Managerial recommendations

The practical contributions outlined above address fundamental knowledge gaps in understanding DTx economic value. However, bridging theory and practice require structured, implementable recommendations that guide stakeholders' decision-making processes. The following managerial recommendations synthesize insights from all three research studies into a cohesive framework for action, providing specific intervention points where stakeholders can potentially enhance DTx economic value generation.

Overview of managerial recommendations

This thesis yields actionable insights and strategic recommendations for key stakeholders across the DTx ecosystem—researchers, engineers, clinicians, HTA specialists, payers, and policymakers. Drawing on ST methodology employed in the third study (Chapter 6), a CLD synthesizes these recommendations into an integrated framework (Figure 27), providing a comprehensive visualization of their interconnected nature.

The CLD approach is particularly well suited for representing the complex dynamics uncovered in this DBA research. Rather than presenting isolated factors, it captures the crucial interactions between elements within the DTx development ecosystem. As noted earlier, "(…) *it is not individual factors that make or break a technology implementation effort but the dynamic interaction between them*" (Greenhalgh et al., 2017, p. 2). The CLD methodology responds directly to this insight by mapping these interactions explicitly. Nguyen et al. (2025, p. 1) affirm that CLDs "*provide decision-makers with a sophisticated yet accessible tool to visualize and understand complex system behavior*." This visualization technique enables stakeholders to comprehend not just individual recommendations, but the systemic relationships among them—revealing how interventions in one area propagate throughout the ecosystem.

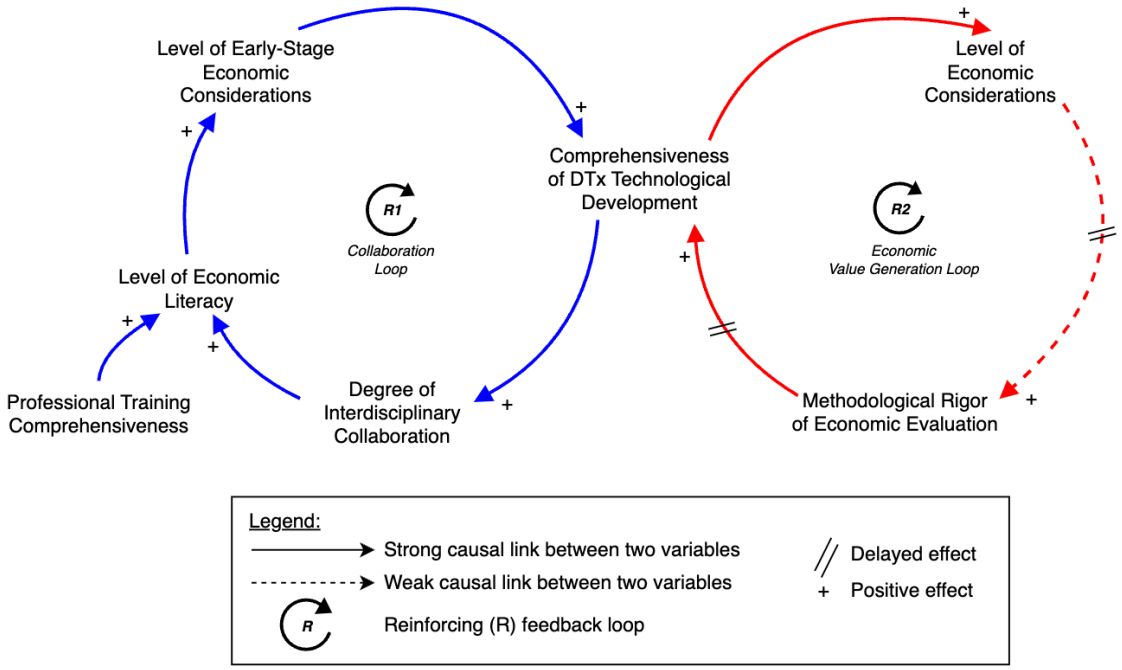
The power of CLDs lies in their ability to reveal causal mechanisms, making them ideally suited for illustrating how early-stage decisions regarding economic value

drivers influence the ultimate economic value of DTx interventions—a central finding of this research. By depicting reinforcing and balancing feedback loops, the CLD illuminates leverage points where targeted interventions can yield maximum impact.

This approach transforms abstract research findings into a pragmatic decision-support tool for DTx stakeholders at all levels (Nguyen et al., 2025). It enables rapid identification of priority areas while demonstrating how specific decisions influence the broader value proposition of DTx interventions. Beyond merely summarizing findings, the CLD serves to outline as a strategic roadmap, guiding evidence-based decision-making for enhancing economic value creation throughout the DTx development lifecycle.

The CLD in Figure 27 conceptualizes the managerial recommendations as an interconnected system, synthesized from a comprehensive review of the three research studies, with particular emphasis on the identified intervention points within the DTx development ecosystem, which are discussed below.

Figure 27. Influence diagram: Managerial recommendations as a system



Five core recommendations, derived from our CLD framework, have been identified to support stakeholders in navigating the complex landscape of DTx economic value creation:

1. **Foster interdisciplinary collaboration in DTx development:** Establish cross-functional teams integrating clinical, technical, and economic expertise throughout the development lifecycle to transform DTx from laboratory concepts into economically viable clinical interventions.

2. **Embed economic considerations in early development stages:** Integrate economic value assessments from the inception of DTx projects through comprehensive checklists, stage-gate criteria, and scenario planning to prevent costly retrofitting of economic considerations to already-developed solutions.

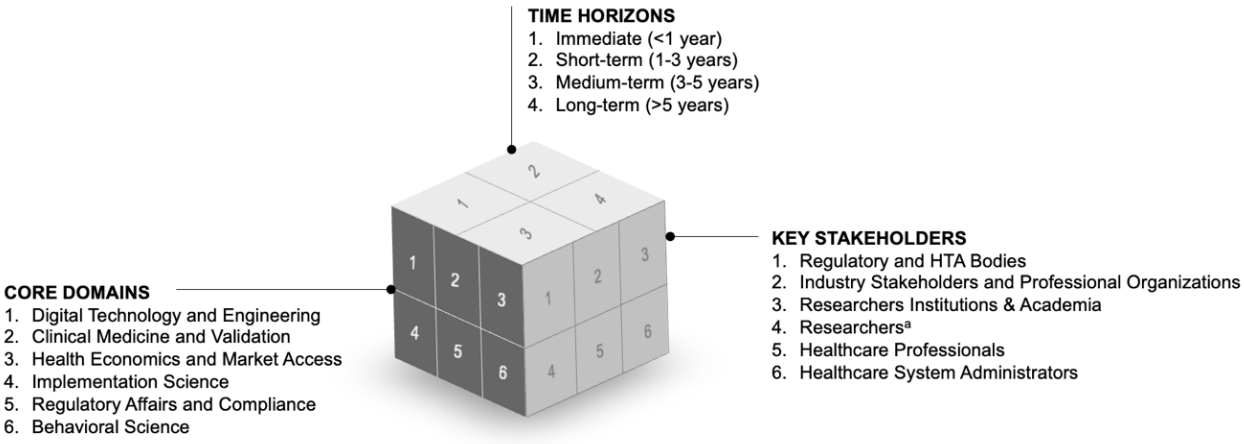
3. **Establish economic integration guidelines across the DTx lifecycle:** Develop standardized frameworks, decision support tools, and professional certification programs specifically tailored for DTx economic evaluation to address the identified economic literacy gap among stakeholders.

4. **Integrate economic value dimensions in professional training:** Broaden professional training curricula beyond clinical and technical considerations to include economic literacy components through specialized education modules, mentorship programs, and cross-training initiatives.

5. **Enhance methodological rigor in DTx economic evaluation:** Develop robust, consistent methodological frameworks that incorporate DTx-specific characteristics to improve the comparability of findings and support more informed decision-making by healthcare providers, payers, and policymakers.

These five recommendations, along with their associated 28 sub-recommendations, are summarized in Table 22 and elaborated in the subsequent section. The proposed interventions are inherently multidimensional, encompassing various stakeholders within the DTx ecosystem across different domains and time horizons, as illustrated in Figure 28.

Figure 28. Cross-dimensional thesis recommendations: Spanning key stakeholders, core domains, and time horizons



[a] *Including research-engineers, health systems and social science researchers, clinician-researchers, and practitioner-researchers.*

Implementation of these recommendations varies considerably, with some requiring greater time, effort, resources, and stakeholder coordination than others. To evaluate implementation requirements and establish a prioritized roadmap, each recommendation was assessed across five critical dimensions: (1) **impact potential**, measuring the degree of enhancement to DTx economic value; (2) **implementation feasibility**, indicating ease of execution; (3) **time to value**, quantifying how rapidly benefits materialize; (4) **stakeholder alignment**, evaluating how effectively the recommendation addresses perspective gaps among key actors; and (5) **systemic influence**, assessing the potential to trigger ecosystem-wide transformation. The assessment of these recommendations, leading to a prioritization on a time horizon, is presented in Table 22 and summarized in Table 21.

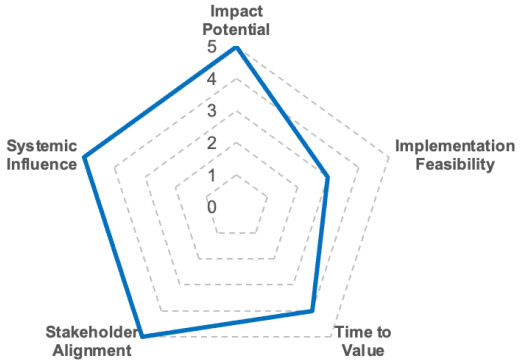
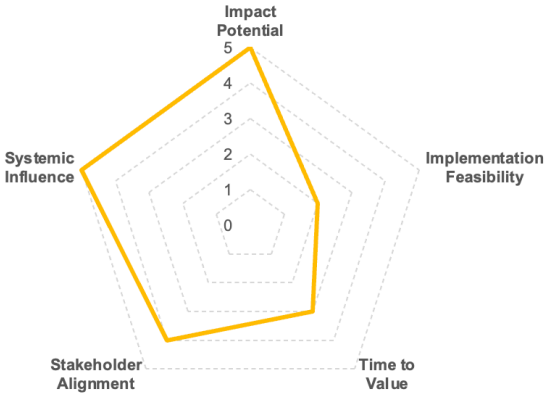
This multifaceted evaluation framework provides stakeholders with a comprehensive understanding of implementation requirements and potential implications, enabling strategic prioritization of interventions specific to each stakeholder group's needs, thereby optimizing resource allocation and maximizing DTx economic value creation across the healthcare ecosystem.

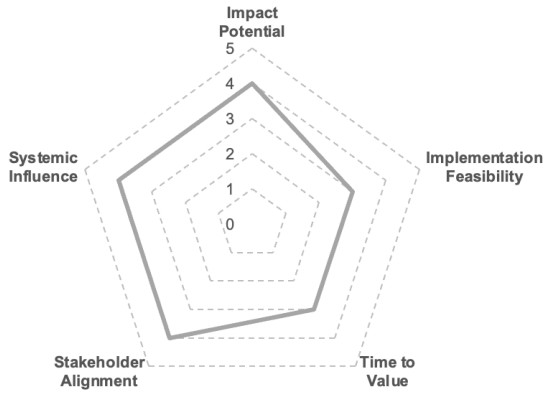
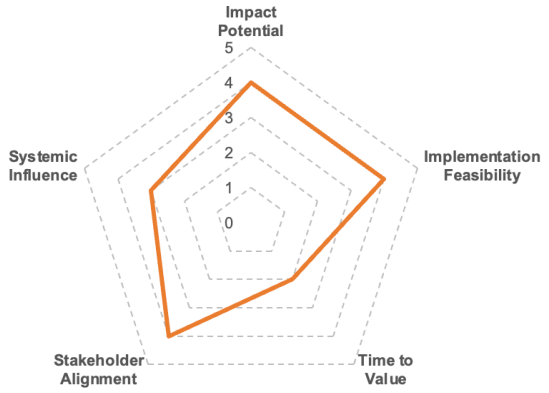
Table 21. Thesis managerial recommendations prioritization

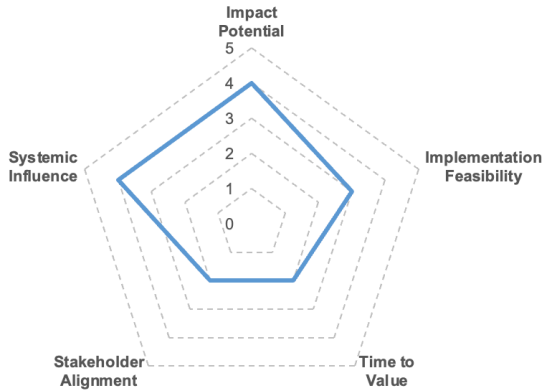
Rank	Recommendations	Implementation Timeline	Impact Potential	Implementation Feasibility	Time to Value	Stakeholder Alignment	Systemic Influence	Total
1	**Foster interdisciplinary collaboration in DTx development**	Immediate	5	3	4	5	5	**22**
2	**Embed economic considerations in early development stages**	Short-term	5	2	3	4	5	**19**
3	**Establish economic integration guidelines across the DTx lifecycle**	Medium-term	4	3	3	4	4	**18**
4	**Integrate economic value dimensions in professional training**	Long-term	4	4	2	4	3	**17**
5	**Enhance methodological rigor in DTx economic evaluation**	Medium-term	4	3	2	2	4	**15**

Legend: Scoring Scale: 1 = Low, 3 = Medium, 5 = High

Table 22. Overview of thesis' recommendations prioritization

Rank	Recommendations	Recommendation Assessment	Sub-recommendations
1	**Foster interdisciplinary collaboration in DTx development**		• To establish translation roles within DTx research and development teams to facilitate a bench-to-bedside approach, transforming DTx from laboratory concepts into clinical tools with direct patient benefit; • To create cross-functional teams that integrate clinical, technical, and economic expertise throughout the development lifecycle; • To establish formal partnerships between academic institutions and industry stakeholders to foster knowledge exchange and align academia-industry research and development priorities; • To implement structured decision-making frameworks that explicitly require multidisciplinary input at critical development milestones.
2	**Embed economic considerations in early development stages**		• To develop comprehensive economic consideration checklists specific to each phase of DTx development process; • To establish comprehensive stage-gate criteria that integrate economic milestones alongside clinical and technical evaluation points when approving subsequent phases of DTx development, implementing agile-adapted sprint cycles that enable continuous economic validation and stakeholder feedback while maintaining regulatory compliance requirements specific to healthcare contexts; • To implement economic scenario planning as a standard component of DTx conceptualization and design; • To establish formal mechanisms for defining and assessing economic impacts during clinical validation, including specific endpoints in clinical trials (e.g., Implementation outcome endpoint in a trial can include, for example, an evaluation of the DTx implementation cost, or a modeling of scaled-up implementation and potential benefits to healthcare resource utilization).

3	**Establish economic integration guidelines across the DTx lifecycle**		• To implement professional certification programs by professional education providers and industry associations focusing on economic aspects of DTx development, such as “mini-HTA for digital health solutions for non-health economist experts”; • To include dedicated economic sessions at clinical and technical domain conferences, organized by professional societies; • To develop publicly accessible training materials led by health economics experts and digital health organizations; • To create interdisciplinary training programs by academic institutions and continuing education providers exposing stakeholders to various aspects of DTx development, including economic considerations; • To develop decision support tools by health economics experts and digital health associations specific to DTx economic evaluation to guide stakeholders through key considerations at each development stage; • To establish economic value benchmarking frameworks by HTA bodies and health economics research groups specifically calibrated for different DTx categories and disease areas.
4	**Integrate economic value dimensions in professional training**		• To integrate economic value considerations into clinical and technical curricula related to digital health and DTx by academic institutions; • To develop specialized continuing education modules on economic value assessment specifically tailored for DTx by professional organizations; • To establish mentorship programs pairing researchers with health economists to facilitate knowledge transfer by research institutions; • To implement cross-training initiatives where team members gain exposure to disciplines outside their primary expertise by DTx developers; • To provide clear educational materials explicating economic evaluation expectations specifically for DTx by regulatory and HTA bodies.

5	**Enhance methodological rigor in DTx economic evaluation**		• To ensure adherence to local and international guidelines for economic evaluations of DTx interventions by researchers and health economists; • To develop standardized methods for assessing the economic impact of DTx by health economics research institutions and HTA bodies, accounting for their context-specific nature and addressing complexities in quantifying their full economic value; • To establish guidance from professional associations, regulators, and HTA bodies on costs and factors to be considered for each perspective (e.g., payer, patient, societal, etc.), facilitating generalization and comparison of findings across economic evaluations; • To adopt a more transparent, systematic, and exhaustive consideration of all costs associated with implementing DTx interventions by health economics researchers, including direct patient out-of-pocket costs and indirect costs, such as productivity loss; • To extend the time horizon of economic evaluations to capture all or most clinical and economic impacts of the respective intervention, incorporating modeling decisions to extrapolate outcome measures over time; • To ensure that trial populations reflect the patient groups that clinical researchers and designers treat in real-world clinical practice, it is necessary to address the biases in participant recruitment observed in the included studies; • To incorporate health equity considerations into economic evaluations by health economics researchers and policy analysts; • To quantify uncertainty and test the robustness of economic evaluation conclusions through sensitivity analysis by health economics researchers; • To develop DTx-specific value assessment frameworks by health economics experts, HTA bodies, and digital health organizations that account for unique characteristics, such as continuous iteration, data generation capabilities, and network effects.

Details of the managerial recommendations

The following section elaborates on these recommendations, with each intervention strategically targeting critical leverage points identified through this research. Our recommendations address two primary reinforcing feedback loops in Figure 27: R1, which focuses on optimizing development processes and enhancing interdisciplinary collaboration in DTx development; and R2, which emphasizes advancing evaluation methodologies to demonstrate clinical and economic value.

Recommendation #1: Foster interdisciplinary collaboration in DTx development

To address the significant gap identified in DTx development approaches between certain stakeholder groups, such as academia and industry representatives, as highlighted in the third study (Chapter 6), a more collaborative and multidisciplinary approach is recommended. This approach aims to strengthen the degree of interdisciplinary collaboration in DTx development (Figure 27).

The research revealed that siloed development processes, focused on short-term solutions and with delayed stakeholder engagement, may significantly impede the generation of economic value. Broader stakeholder engagement should be initiated from the early stages of the DTx development process, including the earlier involvement of commercialization leaders and health economists, as part of the core DTx development team, or in an advisory capacity. This early integration is important, as retrofitting economic considerations to already-developed solutions might not succeed. This challenge parallels the well-established concept of technical debt in software development, where shortcuts or suboptimal decisions made during early development phases create compounding costs and constraints that become increasingly expensive to address over time (Melo et al., 2022). In DTx development, delayed economic consideration creates what can be termed 'economic technical debt' - fundamental developmental decisions made without economic input that later

require costly restructuring to achieve viability. Just as refactoring code to address technical debt becomes exponentially more expensive as systems mature, retrofitting economic considerations into established DTx solutions faces similar exponential cost increases due to interconnected dependencies between clinical functionality, technological architecture, and economic requirements.

Therefore, the DTx development process should evolve toward a more collaborative, cross-disciplinary approach, ultimately becoming interdisciplinary, fully integrating the diverse expertise required to develop these complex interventions. This evolution may necessitate a fundamental shift for some teams and research institutes in how DTx projects are conceptualized and executed, moving from siloed and sequential development processes toward a more holistic, integrated approach (Greenhalgh et al., 2017).

To foster interdisciplinary collaboration in DTx development (*Collaboration loop* R1), several realistic implementable recommendations have been identified for DTx development organizations, industry representatives and research institutions:

1. To establish translation roles within DTx research and development teams to facilitate a bench-to-bedside approach, transforming DTx from laboratory concepts into clinical tools with direct patient benefit;

2. To create cross-functional teams that integrate clinical, technical, and economic expertise throughout the development lifecycle;

3. To establish formal partnerships between academic institutions and industry stakeholders to foster knowledge exchange and align academia-industry research and development priorities;

4. To implement structured decision-making frameworks that explicitly require multidisciplinary input at critical development milestones.

To bridge communication gaps between different teams and stakeholders, a common and shared language around economic considerations for all stakeholders in the DTx ecosystem should be developed. This shared language can support and facilitate better communication and co-constructed understanding across diverse stakeholder groups, especially regarding how DTx economic considerations should be defined and integrated in the DTx development process. The research revealed significant terminological disconnects between stakeholder groups, with clinical, technical, and economic experts often using different terms to describe similar concepts. The implementation of collaborative platforms or forums where stakeholders from different backgrounds can regularly interact and share insights throughout the DTx lifecycle could enhance such communication (Blandford et al., 2018).

By fostering an interdisciplinary and collaborative approach, the DTx development process may lead to the creation of interventions that are not only clinically effective but also economically viable and readily adoptable in real-world healthcare settings. Such an approach could potentially accelerate the development of DTx solutions and improve their chances of successful implementation and deployment within healthcare systems. This collaboration may help bridge the gap between early-stage development and implementation considerations, strengthening the level of economic literacy in DTx development (positive relationship in Figure 27).

The implementation of these recommendations aligns with recent emphasis in the literature for more integrated approaches to digital health innovations (Moshi et al., 2018). By facilitating closer collaboration between diverse stakeholders, this approach has the potential to address key challenges in DTx development, including the need for robust economic evidence and improved alignment between clinical, technological, and economic considerations (Mathews et al., 2019).

Recommendation #2:
Embed economic considerations in early development stages

While interdisciplinary collaboration forms the structural foundation for DTx development, attention must shift toward the practical integration of economic considerations in the earliest development phases. This recommendation addresses the critical timing element identified in the research, where early economic integration yields a substantially greater impact than retrofitting economic considerations to already developed solutions.

The GCM and qualitative research studies highlighted indeed that economic factors are often insufficiently considered, despite their acknowledged importance and impact on a DTx ability to generate economic value, especially early in the DTx development process. Specifically, in Figure 27, a limited *level of early-stage economic considerations* would impact the *comprehensiveness of DTx technological development* (Feedback loop R_1), diminishing the *level of economic considerations* (Feedback loop R_2), which as an output, might hinder the ability of a DTx to generate economic value. The reciprocal relationships among these four above-mentioned variables in R1 and R2 illustrate the interconnected and complex nature of the DTx development ecosystem. The *comprehensiveness of DTx technological development* both influences and is influenced by the *level of early-stage economic considerations*, while simultaneously maintaining a bidirectional relationship with the *level of economic considerations*.

This bidirectional relationship creates both challenges and opportunities in the DTx development process. The research demonstrates that economic considerations viewed as constraints, or outside of researchers' mandates, can enhance technological development and increase DTx potential for deployment within healthcare systems.

The primary managerial recommendation, therefore, is to acknowledge the existence and significance of this relationship between DTx and economic value,

and to integrate economic considerations throughout the entire development process—from initial conceptualization through technological development and clinical validation. Stakeholders involved in early-stage DTx development, such as researchers, engineers, and clinicians, should be encouraged to consider economic factors alongside clinical and technological aspects. This approach involves integrating implementation-related aspects, including economic considerations, as early as possible in DTx development and clinical trials.

The GCM study's bivariate go-zone plot analysis provides further details and prioritizes areas concerning these “implementation-related aspects.” Three clusters were identified as highly important in influencing DTx economic value, yet insufficiently considered in participants' daily decision-making processes: *DTx Implementation*, *DTx Monetization Models*, and *DTx Associated Costs*. Additionally, eight “high priority” factors (factors 8, 11, 18, 30, 32, 40, 52, and 54) were deemed important for *DTx Economic Value* generation but reported as less considered by participants.

Based on these analyses, the proposed conceptual framework of priority clusters and factors driving DTx economic value helps all stakeholders understand how to define and prioritize these early-stage economic considerations (Figure 14 and 13). This framework is intended to guide comprehensive consideration and integration of relevant economic value drivers, ensuring a methodical approach to decision-making.

To operationalize this recommendation, the following practical implementation strategies are proposed for DTx developers, HTA bodies and health economists:

1. To develop comprehensive economic consideration checklists specific to each phase of DTx development process;

2. To establish comprehensive stage-gate criteria that integrate economic milestones alongside clinical and technical evaluation points when approving subsequent phases of DTx development, implementing agile-

adapted sprint cycles that enable continuous economic validation and stakeholder feedback while maintaining regulatory compliance requirements specific to healthcare contexts;

3. To implement economic scenario planning as a standard component of DTx conceptualization and design;

4. To establish formal mechanisms for defining and assessing economic impacts during clinical validation, including specific endpoints in clinical trials (e.g., Implementation outcome endpoints in a trial can include, for example, an evaluation of the DTx implementation cost, or a modeling of scaled-up implementation and potential benefits to healthcare resource utilization).

These implementation strategies should be supported by adopting agile methodologies specifically adapted for healthcare contexts. As noted by Kokol et al. (2022, p.1), agile approaches remain underutilized in digital health software development, despite their potential to “deliver clinical value to patients and public health systems.” The research findings suggest that integrating economic validation into iterative development cycles, rather than deferring it to final stages, could address the systematic deprioritization of economic considerations identified in this study. Such methodologies would involve longer development cycles and more extensive testing than typical software products, but could retain the core benefits of continuous stakeholder feedback while ensuring DTx solutions are economically viable from conception.

Finally, integrating economic considerations early in the DTx lifecycle requires aligning research priorities with economic considerations, adjusting organizational priorities toward more translational aspects, key performance indicators, and team compositions as highlighted in the qualitative research study (Chapter 6). Additionally, addressing identified gaps, such as economic literacy among researchers, and strengthening interdisciplinary collaboration between

stakeholders involved in DTx development and clinical validation, are complementary and crucial steps, as discussed previously.

Recommendation #3:
Establish economic integration guidelines across the DTx lifecycle

Building upon the foundation established through interdisciplinary collaboration and the need to embed economic considerations early in the DTx lifecycle, as revealed by the GCM and qualitative studies, an economic literacy gap persists. These first two recommendations might not be sufficient for stakeholders to effectively consider these factors without relevant tools and frameworks as discussed.

It is therefore recommended to implement additional intervention points to address such an economic literacy gap, and ultimately provide guidance on integrating economic considerations throughout the DTx lifecycle to any stakeholders involved in DTx development.

Complementary to the previous recommendations, health economics education could be enhanced for stakeholders within the DTx ecosystem, and may be achieved through multiple avenues:

1. To implement professional certification programs by professional education providers and industry associations focusing on economic aspects of DTx development, such as “mini-HTA for digital health solutions for non-health economist experts”;

2. To include dedicated economic sessions at clinical and technical domain conferences, organized by professional societies;

3. To develop publicly accessible training materials led by health economics experts and digital health organizations;

4. To create interdisciplinary training programs by academic institutions and continuing education providers exposing stakeholders to various aspects of DTx development, including economic considerations;

5. To develop decision support tools by health economics experts and digital health associations specific to DTx economic evaluation to guide stakeholders through key considerations at each development stage;

6. To establish economic value benchmarking frameworks by HTA bodies and health economics research groups specifically calibrated for different DTx categories and disease areas.

The provision of such guidance necessitates the development of tools and methods to assist relevant stakeholders in understanding how to approach the integration of economic considerations and generate appropriate levels of evidence, both clinically and economically. This integration is not merely additive but transformative to the development process itself. The qualitative study in this thesis suggested several specific tools to facilitate this process. These include conducting preliminary market research, developing simple economic models combined with sustainability plans, and performing mini-HTAs.

The systematic review revealed significant methodological inconsistencies in DTx economic evaluations, suggesting that standardized approaches are urgently needed. By implementing these educational and guidance initiatives, stakeholders may be better equipped to navigate the complex economic landscape of DTx development. This enhanced understanding may, in turn, contribute to the development of more economically viable and successful DTx interventions, ultimately benefiting both healthcare providers and patients.

Recommendation #4:
Integrate economic value dimensions in professional training

Complementary to the previous recommendation, appropriate professional training represents the next critical intervention point in the DTx economic value

ecosystem. The effectiveness of collaboration depends to a certain extent on stakeholders possessing sufficient economic literacy to engage meaningfully across disciplinary boundaries.

However, the research identified significant gaps in economic literacy among DTx developers, particularly those with primarily clinical or technical backgrounds (partially addressed in the previous recommendation). As discussed in the third study (Chapter 6), taking the example of researchers, professional training directly influences economic literacy levels, which in turn influences economic considerations in DTx development, particularly in the early stages.

To address this gap, it is recommended to systematically broaden professional training curricula of stakeholders involved in DTx development, from either pure clinical or pure technical considerations, to also include important and complementary diverse notions of value. To echo participants' interviews in the third paper, too many engineers have not heard the term QALY, and too many clinicians do not have a relevant appreciation of the implications of AI-based interventions for them and their patients. This knowledge deficit creates a significant barrier to economic value optimization, as revealed in the GCM and qualitative research studies. Specifically:

1. To integrate economic value considerations into clinical and technical curricula related to digital health and DTx by academic institutions;
2. To develop specialized continuing education modules on economic value assessment specifically tailored for DTx by professional organizations;
3. To establish mentorship programs pairing researchers with health economists to facilitate knowledge transfer by research institutions;
4. To implement cross-training initiatives where team members gain exposure to disciplines outside their primary expertise by DTx developers;

5. To provide clear educational materials explicating economic evaluation expectations specifically for DTx by regulatory and HTA bodies.

These educational interventions would contribute to enhancing the level of economic literacy across stakeholder groups involved in DTx development. The research demonstrated a clear causal relationship between professional training comprehensiveness and successful integration of economic considerations (Figure 24). It will ultimately strengthen the collaboration loop (R1) in Figure 27, improving the comprehensiveness of DTx technological development and economic value generation.

Recommendation #5:
Enhance methodological rigor in DTx economic evaluation

While the preceding recommendations focus primarily on the development process within feedback loop R1, this final recommendation addresses the *methodological rigor of economic evaluation* within feedback loop R2. The bidirectional relationship between evaluation methods and development processes creates a second reinforcing loop that complements and strengthens the implementation of preceding recommendations.

The systematic literature review of DTx economic evaluations revealed indeed methodological deficits and biases, necessitating specific recommendations for future evaluations, as underscored by the “moderate” methodological rigor observed across the 18 included studies. Participants interviewed in the qualitative research study also highlighted a lack of DTx specific framework and guidance set by professional and authoritative bodies on how economic evaluation should be conducted for DTx to assess the potential economic impact of DTx.

Thus, the *methodological rigor of economic evaluation* in Figure 27 represents a variable that influences, with a time delay, the *comprehensiveness of DTx technological development* and ultimately, the *level of economic considerations* in a DTx process. This relationship suggests that improving evaluation

methodologies will enhance the demonstrated economic value of DTx solutions, which in turn, and with some time delay, will also drive further refinement of evaluation frameworks.

To enhance the quality and rigor of economic evaluations for DTx, several key recommendations have been identified:

1. To ensure adherence to local and international guidelines for economic evaluations of DTx interventions by researchers and health economists;

2. To develop standardized methods for assessing the economic impact of DTx by health economics, research institutions and HTA bodies, accounting for their context-specific nature and addressing complexities in quantifying their full economic value;

3. To establish guidance from professional associations, regulatory authorities, and HTA bodies on costs and factors to be considered for each perspective (e.g., payer, patient, societal, etc.), facilitating generalization and comparison of findings across economic evaluations;

4. To adopt a more transparent, systematic, and exhaustive consideration of all costs associated with implementing DTx interventions by health economics researchers, including direct patient out-of-pocket costs and indirect costs, such as productivity loss;

5. To extend the time horizon of economic evaluations to capture all or most clinical and economic impacts of the respective intervention, incorporating modeling decisions to extrapolate outcome measures over time;

6. To ensure that trial populations reflect the patient groups treated by clinical researchers and designers in real-world clinical practice, it is essential to address the biases in participant recruitment observed in the included studies;

7. To incorporate health equity considerations into economic evaluations by health economics researchers and policy analysts;

8. To quantify uncertainty and test the robustness of economic evaluation conclusions through sensitivity analysis by health economics researchers;

9. To develop DTx-specific value assessment frameworks by health economics experts, HTA bodies, and digital health organizations that account for unique characteristics, such as continuous iteration, data generation capabilities, and network effects.

These proposed methodological recommendations aim to develop a robust, consistent methodological framework that incorporates the unique features distinguishing DTx interventions. By bridging the knowledge gap between clinical, technological, and economic aspects of DTx development, these recommendations address a critical need in the field. The proposed approach, through these five recommendations, may result in DTx interventions that are not only clinically effective but also cost-effective and sustainable within healthcare systems.

The implementation of these recommendations may also lead to more robust evidence generation for DTx, addressing concerns raised by HTA bodies and payers regarding the economic value of these interventions (Moshi et al., 2018). It would enhance the comparability of findings, would support more informed decision-making in the rapidly evolving field of DTx, and ultimately would minimize uncertainties surrounding the adoption of DTx interventions for providers, payers, and patients. By equipping stakeholders with the necessary tools and knowledge to consider economic factors from the early stages of development (recommendation #2).

This approach to enhancing the *degree of interdisciplinary collaboration* (recommendation #1), the *level of* e*conomic literacy* (recommendation #3), and *professional training comprehensiveness* (recommendation #4), aligns with the

recent insistence in the literature for improved methodological rigor in digital health economic evaluations. Moshi et al. (2018) emphasized the need for more robust evaluation frameworks, while the systematic review highlighted the importance of incorporating equity considerations, an aspect often inadequately addressed in current assessments. By addressing the identified gaps and inconsistencies in current evaluation practices, this approach has the potential to strengthen the evidence base for DTx interventions, facilitating more effective integration into healthcare systems and decision-making processes (Mathews et al., 2019; Yeung et al., 2023).

Finally, these recommendations also highlight the need for ongoing collaboration between researchers, policymakers, and industry stakeholders to refine and standardize economic evaluation methods for DTx. This collaborative approach, supported by agile methodologies adapted for healthcare contexts, could lead to the development of more comprehensive and context-specific evaluation frameworks, better equipped to capture the full value proposition of DTx interventions in diverse healthcare settings (Goldsack et al., 2020).

Stakeholder responsibilities

By adopting a systems thinking approach, the thesis has identified interconnected intervention points where focused action can yield significant improvements in DTx economic value generation. The five core recommendations address different aspects of the DTx development ecosystem, from collaboration structures and early-stage economic integration to methodological rigor in evaluation. These recommendations are interconnected and mutually reinforcing, as illustrated by the causal loop diagram (Figure 27). As discussed earlier, the successful implementation of these recommendations requires ongoing collaboration and coordinated action from multiple stakeholders across the DTx ecosystem. Table 23 outlines the responsibilities of key stakeholder groups in implementing each recommendation.

Table 23. Stakeholder responsibilities for implementing thesis recommendations

Rank	Recommendations	Regulatory and HTA Bodies	Industry Stakeholders and Professional Organizations	Research Institutions and Academia	Researchers	HCPs[a]	Healthcare System Administrators
1	Foster interdisciplinary collaboration in DTx development		✓	✓	✓	✓	✓
2	Embed economic considerations in early development stages	✓	✓	✓	✓	✓	
3	Establish economic integration guidelines across the DTx lifecycle	✓	✓				✓
4	Integrate economic value dimensions in professional training	✓	✓	✓			
5	Enhance methodological rigor in DTx economic evaluation	✓	✓	✓	✓		

[a] Healthcare Professionals (HCPs)

Risks of not implementing these managerial recommendations

The preceding sections have established a comprehensive framework of recommendations for enhancing economic value creation throughout the DTx lifecycle. Despite the significant clinical and economic opportunities that DTx presents at both the system and patient levels, failure to implement these recommendations carries substantial risks. Such inaction could impede widespread deployment within healthcare systems. Maintaining the status quo may result in five main consequences, which are introduced below.

Risks of inadequate interdisciplinary collaboration

Continued siloed development approaches risk perpetuating the current fragmentation between clinical, technical, and economic stakeholders. Without robust interdisciplinary collaboration, DTx development will likely remain characterized by limited translation capacity from bench to bedside, delaying or preventing promising DTx solutions from reaching implementation and leading to

unrealized clinical and economic benefits. Stakeholder misalignment, particularly evident in the second and third studies of this thesis (Chapters 5 and 6), presents another significant concern. Divergent priorities and perspectives among the various stakeholders within the DTx ecosystem will continue to create friction in development processes, subsequently extending timelines, increasing development costs, and potentially resulting in solutions that fail to realize their market potential.

Risks of delayed economic consideration

Without embedding economic considerations in early development stages, DTx stakeholders might face significant market access barriers. Solutions developed without early-stage economic considerations might indeed encounter substantial challenges during HTA processes and reimbursement negotiations, delaying or preventing market access entirely. Retrofitting economic considerations represent another major concern, as post-development economic adjustments typically incur significantly higher expenses than addressing economic factors during initial design, potentially rendering promising DTx solutions economically unviable. Misaligned value propositions further complicate deployment, as DTx solutions may address clinical needs effectively but fail to demonstrate meaningful economic value for key stakeholders, limiting adoption incentives and reducing implementation feasibility across healthcare systems.

Risks of inadequate economic integration guidelines

Failure to establish comprehensive economic integration guidelines perpetuates insufficient understanding of stakeholder priorities and reimbursement requirements, thereby exacerbating the “evidence gaps” that frequently characterize DTx (Görgens et al., 2021). Developers may struggle to comprehend evaluation requirements across diverse markets, potentially resulting in fragmented evidence generation strategies and delayed market access. Without standardized frameworks, inconsistent evaluation approaches persist throughout the industry, leaving critical economic dimensions discussed earlier unevaluated. Consequently, economic evaluations of DTx will continue to

yield incomparable results, limiting evidence synthesis capabilities and complicating decision-making processes for payers and health systems. These methodological limitations might undermine stakeholder confidence in DTx value propositions, raising obvious credibility concerns that significantly hinder market access and reimbursement decisions. Furthermore, current methodological approaches may systematically undervalue DTx contributions—particularly regarding indirect benefits, long-term outcomes, and healthcare system transformation potential—resulting in value underestimation that compromises the perceived utility of these interventions.

Risks of inadequate professional training

Insufficient integration of economic dimensions in professional training will perpetuate economic literacy gaps among key stakeholders, an important finding of this thesis. Clinical and technical professionals will continue to lack fundamental economic knowledge, reinforcing siloed thinking and communication barriers across disciplines. This knowledge deficit leads to suboptimal decision-making, as limited economic understanding may drive development processes that prioritize short-term technical achievements over sustainable economic value creation, ultimately compromising the market viability of resulting DTx solutions.

Systemic implications

Beyond these domain-specific risks, failure to implement the recommended interventions carries broader systemic implications for the future of DTx. The promising potential of DTx to address critical healthcare challenges, such as chronic disease management and healthcare workforce shortages, may remain largely unrealized. Market consolidation becomes increasingly likely without improvements in economic value generation, as the DTx market may consolidate around a small number of well-resourced players, reducing competition and potentially limiting innovation. Recent developments illustrate these emerging challenges—two leading international DTx companies with strong established clinical evidence, Pear Therapeutics and Akili Interactive (both US-based), have

respectively filed for Chapter 11 bankruptcy in 2023 and been acquired for a fraction of its original value in 2024.

Perhaps most critically, limited deployment and scalability barriers may prevent DTx from becoming mainstream healthcare interventions. Without addressing the proposed recommendations outlined in this thesis, DTx may remain perpetually positioned as supplementary or peripheral interventions rather than core components of standard care pathways. This marginalization would significantly limit their scalability across healthcare systems, their potential to transform care delivery models, and the ability of patients to benefit from these technological and clinical advancements. The current fragmented approach to economic value in DTx development creates substantial barriers to widespread deployment, as healthcare systems increasingly demand far more than demonstrations of intervention safety and efficacy before implementing new interventions at scale. Without systematic changes to how economic value is conceptualized, assessed, and demonstrated, DTx may struggle to overcome the “pilotitis” that has characterized many digital health innovations (Egermark et al., 2022)—showing promise in controlled environments but failing to achieve mainstream integration into routine care delivery.

These multifaceted risks underscore the critical importance of implementing the recommended interventions in a coordinated, systematic manner, which ultimately can accelerate the development of economically viable DTx interventions that deliver meaningful value throughout the healthcare ecosystem—generating substantial benefits for patients, providers, and healthcare systems alike.

7.3. Conclusions

This chapter has synthesized the research findings to present a comprehensive understanding of DTx economic value and its integration throughout the development lifecycle. The theoretical contributions advance conceptual

frameworks that expand how economic value in DTx is understood, moving beyond traditional cost-effectiveness to capture multidimensional factors across various stakeholder perspectives. They provide conceptual foundations for understanding how economic value is considered, created, and assessed throughout the DTx lifecycle.

The practical contributions translate these theoretical insights into actionable approaches for stakeholders across the DTx ecosystem. By identifying 59 economic value factors, providing standardization approaches for economic evaluations, and offering guidance for addressing stakeholder perception gaps, these contributions directly support practitioners in navigating the challenges of DTx development and implementation. The framework for early economic integration responds to the identified causal relationship in the CLD (Figures 22 and 24) between early-stage considerations and ultimate economic viability.

Most significantly, the five managerial recommendations—fostering interdisciplinary collaboration, embedding early economic considerations, establishing economic integration guidelines, enhancing professional training, and improving methodological rigor in DTx economic evaluations—target specific intervention points where focused action can enhance DTx economic value. The CLD mapping these recommendations (Figure 24) reveals how strategic intervention in key areas can trigger systemic improvements throughout the DTx development ecosystem.

Implementation of these recommendations would address the methodological shortcomings and stakeholder misalignments identified throughout this research. By prioritizing and implementing these recommendations based on impact potential, feasibility, and systemic influence, stakeholders can strategically enhance economic value creation throughout the DTx lifecycle.

This multidimensional framework for action, spanning diverse stakeholder groups across different domains and time horizons, provides a practical roadmap for transforming how economic value is conceptualized, assessed, and integrated in

DTx development—ultimately enhancing the capacity of these innovative interventions to deliver meaningful value for healthcare systems worldwide.

CONCLUSION 8

CHAPTER 8. CONCLUSION

This DBA thesis has established that the path to widespread DTx deployment requires bridging fundamental gaps between clinical innovation and economic viability. Through systematic literature review, GCM, and qualitative investigation, the research reveals that while DTx holds promise for addressing pressing healthcare challenges, its economic value remains inadequately conceptualized, assessed, and integrated throughout development processes.

The research findings reveal significant disconnect between stakeholder groups in how economic value is perceived and prioritized. Researchers—who drive early development decisions—systematically underemphasize economic considerations compared to other stakeholders, creating implementation complexities that persist through the DTx lifecycle (Chapter 5). These gaps arise not merely from knowledge deficits but from deeper structural forces including p*rofessional norms*, experience-driven decision patterns, and *adoption uncertainties* that shape stakeholder behaviour (Chapter 6).

The contribution of this DBA thesis lies in its comprehensive, mixed methods-based approach to understanding and addressing these systemic challenges. By identifying 59 economic value factors across eight thematic clusters, the research provides stakeholders with a shared vocabulary and prioritization framework for economic value discussions. The causal generative mechanisms identified explain persistent barriers to economic integration, while the recommended intervention points offer a strategic roadmap for transformation (Chapter 7).

For policymakers and healthcare leaders, this research suggests that realizing DTx potential requires systematic changes in how digital health innovations are developed, evaluated, and implemented. Beyond individual stakeholder action, the findings call for ecosystem-level transformation in professional education, evaluation methodologies, and collaboration structures to create environments where economically viable DTx solutions can be deployed and scaled.

As healthcare systems worldwide confront the dual challenges of rising chronic disease burden and resource constraints, this research provides timely guidance for navigating the complex landscape of DTx innovation. By implementing the proposed frameworks and recommendations, stakeholders can accelerate the transition from promising pilots to scalable, sustainable DTx solutions that deliver meaningful value for patients, providers, and healthcare systems alike.

8.1. Limitations and Further Research

As discussed, the thesis and associated research work have provided valuable implications for diverse stakeholder groups involved in DTx development and clinical validation, including researchers, potential payers and policymakers. Despite the high priority given to quality and rigor in the design and execution of each cascading study, several limitations must be acknowledged. Addressing these limitations in future studies can further enhance the internal and external validity, as well as the reliability of the findings.

The systematic literature review in the first paper employed a rigorous methodology involving at least two independent researchers at each stage of the study process. This approach ensured a rigorous search and selection process, along with appropriate data extraction and synthesis methods, addressing internal validity concerns. Bias assessment was conducted for each selected study. However, the search strategy may have excluded relevant studies due to the use of a finite list of specific terms, inclusion of only English-language papers, and an exclusive focus on mobile app–based DTx. Future research could expand the search strategy to include recent publications, non-English papers, and DTx using alternative delivery mechanisms beyond mobile phones.

For the GCM study, interrater reliability tests for the two scale ratings fell within the 95% confidence interval, indicating strong internal reliability and valid scale evaluation results. External validity was reinforced by the diverse participant pool (n=62) across geographies involved in multiple GCM stages, as well as in-depth

expert interviews for data interpretation. However, the results presented are context-specific, necessitating careful consideration of external validity issues when interpreting them. Further research could build on these findings by focusing on specific stakeholder groups or incorporating new groups, such as patients, across various contexts and countries, providing a more comprehensive and generalizable understanding of decision-making processes within each stakeholder group.

The qualitative study's use of purposeful sampling for participant recruitment may have introduced self-selection bias. Furthermore, the predominance of researchers from Singapore and public academic institutions potentially limits the generalizability of findings across diverse settings and healthcare systems. This geographical and institutional concentration may have resulted in perspectives that are overly influenced by the Singaporean healthcare context and academic research paradigms, potentially overlooking important considerations from other healthcare systems or private sector entities. To enhance the validity and applicability of these findings, future studies could explore a broader range of researchers' perspectives and profiles on this topic across different contexts, including a more balanced representation of researchers from various geographical regions, healthcare systems, and institutional backgrounds. Additionally, a mixed methods-based approach incorporating quantitative surveys alongside qualitative interviews could provide a more robust and nuanced understanding of researchers' perspectives on DTx economic value considerations.

Also, while this thesis established a causal relationship between early-stage economic considerations and a DTx product's ultimate economic value, the quantification and assessment of how each identified factor might impact the overall economic value have not been performed. This limitation prevents a more precise understanding of the relative importance of each factor and their potential interactions in determining the economic value of a DTx intervention.

Future research might use specific case studies to determine the weightage of each of these factors in contributing to a DTx economic value, quantifying their contributions. A more quantitative approach could extend the list of “priority factors” identified in this thesis into an actual prioritization of each respective factor driving a DTx economic value. This could involve the development of a comprehensive economic model that incorporates the identified factors and allows for sensitivity analyses to assess their relative impacts.

Finally, a limitation of this research is its deliberate focus and emphasis on the development and clinical validation phases of the DTx lifecycle, rather than on the implementation and adoption phases where these innovations could ultimately deliver potential value to patients and healthcare systems. While this thesis established foundational understanding of economic value considerations during early DTx development, it did not examine the complex multifaceted factors that influence DTx adoption, including regulatory, organizational, technological, and behavioral dimensions. The transition from demonstrating economic value potential to realizing that value through widespread adoption involves additional stakeholder considerations, implementation barriers, and success factors that were beyond the scope of this investigation but remain critically important for healthcare transformation. Understanding this adoption process—including the barriers, facilitators, and stakeholder dynamics that determine whether economically viable DTx solutions achieve their intended impact—represents a crucial area for future investigation that builds directly upon this thesis's foundational contributions.

In conclusion, while this DBA thesis and its three cascading studies have provided valuable insights into the economic considerations of DTx development, addressing these limitations in future research will further enhance our understanding of this rapidly evolving field. By expanding the scope of analysis, incorporating diverse perspectives, and employing more quantitative approaches, future studies can build upon this foundation to provide even more robust and actionable insights for stakeholders in the DTx ecosystem.

AI Contribution Statement

In alignment with emerging academic best practices for transparency in research methodologies Automatic citation updates are disabled. To see the bibliography, click Refresh in the Zotero tab., this statement documents the specific uses of AI tools in this thesis dissertation.

Claude 3.7 Sonnet (hereafter “Claude”), a large language model developed by Anthropic, was selected for its enhanced privacy protections relative to comparable models. Claude was utilized in the following three specific capacities:

Research Instrument Development: Claude assisted in refining the focus prompt and two scale ratings (“importance” and “extent of consideration”) used in the GCM study (Chapter 5). These instruments were critical for generating factors impacting DTx economic value during interviews and focus groups, and for subsequent stakeholder assessment. To ensure comprehensive and unambiguous instruments appropriate for the diverse backgrounds of 62 stakeholders completing individual online assessments, iterative prompt engineering was employed. For example, queries such as “*propose five variations of the following focus prompt which aims to identify factors having an impact on the DTx economic value in a focus group discussion*” were used to generate alternatives for my consideration.

Editorial Assistance: Claude was used as a supplementary proofreading tool for individual thesis chapters, complementing traditional human editorial processes. Standardized prompts such as “*check for grammar, spelling, punctuation, clarity, and academic tone of this DBA thesis extract*” were employed to identify potential improvements in the manuscript.

Citation Formatting Verification: The model was utilized to verify APA 7th edition formatting compliance for citations. Citations were extracted from the thesis and submitted to Claude with the prompt “*ensure all citations follow APA 7th edition guidelines*.” Identified formatting errors were subsequently corrected

in Zotero reference management software before being applied to the final document.

Beyond these three specific applications, all intellectual contributions, including research design, data collection, analysis, interpretation of findings, theoretical frameworks, and conclusions are entirely my own original work. Claude was used solely as a tool to enhance quality and efficiency in the limited capacities described above, with all AI-generated content undergoing critical human review and evaluation before incorporation.

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PAPER 1 APPENDICES

Appendix 1A. International prospective register of systematic reviews

NIHR | National Institute for Health and Care Research

PROSPERO
International prospective register of systematic reviews

A systematic review of the economic evaluation associated with clinical-grade mobile application-based interventions

Yoann Sapanel, Xavier Tadeo Campillo, Alexandria M. Remus, Agata Blasiak, Dean Ho, Joanne Su Yin Yoong, Martin L. Cloutier, Gabriel Tremblay, Florian Koerber, Chris L. Hardesty

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided here.

Citation
Yoann Sapanel, Xavier Tadeo Campillo, Alexandria M. Remus, Agata Blasiak, Dean Ho, Joanne Su Yin Yoong, Martin L. Cloutier, Gabriel Tremblay, Florian Koerber, Chris L. Hardesty. A systematic review of the economic evaluation associated with clinical-grade mobile application-based interventions. PROSPERO 2024 Available from https://www.crd.york.ac.uk/PROSPERO/view/CRD42022358616

REVIEW TITLE AND BASIC DETAILS

Review title
A systematic review of the economic evaluation associated with clinical-grade mobile application-based interventions

Original language title
English

Review objectives
1) What is the economic evidence showing costs and cost effectiveness of clinical-grade mobile application-based interventions?
2) What are the methodological approaches used in the economic evaluation of clinical-grade mobile application-based interventions?
3) What are the factors affecting the economic evaluation of clinical-grade mobile application-based interventions?

Keywords
Cost-benefit analysis, Cost-effectiveness, Digital health, Digital therapeutics, Economic value, mHealth, Mobile applications, Systematic review

SEARCHING AND SCREENING

Searches
Relevant literature will be searched according to the PRISMA 2020 guidelines (Moher et al., 2020). PubMed, Cochrane Library, Web of Science, Embase, Business Source Ultimate (EBSCO), CINAHL (EBSCO), Scopus, ProQuest Business Premium Collection, and Wiley Online Library will be searched. Additional searches will be done on the health economic databases and cost-effectiveness analysis registry (i.e., INAHTA International HTA Database and International Journal of Technology Assessment in Health Care and CEA Registry). Search strings will be tailored according to each database requirements. The following keywords will be searched in publications titles and abstracts, as identified by the SPICE framework (Booth, 2006) and in consultation with a research librarian:
(A): “digital therapeutic*” OR “digital health*” OR “digital tech*” OR “mobile health” OR “mhealth” OR “mobile tech*” OR “mobile medical app*” OR “mobile app*” OR “wearable tech*” OR “connected medical devices”; AND
(B): “economic evaluation” OR “economic value” OR “cost-benefit” OR “cost-utility” OR “cost-effectiveness” OR “cost-effective” OR “Quality-Adjusted Life Years” OR “Markov Chains” OR “Models, Economic”
The searches will be limited to English-language publications published up to September 2022. Where applicable, type of publication will be limited to academic journals, articles in press, conference papers, but not abstracts. The reference lists of studies meeting the inclusion criteria will be searched to identify additional relevant studies.

Study design
All published academic papers that include partial economic evaluations (e.g., include cost-of-illness analysis and program cost analysis) and full economic evaluation (e.g., cost-benefit, cost-effectiveness, and cost-utility analyses) studies of mobile application-based interventions will be included.

ELIGIBILITY CRITERIA

Condition or domain being studied
Economic evaluation of clinical-grade interventions delivered directly to patients via mobile applications, used independently or in tandem with in-person or remote clinician-delivered therapy (Digital Therapeutics Alliance, 2022), will be studied. These interventions, part of the digital therapeutics category, are 1.) clinically demonstrated as safe and effective; 2.) by nature patient-focused solutions, designed to be used directly by patients or their caregivers, and accessible through patient-owned devices, meaning for this review, patient-owned smartphones and 3.) able to generate actionable, real-world insights that enable intelligent data-driven care management and clinical decision-making (Digital Therapeutics Alliance, 2022).

Population
Humans, of all ages

Intervention(s) or exposure(s)

Health economic assessment of clinical-grade mobile application-based interventions. Therefore, interventions not delivered directly to patients via mobile applications and that have not demonstrated clinical efficacy in a clinical trial for treating, managing, or preventing a disease or disorder will be excluded.

Comparator(s) or control(s)

Health economic assessment of digital therapeutics, including mobile application-based interventions, is often conducted alongside both randomised and non-randomised studies (Rejon-Parrilla et al., 2022), and could be compared to passive/active control groups, placebo, no intervention or standard of care.

Context

There is emerging evidence that digital therapeutics (DTx), also known as evidence-based therapeutic treatments powered by high-quality software programs, can prevent, manage, or treat chronic conditions and disorders (Digital Therapeutics Alliance, 2022). For the intervention delivery, DTx primarily leverage mobile apps (n=57, 41.9%), followed by web-based systems (n=35, 25.7%), and videogames (n=12, 8.8%) for mental health (n=47, 34.6%), chronic pain and chronic diseases (n=26, 19.1%), smoking and other substance abuse or addiction (n=17, 12.5%) (Santoro et al., 2021).

DTx are said to be one of the most promising avenues for improving healthcare provision on a global scale. They have indeed the potential to disrupt traditional and often inefficient healthcare business models through delivering better clinical outcomes, while providing a superior patient experience. If there is growing evidence of DTx in the clinical setting, less is known about their cost effectiveness profile. However, due to the increasing demand for healthcare services and the rising costs of providing these services, DTx, including must demonstrate their economic value - the extent to which they provide good “value for money” when compared with alternative options. It is a critical part of market access, pricing, and reimbursement.

OUTCOMES TO BE ANALYSED

Main outcomes

From the selected studies, measures of economic evidence will be determined by reporting of individual studies and are likely to include cost per outcome metrics, such as for example, the cost per Quality Adjusted Life Year (QALY) gained, or an incremental cost-effectiveness ratio (ICER) per QALY gained - a measure of the value of health outcomes - which is used as the benchmark for cost-effectiveness (Buntrock et al., 2021). Indication specific outcomes would also be considered, such as mortality and morbidity related endpoints.

Additional outcomes

From the selected studies, the methodological approaches used to generate economic evidence of mobile application-based interventions will be reviewed, and appraised.

DATA COLLECTION PROCESS

Data extraction (selection and coding)

Study selection:
Initial searches will be performed by one reviewer and duplicates will be removed. Two reviewers will independently apply eligibility criteria to titles/abstracts and then full-text articles using Covidence software. Any discrepancies in both searches will be addressed by a third independent reviewer.
Data extraction and coding:
Two reviewers will extract study data independently, with findings compared and agreed. A data extraction spreadsheet (Excel) will be used based on the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS) checklist. The publication year, authors, country, study design, details of the economic evaluation model used, cost perspective, time horizon, estimated costs, (quality-adjusted) life-years gained from the intervention and reported ICER will be extracted. A random sample of 20% of studies will be reviewed by the third reviewer for correctness.

Risk of bias (quality) assessment

Studies eligible to move on from the initial search stage will undergo quality assessment, where detailed information on study characteristics will be collected, based on the CHEERS guidelines checklist.

PLANNED DATA SYNTHESIS

Strategy for data synthesis

A narrative synthesis of the results from the included studies will be presented, focusing explicitly on the existence of relationships between mobile application-based interventions (concept A, measured in terms of presence of a such an intervention) and various economic value measures (concept B, measured as cost-effectiveness). The review will focus on the theoretical relationship between these concepts, extracting, characterising and explaining such relationship, as well as comprehending contextual factors. A concept-centric approach of the literature review will be adopted, with the extracted concepts presented in a measurable concept matrix (Webster & Watson, 2002).

Analysis of subgroups or subsets

None planned

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Funding source
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TIMELINE OF THE REVIEW

Review timeline
Start date: 12 September 2022. End date: 31 March 2023

Date of first submission to PROSPERO
08 September 2022

Date of registration in PROSPERO
19 September 2022

CURRENT REVIEW STAGE

Publication of review results
The intention is to publish the review once completed.The review will be published in English

Stage of the review at this submission

Review stage	Started	Completed
Pilot work		
Formal searching/study identification		
Screening search results against inclusion criteria		
Data extraction or receipt of IP		
Risk of bias/quality assessment		
Data synthesis		

Review status
The review is currently planned or ongoing.

ADDITIONAL INFORMATION

PROSPERO version history

- Version 1.1 published on 19 Sep 2022
- Version 1.0 published on 19 Sep 2022

Review conflict of interest

AR, AB and DH have developed and are evaluating a digital therapeutic for multitasking. The other authors declare that they have no known conflicts of interest.

Country

Singapore

Medical Subject Headings

Cost-Benefit Analysis; Humans; Mobile Applications

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Appendix 1B. Preprint published in JMIR

JMIR Publications
The Leading eHealth Publisher

Economic Evaluation Associated with Clinical-Grade Mobile Application-Based Digital Therapeutic Interventions: Systematic Review

Yoann Sapanel, Xavier Tadeo, Connor T. A. Brenna, Alexandria Remus, Florian Koerber, L. Martin Cloutier, Gabriel Tremblay, Agata Blasiak, Chris L. Hardesty, Joanne Yoong, Dean Ho

Submitted to: Journal of Medical Internet Research
on: March 07, 2023

Preprint
JMIR Publications

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https://preprints.jmir.org/preprint/47094 [unpublished, peer-reviewed preprint]

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Preprint JMIR Publications

Economic Evaluation Associated with Clinical-Grade Mobile Application-Based Digital Therapeutic Interventions: Systematic Review

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Preprint JMIR Publications

Abstract

Background: A new class of interventions called digital therapeutics (DTx) is emerging and shows promise in the treatment of a spectrum of medical disorders and diseases. DTx are software-based interventions which could deliver unprecedented portability and scalability for patients. Their adoption and implementation were accelerated by the need for remote care during the COVID-19 pandemic, and awareness about their utility grew among health care providers, payers, and regulators. Yet, despite increasing clinical evidence that DTx can prevent, manage, or treat chronic conditions and disorders, the digital nature of these technologies creates a new set of challenges to evaluating their cost-effectiveness. As a result, little is known regarding the capacity of DTx to provide economic value to payers, providers, and health systems.

Objective: This study aims to systematically review and summarize published evidence regarding the cost-effectiveness of clinical-grade mobile application-based DTx, as well as explore factors affecting such evaluations.

Methods: A systematic review of economic evaluations of clinical-grade mobile application-based DTx was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Major electronic databases (including PubMed, Cochrane Library, and Web of Science) were searched for eligible studies published from inception to October 28, 2022. Two independent reviewers evaluated the eligibility of all retrieved articles for inclusion. The methodological quality and risk of bias were assessed for included studies.

Results: The search yielded 11,228 abstracts, of which 18 studies are included in this review. Of the 18 studies, 7 (39%) are non-randomized studies-based economic evaluations, 6 (33%) are model-based evaluations and 5 (28%) are randomized clinical trials-based evaluations. Twelve of the studies (67%) used a payer perspective for the economic analysis, while the rest (33%) used a societal perspective. Thirteen of the studies (72%) conducted a full economic evaluation, and 12 of those (92%) found the DTx intervention under assessment to be cost-effective; one study (8%) found the intervention to be cost-effective in only one of the three countries of study. The remaining 5 studies (28%), which focused on a partial economic evaluation, found the DTx intervention under assessment to be cost-saving.

Across the 18 studies included in this review, health care resource utilization was the most often reported cost impacting the DTx economic value of the DTx interventions (16/18, 89%), followed by the cost of the pharmaceutical treatment (12/18, 67%). The participants' baseline characteristics was the most often reported factors influencing DTx economic impact in 12 of the studies (67%). By way of limitations, qualitative deficits in methodology and significant potential biases, including risks of performance bias and of selection bias in participant recruitment, were identified across some of the studies.

Conclusions: This systematic review supports the thesis that DTx interventions have potential economic benefits. However, the distinctive nature of DTx creates a new set of challenges to evaluating such novel technologies, which were not consistently addressed across studies. To provide evidence of economic impact, which is required for DTx adoption and deployment, further evaluations leveraging more comprehensive and standardized economic analyses across settings will be necessary. Clinical Trial: PROSPERO Registration No. CRD42022358616

(JMIR Preprints 07/03/2023:47094)
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Original Manuscript

Preprint JMIR Publications

Economic Evaluation Associated with Clinical-Grade Mobile Application-Based Digital Therapeutic Interventions: Systematic Review

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Preprint JMIR Publications

Abstract

Background: Digital therapeutics (DTx), a class of software-based clinical interventions, are promising new technologies that can potentially prevent, manage, or treat a spectrum of medical disorders and diseases, as well as deliver both unprecedented portability for patients and scalability for healthcare providers. Their adoption and implementation were accelerated by the need for remote care during the COVID-19 pandemic, and awareness about their utility has rapidly grown among providers, payers, and regulators. Despite this, relatively little is known regarding the capacity of DTx to provide economic value in care.

Objective: This study aims to systematically review and summarize published evidence regarding the cost-effectiveness of clinical-grade mobile application-based DTx, as well as explore factors affecting such evaluations.

Methods: A systematic review of economic evaluations of clinical-grade mobile application-based DTx was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Major electronic databases, including PubMed, Cochrane Library, and Web of Science, were searched for eligible studies published from inception to October 28, 2022. Two independent reviewers evaluated the eligibility of all retrieved articles for inclusion in the review. Methodological quality and risk of bias were assessed for each included study.

Results: There are 18 studies included in this review. Seven (39%) are non-randomized studies-based economic evaluations, 6 (33%) are model-based evaluations, and 5 (28%) are randomized clinical trials-based evaluations. The DTx intervention subject to assessment was found to be cost-effective in 12 studies (67%), cost-saving in 5 studies (28%), and cost-effective in only 1 of the 3 countries where it was being deployed in the final study (6%). Qualitative deficiencies in methodology and significant potential for bias, including risks of performance bias and of selection bias in participant recruitment, were identified in several of the included studies.

Conclusion: This systematic review supports the thesis that DTx interventions offer potential economic benefits. However, DTx economic analyses carried out to date exhibit important methodological shortcomings that must be addressed in future evaluations to reduce uncertainty surrounding the widespread adoption of DTx interventions.

Trial registration: PROSPERO Registration No. CRD42022358616.

Keywords

digital health; digital therapeutics; economic evaluation; cost-effectiveness; mobile phone; systematic review

Introduction

Background

The continued rise in chronic and mental health conditions, and commensurately in their associated health care costs, is not a new phenomenon. What *is* new – and reinforced by the COVID-19 pandemic – is the realization of a need for novel approaches to deliver care for these conditions closer to where individuals live and work, such as in their own homes and communities. As health care organizations and providers rush to adapt to this new reality, the adoption of digital technologies has accelerated rapidly [1].

Under the umbrella term "digital technologies," it is crucial to distinguish between three separate categories, which are sometimes conflated or used interchangeably: *wellness and support* solutions, referring to products designed to capture, store, and transmit health data (e.g., telehealth platforms); *diagnostic and monitoring* solutions, involving products that measure and/or track individuals' health status (e.g., connected drug delivery devices); and *digital therapeutics (DTx)*, a new class of medicine that delivers therapeutic interventions directly to patients (e.g., digital behavioral therapy) [2].

Powered by computer software, DTx can deliver evidence-based therapeutic interventions that prevent, manage, or treat a spectrum of medical disorders and diseases directly to patients [2]. Evidence supporting the potential of DTx in optimizing patient care and health outcomes [3], through a more personalized approach to health care, with greater patient education and empowerment, is mounting [4]. As such, DTx have recently been described as the "next paradigm" of modern health care [5].

Interest for DTx began to surge in 2017 when the U.S. Food and Drug Administration (FDA) approved of the first DTx to treat opioid use disorder [6]. Following this, in 2019, Germany became the first country to establish a Fast-Track Process for integrating DTx into the German reimbursement market [7]. Shortly thereafter, Belgium [8], France [9], Japan [10], Korea [11] and the United Kingdom [12], began to implement DTx-specific approval and reimbursement processes. Globally, there are currently around 400 DTx available or under development [13].

While considered a rapidly emerging class of medicine, the economic value of DTx has yet to be understood, resulting in an important knowledge gap limiting their widespread uptake [14,15]. There is currently limited consensus on whether these technologies are cost-effective compared to traditional treatments. Because cost-effectiveness is an important consideration in payers' reimbursement and pricing decisions [15], questions about the potential economic impact of DTx merit exploration [16].

In the context of budgetary constraints and an enduring need for optimal resource allocation in health care, determining the best mix of health services and treatments to maximize clinical outcomes while minimizing costs is critical [17,18]. If DTx can demonstrate their economic value to decision-makers (e.g., public and private payers, regulators, care providers), such evidence is important to facilitate decisions around market access, pricing, and reimbursement (and, therefore, adoption) for these technologies [19]. We therefore seek to systematically answer the question regarding whether this recently emerged class of medical intervention, DTx, has yet been translated to economic value.

Objective

Given the growing body of evidence supporting DTx' potential clinical benefits, the aim of this systematic review is to evaluate published evidence regarding the cost-effectiveness of clinical-grade, mobile-based DTx interventions, as well as explore the costs and factors that drive such economic evaluation (EE).

Methods

Search Strategy

The protocol for this review was registered with PROSPERO a priori: CRD42022358616. A search of the relevant literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [20]. Databases searched for eligible studies included PubMed, Cochrane Library, Web of Science, Embase, Business Source Ultimate (EBSCO), CINAHL (EBSCO), Scopus, ProQuest Business Premium Collection, and Wiley Online Library. The search was conducted between September 5, 2022, and October 28, 2022, and was not constrained by the year of publication. Additionally, secondary searches were executed in the International Network of Agencies for Health Technology Assessment (INAHTA) International Health Technology Assessment (HTA) database and International Journal of Technology Assessment in Health Care. Search strings were tailored according to each database requirement. The following keywords were searched in publications titles and abstracts, as identified by the SPICE (setting, perspective, intervention, comparison, and evaluation) framework [21] and in consultation with a research librarian from the National University of Singapore:

(A): "digital therapeutic*" OR "digital health*" OR "digital tech*" OR "mobile health" OR "mhealth" OR "mobile tech*" OR "mobile medical app*" OR "mobile app*" OR "wearable tech*" OR "connected medical devices"; AND
(B): "economic evaluation" OR "economic value" OR "cost-benefit" OR "cost-utility" OR "cost-effectiveness" OR "cost-effective" OR "Quality-Adjusted Life-Years" OR "Markov Chains" OR "Models, Economic"

Eligibility Criteria

DTx delivery mechanism (e.g., mobile app, web-based systems, or virtual reality) can significantly impact its economic proposition. For this reason, and because DTx primarily leverage mobile apps as a delivery mechanism [22], "smartphone apps" are regarded as the top two (after telemedicine) technology developments anticipated to create the most disruption for established health care practices [23]; hence, this review focuses on clinical-grade mobile application-based DTx. Thus, studies were included based on the following inclusion criteria: (1) published in a peer-reviewed journal within any time frame, (2) the study analyzed a mobile app-based intervention, (3) the therapeutic intervention was delivered directly to patients, (4) the intervention had demonstrated its clinical benefits through at least one case-control study, (5) the study included a partial or full EE, and (6) the publication was available in English. Internet-based and virtual reality-based interventions, solutions for screening, diagnostic and monitoring purposes, telemedicine and remote patient monitoring solutions, and clinical decision support solutions were all excluded. Furthermore, non-peer-reviewed publications (e.g., white papers and editorials), as well as abstract-only papers and those with unavailable full texts, were also excluded.

The reference lists of studies meeting the inclusion criteria were subjected to an additional "backward reference search" in order to identify additional relevant studies.

Study Selection, Data Extraction and Synthesis

After duplicate records were removed, two reviewers (Y.S., X.T.) independently screened the titles and abstracts of all remaining identified studies for inclusion using the systematic review software Covidence. Eligible studies that met inclusion criteria, according to both reviewers, then underwent a full-text review. Conflicting outcomes were discussed between reviewers, and a third party (A.R.) was involved to help reach a consensus when necessary.

Data were extracted using a bespoke online Microsoft Excel 365 spreadsheet. Full data extraction was completed by one reviewer (Y.S.) and verified by a second reviewer (X.T.). Extracted information from each study included: country(s), targeted disease(s), product's primary purpose, study design, perspective, costs considered, time horizon, intervention group sample size, type of control group, clinical outcomes, cost savings, scholars' conclusion on the intervention's cost-effectiveness, uncertainty consideration (discounting and sensitivity analysis) and sources of funding or conflicts of interest. Additional factors directly considered in the EE, and/or factors reported by scholars as impacting the DTx economic impact, through sensitivity analysis or explicitly in the studies' discussion sections, were also extracted. After extraction, the data were narratively synthesized to evaluate their meaning [24]. The additional extracted factors impacting the DTx were clustered into main categories, and organized into a concept matrix [25].

Quality Assessment

Quality assessment of included studies was conducted using the Consensus on Health Economic Criteria (CHEC)-list [26]. Each study received a score of 1, 0.5, or 0 for satisfying, partially satisfying, or not satisfying (respectively) the 19 independent evaluation criteria. The cumulative percentage of criteria satisfied was calculated as an overall 'score' for each article (maximum possible score 19/19 criteria or 100%).

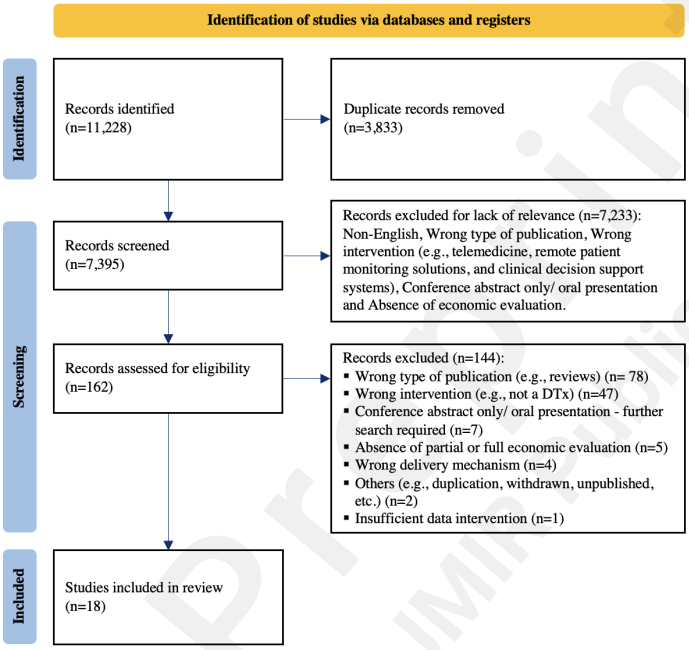
Risk of bias was calculated for each article according to its methodology. For randomized controlled trials, the Cochrane Collaboration Risk of Bias (RoB) tool [27] was used, rating each study as unclear-, low-, or high-risk for selection bias. For non-randomized studies, the RoB in Non-Randomized Studies – of Interventions (ROBINS-I) tool was used to rate the RoB due to confounding, bias in selection of participants into the study, bias in the classification of interventions, bias due to deviation from intended interventions, bias due to missing data, bias in measurement outcomes, and bias in selection of the reported result [28]. Each of these features was rated as low-, moderate-, or serious-RoB, and each study's overall bias was conservatively calculated as the highest-risk measure in any category. Finally, bias in modeling studies was calculated using the Bias in Economic Evaluation (ECOBIAS) checklist, and rated as "Yes", "No", "Partially", "Unclear", or "Not applicable" referring to a study's ability to address each of 22 independent criteria [29]. We elected to consolidate ECOBIAS ratings into the scale's four overarching categories: overall checklist for bias in EE, bias related to structure, bias related to data, and bias related to consistency. For uniformity with the other RoB assessment tools, we rated the bias in each category as low-, moderate-, or high-risk, equivalent to the highest-risk single evaluation for any component criterion, considering "Yes" and "Not applicable" equal to low-risk, "Partialy' and "Unclear" equal to moderate-risk, and "No" equal to high-risk.

Results

Study Selection

After duplicate removal and eligibility screening, 18 studies were included in this review (Figure 1).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.



Study Characteristics

Table 1 summarizes the characteristics and main health economic outcomes associated with the included studies. Overall, the 18 studies in this review were conducted between 2016 and 2022. Among those studies, 10 (56%) [30-39] were conducted in the USA, 2 (11%) [40,41] in the Netherlands, 2 (11%) [42,43] in Sweden, 1 (6%) [44] in Germany, 1 (6%) [45] in Japan, 6% (1/18) [46] in the United Kingdom, and 1 (6%) [47] jointly in the Netherlands, Spain and Taiwan. Further, 10 of the studies (56%) [30-32,34-39,45] were industry-funded, 6 (33%) [40,41,43,44,46,47] were publicly-funded, and the remaining 2 (11%) [33,42] received mixed funding.

The targeted diseases for DTx in the included studies, all among adult patient populations, were urinary incontinence (3/18, 17%) [40,42,43], diabetes (2/18, 11%) [32,36], opioid use disorder (2/18, 11%) [34,35], hypertension (2/18, 11%) [45,46], generalized anxiety disorder

(1/18, 6%) [37], chronic insomnia (1/18, 6%) [31], osteoarthritis (1/18, 6%) [41], lower back pain (1/18, 6%) [44], obesity (1/18, 6%) [30], behavioral health conditions (1/18, 6%) [33], cardiovascular disease (1/18, 6%) [47], both diabetes and cardiovascular disease (1/18, 6%) [39], and both type 2 diabetes and hypertension (1/18, 6%) [38].

Regarding the type of economic evaluation (EE) performed, 7 of the studies (39%) [30-36] involved non-randomized studies-based EE, 6 (33%) [37-39,44,45,47] model-based EE, and 5 (28%) [40-43,46] randomized clinical trial (RCT)-based EE. Twelve studies (67%) used a payer perspective [30-36,38,39,41,45,46], while 6 (33%) used a societal perspective [37,40,42-44,47], with two of the latter group also taking a payer perspective (11%) [37,47]. The time horizon used for the EE was between 6 and 12 months for 10 studies (56%) [32-36,40-43,46], 24 months for 1 study (6%) [31], 36 months for 3 studies (17%) [30,38,44], 60 months for 1 study (6%) [47], 120 months for 1 study (6%) [39], and lifetime for 2 studies (11%) [37,45]. The intervention group sample size ranged between 60 and 305 participants for RCT-based EE, and between 248 and 4790 participants for non-randomized studies-based EE. The interventions were compared to usual care (UC) (13/18, 72%) [30,32-34,36,38,40,41,43-47], pre-intervention (2/18, 11%) [31,39], an informative but non-interventional "control" app (1/18, 6%) [42], non-engagers[1] (1/18, 6%) [35] and traditional cognitive behavioral therapy or no therapy (1/18, 6%) [37].

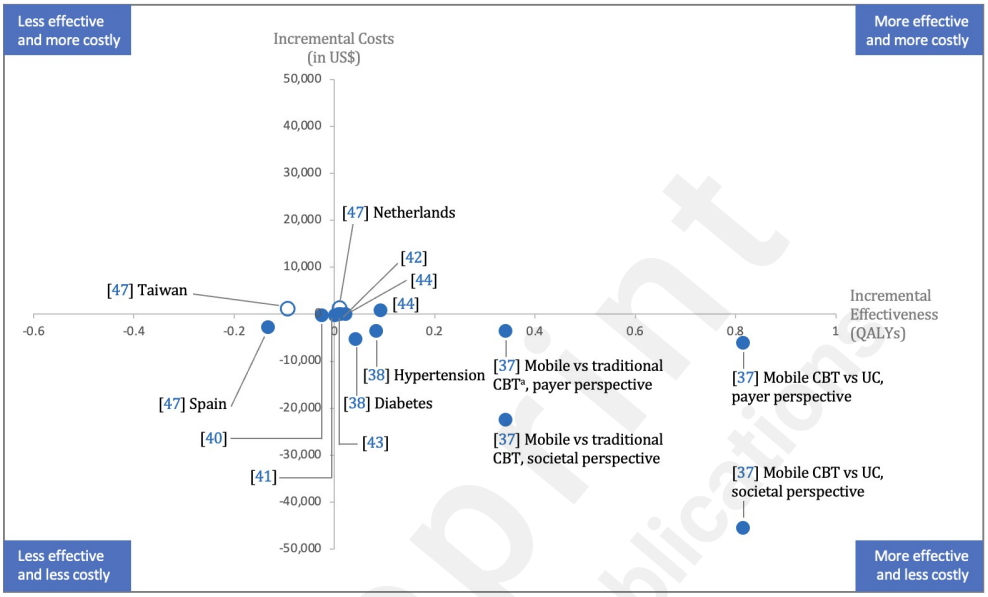
Fourteen of the studies (78%) [30-32,37-47] assessed the impact of the DTx intervention on clinical outcomes. Of those, 11 (79%) [30-32,37-39,42-46] found superior clinical outcomes, 2 (14%) [40,41] found no improvement compared to UC, and 1 (7%) [47] found superior clinical outcomes in only 1 of the 3 countries in which the intervention under study was delivered.

Half of the studies included in this review [37,38,40-42,44-47] conducted a cost-effectiveness analysis (CEA), with 4 also including a cost-utility analysis (CUA) [40-42,44]. Eight studies (44%) conducted a cost analysis (CA) [30-36,39], with a strong emphasis on cost differences using for example pre-post intervention claims data, and 1 study (6%) focused solely on CUA [43]. Of the 10 studies using CEA and/or CUA methods, 7 (70%) presented incremental cost-effectiveness ratio (ICER) values based on the cost per quality-adjusted life-years (QALY) gained to assess the cost-effectiveness of the DTx intervention [37,38,42-45,47]. Meanwhile, 2 (20%) of the CEA and/or CUA studies showed ICER values based on cost per incontinence impact-adjusted life-years gained and cost per mm Hg reduction in blood pressure [40,46]. One study (10%) did not report an ICER, but an incremental net monetary benefit [41].

Of the 10 studies that conducted a full EE, 9 (90%) [37,38,40-46] found the DTx intervention to be cost-effective in the context of study, while 1 study (10%) found the intervention to be cost-effective in only 1 of 3 countries in which it was studied [47]. Specifically, DTx accounted for QALY gains along with cost-savings in 2 studies (20%) [37,38]; QALY gains along with a higher costs at an acceptable ICER in 5 studies (5/10, 50%) [34,35,42,43,46]; QALY losses with cost-savings in 2 studies (20%) [40,47]; and no demonstrable effectiveness difference with cost-savings in 1 study (10%) [41]. Figure 2 represents the 15 different DTx interventions under assessment in the 9 studies (50%) [37,38,40-45,47] that reported cost and QALYs as the outcome measures across the quadrants of the cost-effectiveness plane. The horizontal axis of the plane indicates differences in effects (i.e., health outcomes), while the vertical axis represents differences in costs between the DTx interventions and their respective comparators.

[1] Patients who filled their prescription but did not engage beyond week one and patients who did not fill the prescription.

Figure 2. Cost-effectiveness plane of studies with cost and quality-adjusted Life-years as the outcome measures.



£1.00=US$1.20, €1.00=US$1.06.
[a]CBT: cognitive behavioral therapy.

Of the 8 studies based on partial EE, all (100%) found the DTx intervention under evaluation to be cost-saving [30-36,39].

Table 1. Study characteristics.

Author, country, year	Targeted disease (product primary purpose[a])	Type of evaluation	Perspective	Time horizon (months)	Intervention group sample size	Intervention versus comparator	Intervention led to superior clinical outcomes?	Intervention led to cost-savings? (in US$)	Intervention's being cost-effective? (ICER, in US$)	CHEC (%)
Randomized clinical trial-based economic evaluations										
Ekersund et al [42], Sweden, 2022	Urgency and mixed urinary incontinence (manage)	CEA/ CUA	Societal	12	60	Tät II vs information app	Yes (0.0115 QALY gained)	No (+$144)	Yes ($12,477/ QALY)	92
Pelle et al [41], NL[b], 2022	Osteoarthritis (manage)	CEA/ CUA	Health care payer	6	214	dr. Bart vs UC[c]	No difference	Yes (-$23)	Yes ($56 iNMB[d])	76
McManus et al [46], United Kingdom, 2021	HTN[e] (manage)	CEA	NHS payer	12	305	HOME BP vs UC	Yes (a mean difference in SBP[f] of −3.4 mmHg, and −0.5 mmHg in DBP[g])	No (+$46)	Yes (US$13/ mmHg reduction)	100
Sjöström et al [43], Sweden, 2017	Stress urinary incontinence (manage)	CUA	Societal	12	62	Tät vs UC	Yes (0.00849 QALY gained)	No (+ $69)	Yes ($8,071/ QALY)	95
Loohuis et al [40], NL, 2022	Stress, urgency, or mixed urinary incontinence (manage)	CEA/ CUA	Societal	12	131	URinControl vs UC	No (0.025 QALY loss and 0.043 IIALY[h] gained)	Yes (- $170)	Yes (- $3,918/ IIALYs)	87
Non-randomized studies-based economic evaluations										
Horstman et al [30], United States, 2021	Overweight and obesity (manage)	CA	Payer	36	4,790	Real Appeal vs UC	Yes (3% greater weight loss on average/ participant)	Yes (- $771/ participant)	-	55
Forma et al [31], United States, 2022	Chronic insomnia (treat)	CA	Payer	24	248	Pre-post Somryst treatment intervention	Yes (37.2% insomnia severity index score declined/ participant)	Yes (- $2,059/ participant)	-	39
Sweet et al [32], United States, 2020	Diabetes (prevent)	CA	Employer payer	12	2,027	Omada vs UC	Yes (4.3% average weight loss)	Yes (- $1,169/ participant)	-	55
Abhulimen et al [33], United States, 2018	Behavioral health condition[i] (manage)	CA	Public payer	11	799	myStrengh vs UC	-	Yes (- $382/ participant)	-	53
Velez et al [34], United States, 2022	OUD[j] (treat)	CA	Payer	12	901	reSET-O vs UC	-	Yes (- $2,791/ participant)	-	63
Velez et al [35], United States, 2021	OUD (treat)	CA	Payer	9	444	reSET-O vs non-engagers	-	Yes (- $2,708/ participant)	-	50
Whaley et al [36], United States, 2019	Diabetes (manage)	CA	Employer payer	12	2,261	Livongo program vs UC	-	Yes (- $1,056/ participant)	-	55
Model-based economic evaluations										
Piera-Jiménez et al [47], NL, Spain, TW[k], 2020	CVD (prevent)	CEA (RCT informed, Markov model)	Societal and health care payer	60	120	Do CHANGE 2 vs UC	NL: Yes (0.011 QALY gained) Spain: No (0.134 QALY loss) TW: No (0.094 QALY loss)	NL: No (+ $1,456) Spain: Yes (– $2,666) TW: No (+ $1,127)	NL: No ($131,959/ QALY) Spain: Yes ($19,895/ QALY) TW: No	76
Lewkowicz et al [44], Germany, 2022	Low back pain (manage)	CEA/ CUA (RCT informed, Markov model)	Societal	36	RCT: 53 Model: 10,000	Kaia vs UC	Yes (0.0221 QALY gained)	No (+ $129)	Yes ($5,815/ QALY)	87

Nomura et al [45], Japan, 2022	Hypertension (treat)	CEA (RCT informed, Markov model)	Public health care payer	Lifetime	199	CureApp and UC vs UC	Yes (0.092 QALY gained)	No (+ $962)	Yes ($10,434/ QALY)	92
Kumar et al [37], United States, 2018	Generalized anxiety disorder (prevent/ treat)	CEA (Pilot study informed, Markov model)	Societal and payer	Lifetime	Pilot: 89 Model: 100,000	Mobile CBT vs traditional CBT (Model A) and Mobile CBT vs UC (Model B)	Model A: Yes (34,108 QALYs gained) Model B: Yes (81,492 QALYs gained)	Societal: Model A: Yes (- $2.23bn) Model B: Yes (- $4.54bn) Payer: Model A: Yes (- $339mm) Model B: Yes (- $605mm)	Societal: Model A: Yes (-$65,380/ QALY) Model B: Yes (-$55,710/ QALY) Payer: Model A: Yes (-$9,939/ QALY) Model B: Yes (-$7,424/ QALY)	74
Nordyke et al [38], United States, 2019	Diabetes and HTN (manage)	CEA (Decision tree model)	US commercial payer	36	-	DTx + UC vs UC	T2DM: Yes (0.0427 QALY gained) HTN: Yes (0.0827 QALY gained)	T2DM: Yes (-$5,220) HTN: Yes (-$3,480)	T2DM: Yes (-$122,248/ QALY) HTN: Yes (- $42,080/ QALY)	55
Chen et al [39], United States, 2016	Diabetes and CVD[l] (prevent)	CA (Best available evidence, Markov model)	Public payer	120	1121	pre-post Omada program intervention	Yes (6.8% reduction in body weight/ participant)	Yes (from $11,550 to $14,200/ participant)	-	76

£1.00=US$1.20, €1.00=US$1.06.

[a]Classified as "manage" medical disorders and conditions (e.g., manage chronic conditions that can be controlled but not cured, including symptoms management), "treat" (e.g., towards permanent recovery such as for addictions and chronic insomnia), or "prevent" (e.g., secondary prevention of cardiovascular diseases).
[b]NL: the Netherlands.
[c]UC: usual care.
[d]iNMB: incremental net monetary benefit, which is easier to interpret than the ICER when differences are small [41].
[e]HTN: hypertension.
[f]SBP: systolic blood pressure.
[g]DBP: diastolic blood pressure.
[h]IIALY: incontinence impact adjusted life-years.
[i]Including depression, anxiety, insomnia, and substance use disorders.
[j]OUD: opioid use disorder.
[k]TW: Taiwan.
[l]CVD: cardiovascular disease.

Quality Assessment

The level of methodological detail presented in the included studies varied but was overall high. The mean study quality score, determined using the CHEC-list, was 71% (range 39% - 100%) (Multimedia Appendix 1). Quality is the highest among EE based on RCTs, and lowest among those based on non-randomized studies (Multimedia Appendix 1). Common areas for point deduction included no mention of ethical and distributional considerations, the single most common quality issue, limited descriptions of interventions' alternatives (i.e., of any interventions received by control groups), unjustified decisions to utilize narrow methodological perspectives (e.g., health care resource utilization rather than societal perspectives), a lack of incremental analysis of costs and outcomes (i.e., an ICER), and no discussion of generalizability to other settings and patient populations. In contrast, most included studies measured and valued outcomes appropriately, clearly described study populations, and explicitly acknowledged potential conflicts of interest. Study quality did not significantly associate with the year of publication.

If all RCT-based EE (5/5) performed sensitivity analyses (i.e., univariate and multivariate scenarios, as well as one-way and multiway deterministic sensitivity analyses), only 29% of

non-randomized-based EE (2/7) [33,34] did so (i.e., multiway deterministic sensitivity analyses). 83% of model-based EE (5/6) [37-39,44,45] performed sensitivity analyses (i.e., one-way and multiway deterministic sensitivity analyses, as well as probabilistic sensitivity analyses).

RoB was similarly heterogenous for RCT, non-randomized studies, and modeling studies, with important overall risks of bias across studies. Among RCTs, none were classified as low RoB in any of the six categories. Due to the digital nature of the DTx, participants (or personnel) were not blind-to-assignment and could therefore expect to receive either an active treatment or a placebo. As a result, most RCT-based studies (4/5, 80%) [40,41,43,46] were classified as high risk of performance bias. One study used an "information app" for the comparator group, and without clear consequence on the potential performance bias, it was classified as unclear [42]. Two studies (2/5, 40%) [40,41] were classified as high-risk for attrition bias related to incomplete outcome data resulting from a high degree of participant attrition not fully accounted for in the analyses (Multimedia Appendix 2). Common sources of "other bias" were potential selection biases in participant recruitment, leading to potential imbalance between groups in baseline variables (such as age, educational level, or disease severity).

Among non-randomized studies, none received an overall low-risk classification (Multimedia Appendix 3): 57% (4/7) [30,32,33,36] were graded as moderate risk and 42% (3/7) [31,34,35] as high risk, in all cases due to moderate- or high-risk classifications in 1 – 3 (of 7) scoring categories. All non-randomized studies demonstrate low RoB in the classification of interventions and a lack of deviation from intended interventions, as well as in the measurement of outcomes and selection of reported results. The greatest source of potential bias among these non-randomized studies was in the selection of participants into the study, as patients often self-selected or were recruited into intervention groups based on potentially confounding factors. For example, two studies of the opioid abstinence tool reSET-O were graded as serious risk in this category because the intervention group comprised patients who sought out a reSET-O prescription or filled one provided by a prescriber, while the control group comprised patients who did not actively seek treatment in the same way [34,35].

Finally, among modeling studies, RoB was classified as unclear in the category of bias related to internal consistency in all 6 studies, none of which explicitly reported exploring this (Multimedia Appendix 4). The highest RoB among these studies tended to arise from Part A of the checklist: the "overall checklist for bias in economic evaluation." Within this category, 66% (4/6) [37-39,45] studies were graded as high-risk, and 16% (1/6) [44] as moderate RoB. Common sources of potential bias among modeling studies were narrow perspectives without justification, a lack of ordinal ICER, and a short time horizon relative to the outcome of interest.

Costs and Factors Impacting the Economic Value of DTx

The costs and factors associated with the economic impact of the DTx interventions, which were obtained through sensitivity analysis or outlined in the discussion sections of the individual studies as having an impact on DTx economic value, were extracted from the selected studies (Table 2). These costs and factors reflect, above all, the medical conditions and disorders under consideration, as well as the study design and methods for measuring economic outcomes. Nevertheless, there are some common key findings that are worth noting.

Table 2. Costs and factors impacting the economic value of DTx.

	Societal perspective studies						Payer perspective studies										
	Loohuis et al [40], 2022	Sjöström et al [43], 2017	Ekersund et al [42], 2022	Kumar et al [37], 2018	Piera-Jiménez et al [47], 2022	Lewkowicz et al [44], 2022	Sweet et al [32], 2020	Whaley et al [36], 2019	Chen et al [39], 2016	Horstman et al [30], 2021	McManus et al [46], 2021	Nomura et al [45], 2022	Nordyke et al [38], 2019	Velez et al [34], 2022	Velez et al [35], 2021	Pelle et al [41], 2022	Forma et al [31], 2022	Abhulimen et al [33], 2018
Direct medical and non-medical costs																		
Pharmaceutical treatment[a]	●	○	○	○		○	○	●	●		○	○	●				○	
Cost of the DTx				○	●	●	○			○		●						
HRU[b]: Primary care[c]	○				○	○					○					○		
HRU: Outpatient care[d]	○			●	○	○	○	●	●	●	○			○	○	○	○	○
HRU: Inpatient care[e]	○			●	●		●	○	●	○	○	○	●	●	●	○	●	●
HRU: ED[f] visits	○			○			○	○	○		○			●	●		●	●
HRU: Health support intervention[g]	○	○	○		○	●					○							
Intervention-specific training[h]					○						○							
Participants' time spent on the DTx[i]		●	●		○													
Indirect medical and non-medical costs																		
Productivity impact[j]	○			●		○												
DTx maintenance	○																	
Influencing factors																		
Participants' baseline characteristics[k]	●	○		○	●			○	●	●	○		●	○	○			○
Reimbursement rate						●												
Treatment adherence											○			○	○			
Attrition rate[l]						●	○	○	○	●	○	●	●	○				○
Degree of clinical inertia											○		●					
Sustained DTx clinical effectiveness[m]				○		●			○		○	○	●					

● Factors considered and/or directly cited by researchers as impacting the cost-effectiveness of DTx.
○ Factors reported by researchers as having an "important" or "significant" impact on, or which were deemed as "decisive" to, the cost-effectiveness of DTx.

[a]Including core costs originating from spending related to treatment of medical disorders and diseases, such as diabetes, or materials/aids, as in the case of incontinence.
[b]Health care resource utilization.
[c]General practitioner, physical therapist, occupational therapist, exercise therapist, dietician, or other primary care practitioner.
[d]Outpatient or ambulatory care visits, medical specialist consultations, physician services, as well as pathology and laboratory services.
[e]Including partial hospitalizations.
[f]Emergency department.
[g]Health assistance interventions and supports provided by health care workers.
[h]Training and educational sessions related to the optimal implementation of the intervention, including in-person or online sessions, for either patients or clinicians.
[i]Costs associated with the time spent by study participants using the DTx.
[j]Productivity losses such as absenteeism and disability days.
[k]Demographic and risk factor profiles of the study participants, such as race, age, gender, ethnicity, disease evolution, and severity or presence of comorbidities.
[l]Including study participants' engagement level with the DTx.
[m]Medium- to long-term relative effectiveness of the DTx intervention, including its effect on preventing or delaying disease onset.

Health Care Resource Utilization

Health care resource utilization – which includes primary care, outpatient care, inpatient care,

emergency department visits, and health support intervention – was the most frequently examined and reported cost across studies (18/18, 100%) [30-47]. Among those, inpatient care-related costs were shown to have a potential impact on DTx economic impact in 15 studies (78%) [30-41,45-47]. Inpatient care was further categorized as a "decisive factor" (i.e., having a significant impact on the economic impact of DTx [37]) in half of the studies [30-35,37-39].

Pharmaceutical Treatment

The expenditures originating directly from treating medical conditions or disorders, such as those related to the consumption of drugs (e.g., frequency and dose) or materials/aids, were considered in 67% of the studies (12/18) [31,32,36-40,42-46].

In some cases, DTx interventions have been shown to improve treatment adherence [34,35] and, as a result, might increase some expenses such as overall drug therapy costs or costs associated with higher rates of utilization of certain clinician services (e.g., psychiatry services, outpatient visits, and pathology/drug testing). However, in many cases those expenses were largely compensated by the cost savings in the included studies, especially in HRU [34,35]. For example, in a trial by McManus et al, participants who used DTx were more likely to have their antihypertensive drugs adjusted during the study (i.e., dosage or change in drugs) [46].

In other cases, the clinical benefits of DTx treatments may be able to reduce or eliminate the need for pharmacotherapies, thereby lowering total medical expenditures. However, Nordyke et al [38] and McManus et al [46] noted that despite evidence of DTx clinical efficacy, there may be a delay in deprescribing drugs from health care professionals – a phenomenon known as clinical inertia, which may reduce the potential economic benefits of DTx.

Participants' Baseline Characteristics

More than half of the studies (12/18) [30,33-40,43,46] pointed out that participants' baseline characteristics, such as age, gender, ethnicity, education level, baseline disease severity, risk factors, and costs, had an impact on the economic value of the intervention. Loohuis et al [40] conducted a subgroup analysis that revealed differences in DTx effects and costs not only by disease severity, but also by recruitment type: participants recruited via social media incurred lower associated costs and experienced a lesser treatment effect than those recruited by a general practitioner.

Whaley et al [36] hypothesized that individuals with higher health care needs who accepted the program invitation generally had higher baseline levels of comorbidity and health care spending compared with those who did not enroll, and therefore were more motivated to try a new intervention, and hence more likely to voluntarily enroll in a digital intervention. Piera-Jiménez et al [47] also noted that the willingness of individuals to adopt an intervention strongly impacts the success of DTx intervention.

Attrition Rate

More than half of the studies (10/18) [30,32-34,36,38,39,44-46] considered the potential causal effect of attrition rate, which can be a critical factor [44], to the DTx economic impact. Discrepancies in the way such factor was evaluated should be noted. First, as highlighted by Lewkowicz et al [44], a DTx intervention's attrition rates in RCT-based EE might simply not be reported or may not "represent real-world engagement and program dropout rates". Second, some studies defined a minimum level of engagement for participants' data to be included for

extraction and analysis; for example, in Pelle et al [41], an RCT-based EE, 63 participants were excluded for suboptimal level of engagement. Finally, in claims-based EE, the impact of a DTx intervention was evaluated based on a patient population that, by definition, filled their prescription and engaged with the therapeutic, and might have led to bias in the selection of participants into the study (Multimedia Appendix 4). As Nomura et al [49] highlighted, "achieving good cost-effectiveness for DTx might require sensitive handling to balance the appropriate DTx app usage duration with DTx costs and expected attrition rate." Attrition rate may have also resulted in incomplete outcome data, a potential RoB in half of the RCT and non-randomized studies-based EE (Multimedia Appendices 2 and 3) [31-34,40,41].

Discussion

Economic evaluations (EE) of new therapies and clinical interventions are critical for market access and adoption since they provide decision-makers with important information regarding their "value for money." This systematic review includes 18 studies that conducted EE of clinical-grade, mobile-based DTx. The relatively small number of included studies (which is consistent with other recent systematic reviews of digital health solutions [50]) attests to the paucity of published literature on DTx, which also explains the scarcity of evidence pertaining to the economic value of these intervention modalities [51].

All 18 of the included studies were conducted in developed countries, with 12 supported by industry funding [30-39,45,46], and 6 by public organizations [40-44,47]. While the prevalence of industry-funded research may potentially introduce commercial bias – which is acknowledged in the present review – it also underscores the contributions of both public and private organizations to generating evidence for informed treatment decision-making when DTx options are available.

Heterogeneity Among Included Studies

The included studies exhibit significant heterogeneity with respect to DTx intervention, type of EE, and methodology (Table 1). This review combines EE based on both clinical trial results and decision modeling to examine DTx applications for a spectrum of diseases across various settings and for different payers. Specifically, 4 studies [33-36] did not report the clinical outcomes of the intervention, only 10 reported an ICER [37,38,40-47], and only 7 reported cost and QALYs as the outcome measures [37,38,42-45,47]. As a result of this heterogeneity, a robust meta-analysis of this data was not feasible, making it impossible to provide numerical answers regarding the cost-effectiveness of DTx interventions. The study heterogeneity also hinders the comparability and generalizability of the findings and makes the EE results difficult to interpret.

Adding to this challenge, the context-specific nature of DTx interventions is evident in a multisite RCT conducted by Piera-Jiménez et al [47], which evaluated the economic impact of the same intervention implemented in three different countries: the Netherlands, Spain, and Taiwan. The study found the DTx led to QALY gains in the Netherlands, but not in Spain or Taiwan, while cost savings were observed in Spain, but not in the Netherlands or Taiwan.

Methodological Characteristics of Included Studies

With a mean CHEC score of 71% across all 18 studies, the methodological rigor across included studies is of moderate quality, ranging from an average of 90% for RCT-based EE to 77% for

model-based EE to 53% for EE based on non-randomized studies. In particular, the evaluations based on non-randomized studies – all of which were funded by industry – adopted a payer-only perspective, which may be too narrow to broadly inform implementation decisions since it excludes direct patient out-of-pocket costs, indirect costs such as productivity loss, and other factors that can impact the long-term utility of an intervention. Further, none of the EE based on non-randomized studies performed an incremental analysis of costs and outcomes of the alternatives to DTx (e.g., standard therapy). Lastly, only 29% of non-randomized-study-based EE performed sensitivity analysis, which is a best practice for quantifying uncertainty and testing the robustness of a study's conclusions [52].

Another methodological deficit stems from the fact that while the majority of DTx interventions were reported to have significant impacts on costs and outcomes over a patient's lifetime, most of the studies utilized a time horizon too short to capture all or most clinical and economic impacts of the respective intervention. Specifically, the average time horizon of the RCT-based EE was 10.8 months, while that of non-randomized-studies-based EE was 17.8 months. Only 2 studies [37,45] adopted a lifetime horizon and only 6 studies [37-39,44,45,47] included modeling decisions to extrapolate the outcomes measures over time. This incongruity between the claimed lasting impacts of DTx and the limited time horizons over which they were evaluated implies that DTx should be assessed over longer periods of time [41,44,46,47]. In turn, determining the long-term economic effects of DTx and advancing understanding as to where their adoption may add value requires more comprehensive modeling [54].

Modeling can also ensure that trial populations reflect patient groups treated in real-world clinical practice, which is an important consideration as this review identified various biases in participant recruitment. Such biases might result in imbalances in relevant baseline characteristics between patient groups, which can also hinder health equity considerations. As a case in point, in 11 studies [30-33,35,36,41-43,46,47], participants were required to have internet access, a smartphone or a tablet, the skills necessary to use a personal computer, medical insurance, or employment in order to participate – requirements that may limit the participation of members of marginalized or socioeconomically vulnerable groups. By contrast, only 3 studies [32,43,46] addressed ethical and distributional issues inherent in the implementation of digital technologies.

Across studies employing the same perspective, disparities in the costs taken into account were also noted (Table 2). The importance of time and expertise required for patient education on using and managing DTx technology [53] was only considered in 2 studies [46,47]. Similarly, only 1 study [40] factored in the ongoing maintenance costs of the DTx. Highlighting the criticality of taking stock of all costs, Lewkowicz et al [44] applied a societal perspective and reported that their model accounted for 61% of costs related to conventional treatment for low back pain when only direct costs were considered and for 81% when indirect costs were included, using a publicly available cost-of-illness study as a benchmark. Future DTx EE will therefore benefit from more transparent, systematic, and exhaustive consideration of all of the costs that implementing DTx interventions entails, including long-term health care costs that may not be directly disease- or intervention-related as per ISPOR's recommendations [52].

Altogether, the studied DTx interventions were found to be cost-effective in 9 of the 10 studies that performed a full EE [37,38,40-46] and cost-saving in the remaining 8 studies that performed a partial EE [30-36,39]. In 5 of the 18 studies [42-45,47], the DTx interventions presented a trade-off between costs and effects (i.e., intervention being more effective and

more costly than the comparators). However, in 3 of these 5 studies [42,43,45], the highest ICERs obtained through sensitivity analysis fell below the willingness-to-pay threshold established in the respective countries in which they were performed, providing reassurance about their potential economic benefits.

The findings from this review indicate that DTx – at least in some use cases and local contexts – can be cost-effective and offer economic value to payers while simultaneously improving care for patients. However, consistent with the existing literature [51,54], qualitative deficits in methodology as well as significant potential biases in EE should be addressed going forward.

The review emphasizes the importance of adhering to established best practices and of developing a robust, consistent methodological framework that incorporates the unique features that distinguish DTx interventions from conventional therapies or current standard of care [51]. In the future, DTx EE analysis will need to adhere to local and international guidelines, employ generalizable tools and metrics for enhanced comparability of the findings, and be both long-term focused and all-inclusive when factoring in value and cost. Such efforts are crucial for minimizing provider, payer, and patient uncertainty surrounding the adoption of DTx interventions.

Limitations

Although we aimed to provide a comprehensive and systematic review of the economic value of clinical-grade mobile-based DTx, there are several limitations to be acknowledged. First, only studies written in the English language were included. Those studies were identified using a finite list of specific search terms, however, widely varying terminologies exist in the literature with reference to DTx, such as medical apps, digital therapies, or simply digital health technologies. As a result, it is possible that not all relevant studies assessing the economic impact of DTx may have been identified. Second, DTx interventions can be delivered through different modalities, including but not limited to virtual reality devices, mobile apps, online platforms, or a combination of these. In order to draw robust conclusions about mobile DTx as an emerging category of technologies in the clinical arena, this review focused exclusively on mobile app-based DTx to the exclusion of multimodal DTx or those not primarily using a mobile app as the core delivery mechanism.

Conclusions

This systematic review synthesizes the available evidence about the potential economic benefits of clinical-grade mobile-based DTx, as well as some of the qualitative deficits in DTx economic evaluation methodology, which can be used to guide future research on the subject. Specific areas that can benefit from more research, and which would further support market access decision-making and adoption of DTx, include evaluating DTx interventions in more diverse populations, across a greater variety of local contexts, and over longer time horizons.

Acknowledgements

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Contributions

Y.S., A.R. and M.L.C. conceptualized the study. Y.S. and X.T. conducted the literature searches, literature screening, study analysis and data collection. C.T.A.B. performed the quality

assessment and risk-of-bias appraisal. Y.S., X.T. and C.T.A.B. completed the data synthesis with input from the contributors and drafted the manuscript. A.R., F.K., L.M.C., G.T., A.B., C.L.H., J.Y. and D.H. contributed to refining all sections and critically editing the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of Interest

G.T. is employee of Cytel Canada Health Inc, Canada. F.K. is employee of IU International University of Applied Sciences, Germany and Flying Health GmbH, Germany. C.L.H. is employee of Pureland Global Venture Pte Ltd, Singapore. A.B. and D.H. are coinventors of previously filed pending patents on artificial intelligence–based therapy development. The other authors Y.S., X.T., C.T.A.B., A.R., L.M.C. and J.Y. have no conflicts.

Multimedia Appendix 1

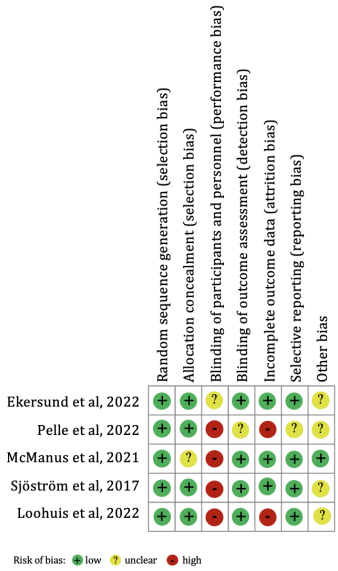
Consensus on Health Economic Criteria quality assessment.

	RCT-based EE					Non-randomized studies-based EE							Model-based EE					
	Ekersund et al, 2022	Pelle et al, 2022	McManus et al, 2021	Sjöström et al, 2017	Loohuis et al, 2022	Horstman et al, 2021	Forma et al, 2022	Sweet et al, 2020	Abhulimen et al, 2018	Vélez et al, 2022	Vélez et al, 2021	Whaley et al, 2019	Piera-Jiménez et al, 2020	Lewkowicz et al, 2022	Nomura et al, 2022	Kumar et al, 2018	Nordyke et al, 2019	Chen et al, 2016
Is the study population clearly described?	1	1	1	1	1	1	1	1	0.5	1	0.5	1	1	1	1	0.5	1	1
Are competing alternatives clearly described?	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0
Is a well-defined research question posed in answerable form?	0.5	1	1	1	0.5	0.5	0.5	0.5	0.5	1	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Is the economic study design appropriate to the stated objective?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Is the chosen time horizon appropriate to include relevant costs and consequences?	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
Is the actual perspective chosen appropriate?	1	0	1	1	1	0	0	0	0	0	0	0	1	1	1	1	0	0
Are all important and relevant costs for each alternative identified?	1	1	1	1	1	0.5	0	0	0	0	0	0.5	1	1	1	1	0	1
Are all costs measured appropriately in physical units?	1	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	0	1
Are costs valued appropriately?	1	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	0	1
Are all important and relevant outcomes for each alternative identified?	1	1	1	1	1	1	1	1	0.5	1	1	1	1	1	1	1	1	1
Are all outcomes measured appropriately?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are outcomes valued appropriately?	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1
Is an incremental analysis of costs and outcomes of alternatives performed?	1	1	1	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0
Are all future costs and outcomes discounted appropriately?	1	1	1	1	1	0	0	0	1	0	1	0	1	1	1	1	1	1
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	1	1	1	1	1	0	0	0	1	1	0	0	0	1	1	1	1	1
Do the conclusions follow from the data reported?	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1
Does the study discuss the generalizability of the results to other settings and patient/client groups?	1	0	1	0.5	0	0.5	0	0	0.5	1	0	0.5	0	0	1	1	0	1
Does the article indicate potential conflicts of interest of study researcher(s) and funder(s)?	1	0.5	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are ethical and distributional issues discussed appropriately?	0	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0
TOTAL SCORE	**92%**	**76%**	**100%**	**95%**	**87%**	**55%**	**39%**	**55%**	**53%**	**63%**	**50%**	**55%**	**76%**	**87%**	**92%**	**74%**	**55%**	**76%**

Answers to the questions: no partially yes

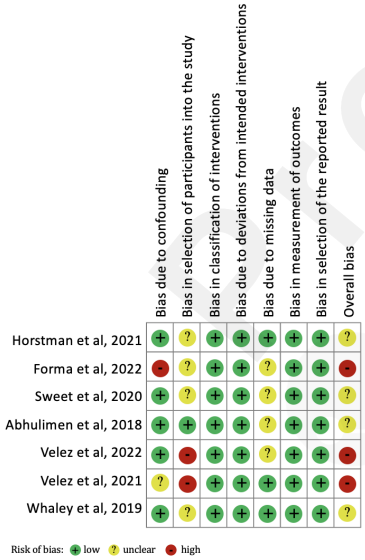
Multimedia Appendix 2

Risk of bias for randomized clinical trial-based economic evaluations.



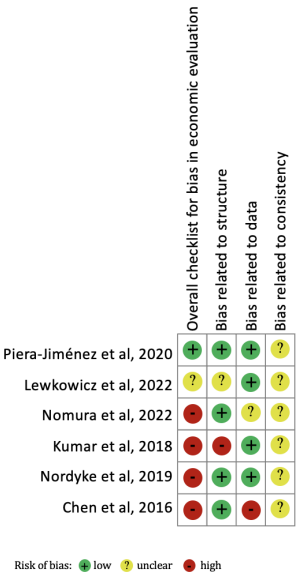
Multimedia Appendix 3

Risk of bias for non-randomized studies-based economic evaluations.



Multimedia Appendix 4

Risk of bias for model-based economic evaluations.



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Abbreviations

BN: billion
CA: cost analysis
CBT: cognitive behavioral therapy
CEA: cost-effectiveness analysis
CHEC: consensus on health economic criteria
COD: cost-outcome description
CUA: cost-utility analysis
CVD: cardiovascular disease
DBP: diastolic blood pressure
DPP: diabetes prevention program
DTx: digital therapeutics
ECOBIAS: economic evaluation bias
ED: emergency department
EE: economic evaluations
FDA: Food and Drug Administration
GAD: generalized anxiety disorder
HRU: health care resource utilization
HTA: health technology assessment
HTN: hypertension
ICER: incremental cost-effectiveness ratio
IIALY: incontinence impact adjusted life years
INAHTA: international network of agencies for health technology assessment
iNMB: incremental net monetary benefit
ISI insomnia severity index
LBP: low back pain
MM: million
NL: Netherlands
OUD: opioid use disorder
PPPM: per participant per month
PRISMA: preferred reporting items for systematic reviews and meta-analyses
QALY: quality-adjusted life-year
RCT: randomized controlled trial
Rob: risk of bias
SBP: systolic blood pressure
TW: Taiwan
UC: usual care
UK: United Kingdom
USA: United States of America

Supplementary Files

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Figures

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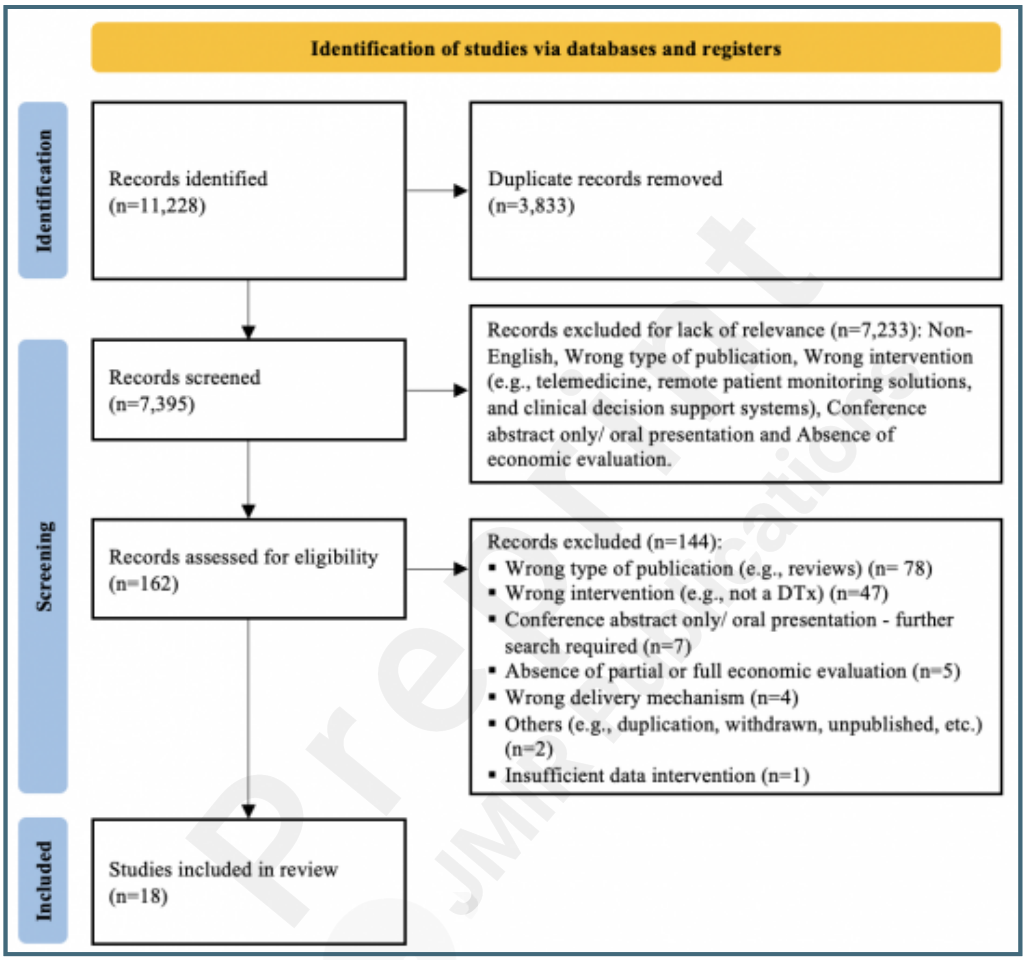
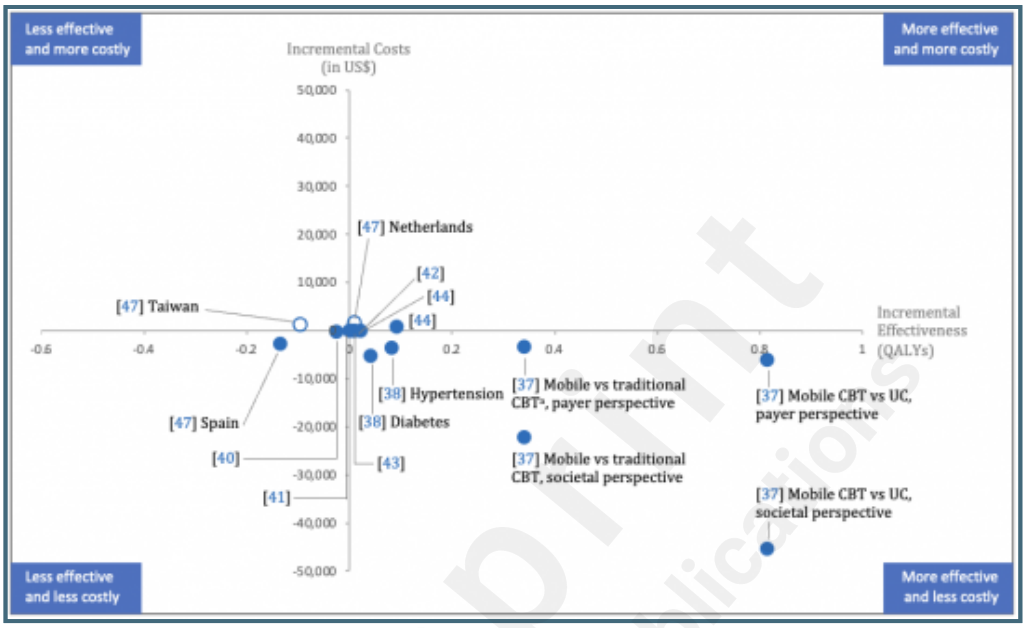
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.



Cost-effectiveness plane of studies with cost and quality-adjusted life-years as the outcome measures.



Multimedia Appendixes

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Consensus on Health Economic Criteria quality assessment.
URL: http://asset.jmir.pub/assets/4acdae6a7a4afd03675b538d53ca041a.png

Risk of bias for randomized clinical trial-based economic evaluations.
URL: http://asset.jmir.pub/assets/1ed766919e2af04d132a4c00248c787e.png

Risk of bias for non-randomized studies-based economic evaluations.
URL: http://asset.jmir.pub/assets/2d93cb4f5b167ffb7cdde11a7e31df4a.png

Risk of bias for model-based economic evaluations.
URL: http://asset.jmir.pub/assets/895dec48d9bd7621fd8840609f815b1b.png

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Appendix 1C. Article published in JMIR

Review

Economic Evaluation Associated With Clinical-Grade Mobile App–Based Digital Therapeutic Interventions: Systematic Review

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Abstract

Background: Digital therapeutics (DTx), a class of software-based clinical interventions, are promising new technologies that can potentially prevent, manage, or treat a spectrum of medical disorders and diseases as well as deliver unprecedented portability for patients and scalability for health care providers. Their adoption and implementation were accelerated by the need for remote care during the COVID-19 pandemic, and awareness about their utility has rapidly grown among providers, payers, and regulators. Despite this, relatively little is known about the capacity of DTx to provide economic value in care.

Objective: This study aimed to systematically review and summarize the published evidence regarding the cost-effectiveness of clinical-grade mobile app–based DTx and explore the factors affecting such evaluations.

Methods: A systematic review of economic evaluations of clinical-grade mobile app–based DTx was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines. Major electronic databases, including PubMed, Cochrane Library, and Web of Science, were searched for eligible studies published from inception to October 28, 2022. Two independent reviewers evaluated the eligibility of all the retrieved articles for inclusion in the review. Methodological quality and risk of bias were assessed for each included study.

Results: A total of 18 studies were included in this review. Of the 18 studies, 7 (39%) were nonrandomized study–based economic evaluations, 6 (33%) were model-based evaluations, and 5 (28%) were randomized clinical trial–based evaluations. The DTx intervention subject to assessment was found to be cost-effective in 12 (67%) studies, cost saving in 5 (28%) studies, and cost-effective in 1 (6%) study in only 1 of the 3 countries where it was being deployed in the final study. Qualitative deficiencies

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in methodology and substantial potential for bias, including risks of performance bias and selection bias in participant recruitment, were identified in several included studies.

Conclusions: This systematic review supports the thesis that DTx interventions offer potential economic benefits. However, DTx economic analyses conducted to date exhibit important methodological shortcomings that must be addressed in future evaluations to reduce the uncertainty surrounding the widespread adoption of DTx interventions.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42022358616; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022358616

(J Med Internet Res 2023;25:e47094) doi: 10.2196/47094

KEYWORDS

digital health; digital therapeutics; economic evaluation; cost-effectiveness; mobile phone; systematic review

Introduction

Background

The continued rise in chronic and mental health conditions, and commensurately in their associated health care costs, is not a new phenomenon. What is new—and reinforced by the COVID-19 pandemic—is the realization of a need for novel approaches to deliver care for these conditions closer to where individuals live and work, such as in their own homes and communities. As health care organizations and providers rush to adapt to this new reality, the adoption of digital technologies has accelerated rapidly [1].

Under the umbrella term digital technologies, it is crucial to distinguish between 3 separate categories, which are sometimes conflated or used interchangeably: *wellness and support* solutions, referring to products designed to capture, store, and transmit health data (eg, telehealth platforms); *diagnostic and monitoring* solutions, involving products that measure or track individuals' health status or both (eg, connected drug delivery devices); and *digital therapeutics (DTx)*, a new class of medicine that delivers therapeutic interventions directly to patients (eg, digital behavioral therapy) [2].

Powered by computer software, DTx can deliver evidence-based therapeutic interventions that prevent, manage, or treat a spectrum of medical disorders and diseases directly to patients [2]. Evidence supporting the potential of DTx in optimizing patient care and health outcomes [3] through a more personalized approach to health care, with greater patient education and empowerment, is mounting [4]. As such, DTx have recently been described as the "next paradigm" of modern health care [5].

Interest in DTx began to surge in 2017 when the US Food and Drug Administration approved the first DTx for the treatment of opioid use disorders [6]. Subsequently, in 2019, Germany became the first country to establish a Fast-Track Process for integrating DTx into the German reimbursement market [7]. Shortly thereafter, Belgium [8], France [9], Japan [10], South Korea [11], and the United Kingdom [12] began to implement DTx-specific approval and reimbursement processes. Globally, there are currently approximately 400 DTx available or under development [13].

Although considered a rapidly emerging class of medicine, the economic value of DTx is yet to be understood, resulting in an important knowledge gap that limits its widespread uptake [14,15]. There is currently limited consensus on whether these technologies are cost-effective compared with traditional treatments. Because cost-effectiveness is an important consideration in payers' reimbursement and pricing decisions [15], questions regarding the potential economic impact of DTx merit exploration [16].

In the context of budgetary constraints and the enduring need for optimal resource allocation in health care, determining the best mix of health services and treatments to maximize clinical outcomes while minimizing costs is critical [17,18]. If DTx can demonstrate its economic value to decision makers (eg, public and private payers, regulators, and care providers), such evidence is important to facilitate decisions around market access, pricing, and reimbursement (and, therefore, adoption) for these technologies [19]. Therefore, we sought to systematically answer the question of whether this recently emerged class of medical intervention, DTx, has yet been translated to economic value.

Objective

Given the growing body of evidence supporting the potential clinical benefits of DTx, the aim of this systematic review was to evaluate the published evidence regarding the cost-effectiveness of clinical-grade, mobile app–based DTx interventions and explore the costs and factors that drive such economic evaluation (EE).

Methods

Search Strategy

The protocol for this review was registered with PROSPERO a priori (CRD42022358616). A search of the relevant literature was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines [20]. Databases searched for eligible studies included PubMed, Cochrane Library, Web of Science, Embase, Business Source Ultimate (EBSCO), CINAHL (EBSCO), Scopus, ProQuest Business Premium Collection, and the Wiley Online Library. The search was conducted between September 5, 2022, and October 28, 2022, and was not constrained by the year of publication. In addition, secondary searches were executed in the International Network of Agencies for Health Technology Assessment International Health Technology Assessment database and the *International Journal of*

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Technology Assessment in Health Care. The search strings were tailored according to each database requirement. The following keywords were searched in publication titles and abstracts, as identified by the setting, perspective, intervention, comparison, and evaluation framework [21] and in consultation with a research librarian from the National University of Singapore:

(A): "digital therapeutic*" OR "digital health*" OR "digital tech*" OR "mobile health" OR "mhealth" OR "mobile tech*" OR "mobile medical app*" OR "mobile app*" OR "wearable tech*" OR "connected medical devices"; AND

(B): "economic evaluation" OR "economic value" OR "cost-benefit" OR "cost-utility" OR "cost-effectiveness" OR "cost-effective" OR "Quality-Adjusted Life-Years" OR "Markov Chains" OR "Models, Economic."

Eligibility Criteria

DTx delivery mechanism (eg, mobile apps, web-based systems, or virtual reality) can significantly impact its economic proposition. Therefore, because DTx primarily leverage mobile apps as a delivery mechanism [22], and "smartphone apps" are regarded as the top 2 (after telemedicine) technology developments anticipated to create the most disruption for established health care practices [23]; hence, this review focuses on clinical-grade mobile app–based DTx. Thus, studies were included based on the following inclusion criteria: (1) published in a peer-reviewed journal within any time frame, (2) the study analyzed a mobile app–based intervention, (3) the therapeutic intervention was delivered directly to patients, (4) the intervention demonstrated its clinical benefits through at least 1 case-control study, (5) the study included a partial or full EE, and (6) the publication was available in English. Internet-based and virtual reality–based interventions, solutions for screening, diagnostic and monitoring purposes, telemedicine and remote patient monitoring solutions, and clinical decision support solutions were excluded. Furthermore, non–peer-reviewed publications (eg, white papers and editorials), abstract-only papers, and those with unavailable full text were also excluded.

The reference lists of studies that met the inclusion criteria were subjected to an additional "backward reference search" to identify additional relevant studies.

Study Selection, Data Extraction, and Data Synthesis

After duplicate records were removed, 2 reviewers (YS and XT) independently screened the titles and abstracts of all remaining identified studies for inclusion using the systematic review software Covidence (Veritas Health Innovation). Eligible studies that met the inclusion criteria, according to both reviewers, then underwent a full-text review. Conflicting outcomes were discussed between reviewers, and a third researcher (AR) was involved to help reach a consensus when necessary.

Data were extracted using a bespoke web-based Microsoft Excel 365 spreadsheet. Full data extraction was completed by 1 reviewer (YS) and verified by a second reviewer (XT). The extracted information from each study included country, targeted disease, product's primary purpose, study design, perspective, costs considered, time horizon, intervention group sample size, type of control group, clinical outcomes, cost savings, scholars' conclusion on the intervention's cost-effectiveness, uncertainty consideration (discounting and sensitivity analysis), and sources of funding or conflicts of interest. Additional factors directly considered in the EE and factors reported by scholars as impacting the DTx's economic impact, through sensitivity analysis or explicitly in the studies' discussion sections, were also extracted. After extraction, the data were narratively synthesized to evaluate their meaning [24]. The additional extracted factors impacting the DTx were clustered into main categories and organized into a concept matrix [25].

Quality Assessment

Quality assessment of the included studies was conducted using the Consensus Health Economic Criteria (CHEC) list [26]. Each study received a score of 1, 0.5, or 0 for satisfying, partially satisfying, or not satisfying, respectively, the 19 independent evaluation criteria. The cumulative percentage of criteria satisfied was calculated as an overall "score" for each article (maximum possible score: 19/19 criteria or 100%).

The risk of bias (RoB) was calculated for each article according to its methodology. For randomized controlled trials (RCTs), the Cochrane Collaboration RoB tool [27] was used, rating each study as unclear, low, or high risk for selection bias. For nonrandomized studies, the Risk of Bias in Non-Randomized Studies of Interventions tool was used to rate the RoB owing to confounding, bias in selection of participants into the study, bias in the classification of interventions, bias owing to deviation from intended interventions, bias owing to missing data, bias in measurement outcomes, and bias in selection of the reported result [28]. Each of these features was rated as low, moderate, or serious RoB, and each study's overall bias was conservatively calculated as the highest-risk measure in any category. Finally, bias in modeling studies was calculated using the Bias in Economic Evaluation checklist, and rated as "Yes," "No," "Partially," "Unclear," or "Not applicable" referring to a study's ability to address each of 22 independent criteria [29]. We elected to consolidate the Bias in Economic Evaluation ratings into the scale's 4 overarching categories: overall checklist for bias in EE, bias related to structure, bias related to data, and bias related to consistency. For uniformity with the other RoB assessment tools, we rated the bias in each category as low, moderate, or high risk, equivalent to the highest-risk single evaluation for any component criterion, considering "Yes" and "Not applicable" to be equal to low risk, "Partially" and "Unclear" to be equal to moderate risk, and "No" to be equal to high risk.

Results

Study Selection

After duplicate removal and eligibility screening, 18 studies were included in this review (Figure 1).

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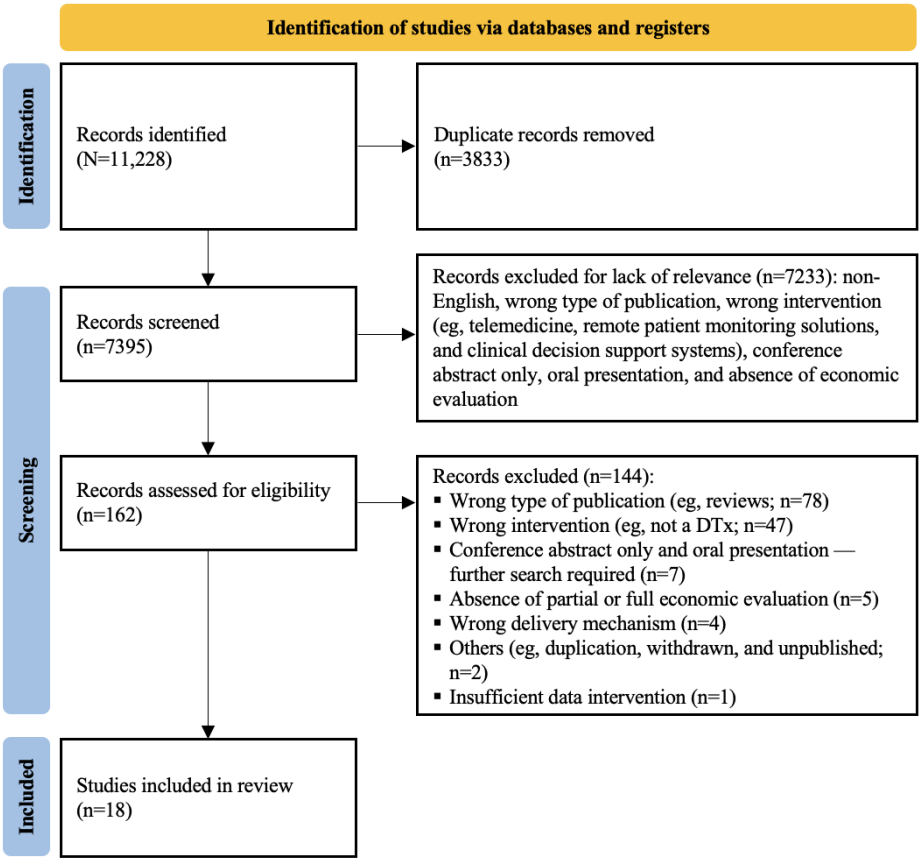
Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. DTx: digital therapeutics.



Study Characteristics

Table 1 summarizes the characteristics and main health economic outcomes associated with the included studies. Overall, the 18 studies in this review were conducted between 2016 and 2022. Of the 18 studies, 10 (56%) [30-39] were conducted in the United States; 2 (11%) [40,41] in the Netherlands; 2 (11%) [42,43] in Sweden; 1 (6%) [44] in Germany; 1 (6%) [45] in Japan; 1 (6%) [46] in the United Kingdom; and 1 (6%) [47] jointly in the Netherlands, Spain, and Taiwan. Furthermore, of the 18 studies, 10 (56%) [30-32,34-39,45] were industry funded, 6 (33%) [40,41,43,44,46,47] were publicly funded, and the remaining 2 (11%) [33,42] received mixed funding.

The targeted diseases for DTx in the included studies, all among adult patient populations, were urinary incontinence (3/18, 17%) [40,42,43], diabetes (2/18, 11%) [32,36], opioid use disorder (2/18, 11%) [34,35], hypertension (2/18, 11%) [45,46], generalized anxiety disorder (1/18, 6%) [37], chronic insomnia (1/18, 6%) [31], osteoarthritis (1/18, 6%) [41], lower back pain (1/18, 6%) [44], obesity (1/18, 6%) [30], behavioral health conditions (1/18, 6%) [33], cardiovascular disease (1/18, 6%) [47], both diabetes and cardiovascular disease (1/18, 6%) [39], and both type 2 diabetes and hypertension (1/18, 6%) [38].

Regarding the type of EE performed, of the 18 studies, 7 (39%) [30-36] involved nonrandomized study–based EE, 6 (33%) [37-39,44,45,47] involved model-based EE, and 5 (28%) [40-43,46] involved RCT-based EE. Of the 18 studies, 12 (67%) used a payer perspective [30-36,38,39,41,45,46], whereas 6 (33%) used a societal perspective [37,40,42-44,47], with 2 (11%) of the latter group also taking a payer perspective [37,47]. The time horizon used for the EE was between 6 and 12 months for 56% (10/18) of the studies [32-36,40-43,46], 24 months for 6% (1/18) of the studies [31], 36 months for 17% (3/18) of the studies [30,38,44], 60 months for 6% (1/18) of the studies [47], 120 months for 6% (1/18) of the studies [39], and lifetime for 11% (2/11) of the studies [37,45]. The intervention group sample sizes ranged between 60 and 305 participants for RCT-based EE and between 248 and 4790 participants for nonrandomized

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study–based EE. The interventions were compared with usual care (13/18, 72%) [30,32-34,36,38,40,41,43-47], preintervention (2/18, 11%) [31,39], an informative but noninterventional "control" app (1/18, 6%) [42], patients who filled their prescription but did not engage beyond week 1 and patients who did not fill the prescription (1/18, 6%) [35], and traditional cognitive behavioral therapy or no therapy (1/18, 6%) [37].

Of the 18 studies, 14 (78%) [30-32,37-47] assessed the impact of the DTx intervention on clinical outcomes. Of the 14 studies, 11 (79%) [30-32,37-39,42-46] found superior clinical outcomes, 2 (14%) [40,41] found no improvement compared with usual care, and 1 (7%) [47] found superior clinical outcomes in only 1 of the 3 countries in which the intervention under study was delivered.

Half (9/18, 50%) of the studies included in this review [37,38,40-42,44-47] conducted a cost-effectiveness analysis (CEA), with 4 (22%) also including a cost-utility analysis (CUA) [40-42,44]. Of the 18 studies, 8 (44%) conducted a cost analysis [30-36,39], with a strong emphasis on cost differences using, for example, pre-post intervention claims data, and 1 (6%) study focused solely on CUA [43]. Of the 10 studies using CEA and CUA methods, 7 (70%) presented incremental cost-effectiveness ratio (ICER) values based on the cost per quality-adjusted life year (QALY) gained to assess the cost-effectiveness of the DTx intervention [37,38,42-45,47]. Meanwhile, 20% (2/10) of the CEA and CUA studies showed ICER values based on cost per incontinence impact–adjusted life years gained and cost per mm Hg reduction in blood pressure [40,46]. In total, 10% (1/10) of the studies did not report an ICER but an incremental net monetary benefit [41].

Of the 10 studies that conducted a full EE, 9 (90%) [37,38,40-46] found the DTx intervention to be cost-effective in the context of the study, whereas 1 (10%) study found the intervention to be cost-effective in only 1 of the 3 countries in which it was studied [47]. Specifically, DTx accounted for QALY gains along with cost savings in 20% (2/10) of the studies [37,38], QALY gains along with higher costs at an acceptable ICER in 50% (5/10) of the studies [34,35,42,43,46], QALY losses with cost savings in 20% (2/10) of the studies [40,47], and no demonstrable effectiveness difference with cost savings in 20% (1/10) of the studies [41]. Figure 2 represents the 15 different DTx interventions under assessment in the 50% (9/18) of the studies [37,38,40-45,47] that reported cost and QALYs as the outcome measures across the quadrants of the cost-effectiveness plane. The horizontal axis of the plane indicates differences in effects (ie, health outcomes), whereas the vertical axis represents the differences in costs between the DTx interventions and their respective comparators.

Of the 8 studies based on partial EE, all 8 (100%) found the DTx intervention under evaluation to be cost saving [30-36,39].

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Table 1. Study characteristics.

Study; country	Targeted disease (categories of DTx[a,b])	Type of evaluation	Perspective	Time horizon (months)	Intervention group sample size	Intervention vs comparator	Did the intervention lead to superior clinical outcomes?	Did the intervention lead to cost savings (in US $)?	Is the intervention cost-effective (incremental cost-effectiveness ratio, in US $)?	Consensus Health Economic Criteria (%)
Randomized clinical trial–based economic evaluations										
Ekersund et al [42], 2022; Sweden	Urgency and mixed urinary incontinence (manage)	CEA[c] and CUA[d]	Societal	12	60	Tät II vs information app	Yes (0.0115 QALY[e] gained)	No (+144)	Yes (12477/QALY)	92
Pelle et al [41], 2022; NL[f]	Osteoarthritis (manage)	CEA and CUA	Health care payer	6	214	Dr Bart vs UC[g]	No difference	Yes (−23)	Yes (56 iNMB[h])	76
McManus et al [46], 2021; United Kingdom	HTN[i] (manage)	CEA	NHS[j] payer	12	305	Home and Online Management and Evaluation of Blood Pressure vs UC	Yes (a mean difference in SBP[k] of −3.4mm Hg, and −0.5 mm Hg in DBP[l])	No (+46)	Yes (13/mm Hg reduction)	100
Sjöström et al [43], 2017; Sweden	Stress urinary incontinence (manage)	CUA	Societal	12	62	Tät vs UC	Yes (0.00849 QALY gained)	No (+69)	Yes (8071/QALY)	95
Loohuis et al [40], 2022; NL	Stress, urgency, or mixed urinary incontinence (manage)	CEA and CUA	Societal	12	131	URinControl vs UC	No (0.025 QALY loss and 0.043 IIALY[m] gained)	Yes (−170)	Yes (−3918/IIALYs)	87
Nonrandomized study–based economic evaluations										
Horstman et al [30], 2021; United States	Overweight and obesity (manage)	CA[n]	Payer	36	4790	Real Appeal vs UC	Yes (3% greater weight loss on average per participant)	Yes (−771/participant)	—[o]	55
Forma et al [31], 2022; United States	Chronic insomnia (treat)	CA	Payer	24	248	Pre-post Somryst treatment intervention	Yes (37.2% insomnia severity index score declined/participant)	Yes (−2059/participant)	—	39
Sweet et al [32], 2020; United States	Diabetes (prevent)	CA	Employer and payer	12	2027	Omada vs UC	Yes (4.3% average weight loss)	Yes (−1169/participant)	—	55
Abhulimen et al [33], 2018; United States	Behavioral health condition[p] (manage)	CA	Public and payer	11	799	myStrengh vs UC	—	Yes (−382/participant)	—	53

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Study; country	Targeted disease (categories of DTx[a,b])	Type of evaluation	Perspective	Time horizon (months)	Intervention group sample size	Intervention vs comparator	Did the intervention lead to superior clinical outcomes?	Did the intervention lead to cost savings (in US $)?	Is the intervention cost-effective (incremental cost-effectiveness ratio, in US $)?	Consensus Health Economic Criteria (%)
Velez et al [34], 2022; United States	OUD[q] (treat)	CA	Payer	12	901	reSET-O vs UC	—	Yes (−2791/participant)	—	63
Velez et al [35], 2021; United States	OUD (treat)	CA	Payer	9	444	reSET-O vs nonengagers	—	Yes (−2708/participant)	—	50
Whaley et al [36], 2019; United States	Diabetes (manage)	CA	Employer and payer	12	2261	Livongo program vs UC	—	Yes (−1056/participant)	—	55
Model-based economic evaluations										
Piera-Jiménez et al [47], 2020; NL, Spain, and TW[r]	CVD[s] (prevent)	CEA (RCT[t] informed and Markov model)	Societal and health care payer	60	120	Do change 2 vs UC	NL: yes (0.011 QALY gained); Spain: no (0.134 QALY loss); TW: no (0.094 QALY loss)	NL: no (+1456); Spain: yes (−2666); TW: no (+1127)	NL: no (131959/QALY); Spain: yes (19895/QALY); TW: no	76
Lewkowicz et al [44], 2022; Germany	Low back pain (manage)	CEA and CUA (RCT informed and Markov model)	Societal	36	RCT: 53 model: 10,000	Kaia vs UC	Yes (0.0221 QALY gained)	No (+129)	Yes (5815/QALY)	87
Nomura et al [45], Japan, 2022	Hypertension (treat)	CEA (RCT informed and Markov model)	Public health care payer	Lifetime	199	CureApp and UC vs UC	Yes (0.092 QALY gained)	No (+962)	Yes (10434/QALY)	92
Kumar et al [37], 2018; United States	Generalized anxiety disorder (prevent/treat)	CEA (pilot study informed and Markov model)	Societal and payer	Lifetime	Pilot: 89 model: 100,000	Mobile CBT[u] vs traditional CBT (model A) and mobile CBT vs UC (model B)	Model A: yes (34,108 QALYs gained); model B: yes (81,492 QALYs gained)	Societal: model A: yes (−2.23 billion); model B: yes (−4.54 billion); payer: model A: yes (−339 million); model B: yes (−605 million)	Societal: model A: yes (−65380/QALY); model B: yes (−55710/QALY); payer: model A: yes (−9939/QALY); model B: yes (−7424/QALY)	74

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Study; country	Targeted disease (categories of DTx[a,b])	Type of evaluation	Perspective	Time horizon (months)	Intervention group sample size	Intervention vs comparator	Did the intervention lead to superior clinical outcomes?	Did the intervention lead to cost savings (in US $)?	Is the intervention cost-effective (incremental cost-effectiveness ratio, in US $)?	Consensus Health Economic Criteria (%)
Nordyke et al [38], 2019; United States	Diabetes and HTN (manage)	CEA (decision tree model)	US commercial payer	36	—	DTx+UC vs UC	T2DM[v]: yes (0.0427 QALY gained); HTN: yes (0.0827 QALY gained)	T2DM: yes (−5220); HTN: yes (−3480)	T2DM: yes (−122,248QALY); HTN: yes (−42,080QALY)	55
Chen et al [39], 2016; United States	Diabetes and CVD (prevent)	CA (best available evidence and Markov model)	Public and payer	120	1121	Pre-post Omada program intervention	Yes (6.8% reduction in body weight per participant)	Yes (from 11,550 to 14,200 per participant)	—	76

[a]DTx: digital therapeutics.

[b]Classified as "manage" medical disorders and conditions (eg, manage chronic conditions that can be controlled but not cured, including symptoms management), "treat" (eg, toward permanent recovery, such as for addictions and chronic insomnia), or "prevent" (eg, secondary prevention of cardiovascular diseases).

[c]CEA: cost-effectiveness analysis.

[d]CUA: cost-utility analysis.

[e]QALY: quality-adjusted life year.

[f]NL: the Netherlands.

[g]UC: usual care.

[h]iNMB: incremental net monetary benefit, which is easier to interpret than the incremental cost-effectiveness ratio when differences are small [41].

[i]HTN: hypertension.

[j]NHS: National Health Service.

[k]SBP: systolic blood pressure.

[l]DBP: diastolic blood pressure.

[m]IIALY: incontinence impact–adjusted life years.

[n]CA: cost analysis.

[o]Not available.

[p]Including depression, anxiety, insomnia, and substance use disorders.

[q]OUD: opioid use disorder.

[r]TW: Taiwan.

[s]CVD: cardiovascular disease.

[t]RCT: randomized controlled trial.

[u]CBT: cognitive behavioral therapy.

[v]T2DM: type 2 diabetes mellitus.

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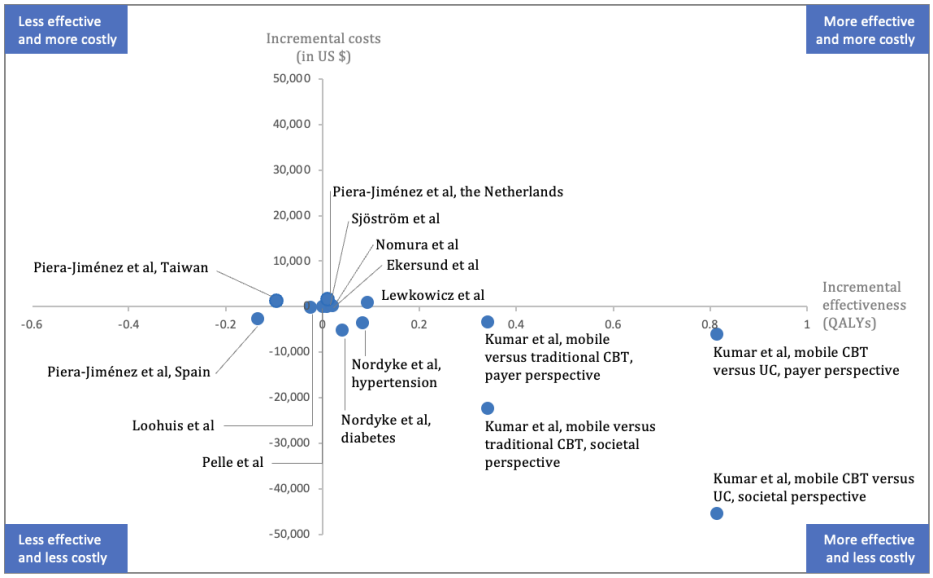
Figure 2. Cost-effectiveness plane of studies with cost and quality-adjusted life years as the outcome measures [37,38,40-45,47]. CBT: cognitive behavioral therapy; QALY: quality-adjusted life year; UC: usual care.



Quality Assessment

The level of methodological detail presented in the included studies varied but was overall high. The mean study quality score, determined using the CHEC list, was 71% (SD 0.18%; Multimedia Appendix 1 [30-47]). Quality was the highest among EE based on RCTs and the lowest among those based on nonrandomized studies (Multimedia Appendix 1). Common areas for point deduction included no mention of ethical and distributional considerations, the single most common quality issue, limited descriptions of interventions' alternatives (ie, of any interventions received by control groups), unjustified decisions to use narrow methodological perspectives (eg, health care resource use rather than societal perspectives), a lack of incremental analysis of costs and outcomes (ie, an ICER), and no discussion of generalizability to other settings and patient populations. In contrast, most of the included studies measured and valued outcomes appropriately, clearly described study populations, and explicitly acknowledged the potential conflicts of interest. Study quality was not significantly associated with the year of publication.

Although all RCT-based EE (5/5, 100%) performed sensitivity analyses (ie, univariate and multivariate scenarios as well as one-way and multiway deterministic sensitivity analyses), only 29% (2/7) of the nonrandomized study–based EE [33,34] did so (ie, multiway deterministic sensitivity analyses). In total, 83% (5/6) of model-based EE [37-39,44,45] performed sensitivity analyses (ie, one-way and multiway deterministic sensitivity analyses as well as probabilistic sensitivity analyses).

RoB was similarly heterogeneous for RCTs, nonrandomized studies, and modeling studies, with important overall risks of bias across studies. None of the RCTs were classified as having a low RoB in any of the 6 categories. Owing to the digital nature of the DTx, participants (or personnel) were not blind to assignment and could therefore expect to receive either an active treatment or a placebo. Consequently, most RCT-based studies (4/5, 80%) [40,41,43,46] were classified as having a high risk of performance bias. One study used an "information app" for the comparator group, and without clear consequence on the potential performance bias, it was classified as unclear [42]. In total, 40% (2/5) of the studies [40,41] were classified as high risk for attrition bias related to incomplete outcome data resulting from a high degree of participant attrition that was not fully accounted for in the analyses (Multimedia Appendix 2 [40-43,46]). Common sources of "other bias" were potential selection biases in participant recruitment, leading to potential imbalance between groups in baseline variables (such as age, educational level, or disease severity).

Among the nonrandomized studies, none received an overall low-risk classification (Multimedia Appendix 3 [30-36]): 57% (4/7) [30,32,33,36] were graded as moderate risk and 42% (3/7) [31,34,35] as high risk, in all cases owing to moderate- or high-risk classifications in 1 to 3 (out of 7) scoring categories. All nonrandomized studies demonstrated a low RoB in the classification of interventions, potential deviation from intended interventions, measurement of outcomes, and selection of reported results. The greatest source of potential bias among these nonrandomized studies was the selection of participants in the study, as patients often self-selected or were recruited into intervention groups based on potentially confounding factors. For example, 2 studies of the opioid abstinence tool reSET-O were graded as serious risk in this category because

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the intervention group comprised patients who sought a reSET-O prescription or filled one provided by a prescriber, whereas the control group comprised patients who did not actively seek treatment in the same way [34,35].

Finally, among the modeling studies, RoB was classified as unclear in the category of bias related to internal consistency in all 6 studies, none of which explicitly reported exploring this (Multimedia Appendix 4 [37-39,44,45,47]). The highest RoB among these studies tended to arise from part A of the checklist: the "overall checklist for bias in economic evaluation." Within this category, 66% (4/6) [37-39,45] of the studies were graded as high RoB and 16% (1/6) [44] as moderate RoB. Common sources of potential bias among modeling studies were narrow perspectives without justification, a lack of ordinal ICER, and a short time horizon relative to the outcome of interest.

Costs and Factors Impacting the Economic Value of DTx

Overview

The costs and factors associated with the economic impact of the DTx interventions, which were obtained through sensitivity analysis or outlined in the discussion sections of the individual studies as having an impact on DTx economic value, were extracted from the selected studies (Table 2). These costs and factors reflect, above all, the medical conditions and disorders under consideration as well as the study design and methods for measuring economic outcomes. Nevertheless, there are some common key findings that are worth noting.

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Table 2. Costs and factors impacting the economic value of digital therapeutics (DTx).

	Societal-perspective studies						Payer-perspective studies											
	[40]	[43]	[42]	[37]	[47]	[44]	[32]	[36]	[39]	[30]	[46]	[45]	[38]	[34]	[35]	[41]	[31]	[33]
Direct medical and nonmedical costs																		
Pharmaceutical treatment[a]	● [b]	○ [c]	○	○	—[d]	○	○	●	●	—	○	○	●	—	—	—	○	—
Cost of the DTx	—	—	—	○	●	●	○	—	—	○	—	●	—	—	—	—	—	—
HRU[e]: primary care[f]	○	—	—	—	○	○	—	—	—	—	○	—	—	—	—	○	—	—
HRU: outpatient care[g]	○	—	—	●	○	○	○	●	●	●	○	—	—	○	○	○	○	○
HRU: inpatient care[h]	○	—	—	●	●	—	●	○	●	○	○	○	●	●	●	○	●	●
HRU: ED[i] visits	○	—	—	○	—	—	○	○	○	—	○	—	—	●	●	—	●	●
HRU: health support intervention[j]	○	○	○	—	○	●	—	—	—	—	○	—	—	—	—	—	—	—
Intervention-specific training[k]	—	—	—	—	○	—	—	—	—	—	○	—	—	—	—	—	—	—
Participants' time spent on the DTx[l]	—	●	●	—	○	—	—	—	—	—	—	—	—	—	—	—	—	—
Indirect medical and nonmedical costs																		
Productivity impact[m]	○	—	—	●	—	○	—	—	—	—	—	—	—	—	—	—	—	—
DTx maintenance	○	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Influencing factors																		
Participants' baseline characteristics[n]	●	○	—	○	●	—	—	○	●	●	○	—	●	○	○	—	—	○

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	Societal-perspective studies						Payer-perspective studies											
	[40]	[43]	[42]	[37]	[47]	[44]	[32]	[36]	[39]	[30]	[46]	[45]	[38]	[34]	[35]	[41]	[31]	[33]
Reimbursement rate	—	—	—	—	—	●	—	—	—	—	—	—	—	—	—	—	—	—
Treatment adherence	—	—	—	—	—	—	—	—	—	—	○	—	—	○	○	—	—	—
Attrition rate[o]	—	—	—	—	—	●	○	○	○	●	○	●	●	○	—	—	—	○
Degree of clinical inertia	—	—	—	—	—	—	—	—	—	—	○	—	●	—	—	—	—	—
Sustained DTx clinical effectiveness[p]	—	—	—	○	—	●	—	—	○	—	○	○	●	—	—	—	—	—

[a]Including core costs originating from spending related to treatment of medical disorders and diseases, such as diabetes, or materials and aids, as in the case of incontinence.

[b]Factors considered and directly cited by researchers as impacting the cost-effectiveness of DTx.

[c]Factors reported by researchers as having an "important" or "significant" impact on, or which were deemed as "decisive" to, the cost-effectiveness of DTx.

[d]Not applicable.

[e]HRU: health care resource use.

[f]General practitioners, physical therapists, occupational therapists, exercise therapists, dieticians, or other primary care practitioners.

[g]Outpatient or ambulatory care visits, medical specialist consultations, physician services, and pathology and laboratory services.

[h]Including partial hospitalizations.

[i]ED: emergency department.

[j]Health assistance interventions and support provided by health care workers.

[k]Training and educational sessions related to the optimal implementation of the intervention, including in-person or web-based sessions, for either patients or clinicians.

[l]Costs associated with the time spent by study participants using the DTx.

[m]Productivity losses such as absenteeism and disability days.

[n]Demographic and risk factor profiles of the study participants, such as race, age, gender, ethnicity, disease evolution, and severity or presence of comorbidities.

[o]Including study participants' engagement level with the DTx.

[p]Medium- to long-term relative effectiveness of the DTx intervention, including its effect on preventing or delaying disease onset.

Health Care Resource Use

Health care resource use, which includes primary care, outpatient care, inpatient care, emergency department visits, and health support intervention, was the most frequently examined and reported cost across studies (18/18, 100%) [30-47]. Of the 18 studies, inpatient care–related costs were shown to have a potential impact on the economic impact of DTx in 15 (78%) studies [30-41,45-47]. Inpatient care was further categorized as a "decisive factor" (ie, having a significant impact on the economic impact of DTx [37]) in half (9/18, 50%) of the studies [30-35,37-39].

Pharmaceutical Treatment

The expenditures originating directly from treating medical conditions or disorders, such as those related to the consumption of drugs (eg, frequency and dose) or materials and aids, were considered in 67% (12/18) of the studies [31,32,36-40,42-46].

In some cases, DTx interventions have been shown to improve treatment adherence [34,35] and, as a result, might increase some expenses such as overall drug therapy costs or costs associated with higher rates of use of certain clinician services (eg, psychiatry services, outpatient visits, and pathology or drug testing). However, in many cases, these expenses were largely compensated by the cost savings in the included studies, especially in health care resource use [34,35]. For example, in

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a trial by McManus et al [46], participants who used DTx were more likely to have their antihypertensive drugs adjusted during the study (ie, dosage or change in drugs).

In other cases, the clinical benefits of DTx treatments may be able to reduce or eliminate the need for pharmacotherapies, thereby lowering total medical expenditures. However, Nordyke et al [38] and McManus et al [46] noted that despite evidence of DTx clinical efficacy, there may be a delay in deprescribing drugs from health care professionals—a phenomenon known as clinical inertia, which may reduce the potential economic benefits of DTx.

Participants' Baseline Characteristics

More than half (12/18, 67%) of the studies [30,33-40,43,46] pointed out that participants' baseline characteristics, such as age, gender, ethnicity, education level, baseline disease severity, risk factors, and costs, had an impact on the economic value of the intervention. Loohuis et al [40] conducted a subgroup analysis that revealed differences in DTx effects and costs not only by disease severity but also by recruitment type: participants recruited via social media incurred lower associated costs and experienced a lesser treatment effect than those recruited by a general practitioner.

Whaley et al [36] hypothesized that individuals with higher health care needs who accepted the program invitation generally had higher baseline levels of comorbidity and health care spending than those who did not enroll and therefore were more motivated to try a new intervention and more likely to voluntarily enroll in a digital intervention. Piera-Jiménez et al [47] also noted that the willingness of individuals to adopt an intervention strongly impacts the success of a DTx intervention.

Attrition Rate

More than half (10/18, 56%) of the studies [30,32-34,36,38,39,44-46] considered the potential causal effect of attrition rate, which can be a critical factor [44], on the DTx economic impact. Discrepancies in the manner in which such factors were evaluated should be noted. First, as highlighted by Lewkowicz et al [44], a DTx intervention's attrition rates in RCT-based EE might simply not be reported or may not "represent real-world engagement and program dropout rates." Second, some studies defined a minimum level of engagement for participants' data to be included for extraction and analysis; for example, in the study by Pelle et al [41], an RCT-based EE, 63 participants were excluded for suboptimal level of engagement. Finally, in claims-based EE, the impact of a DTx intervention was evaluated based on a patient population that, by definition, filled their prescription and engaged with the therapeutic, which might have led to bias in the selection of participants in the study (Multimedia Appendix 4). As Nomura et al [45] highlighted, "achieving good cost-effectiveness for DTx might require sensitive handling to balance the appropriate DTx app usage duration with DTx costs and expected attrition rate." The attrition rate may have also resulted in incomplete outcome data, a potential RoB in half of the RCT and nonrandomized study–based EE (Multimedia Appendices 2 and 3) [31-34,40,41].

Discussion

Main Findings

The EE of new therapies and clinical interventions is critical for market access and adoption because they provide decision makers with important information regarding their "value for money." This systematic review included 18 studies that evaluated the EE of clinical-grade, mobile app–based DTx. The relatively small number of included studies (which is consistent with other recent systematic reviews of digital health solutions [48]) attests to the paucity of published literature on DTx, which also explains the scarcity of evidence pertaining to the economic value of these intervention modalities [49].

All 18 included studies were conducted in high-income countries, with 12 supported by industry funding [30-39,45,46] and 6 by public organizations [40-44,47]. Although the prevalence of industry-funded research may potentially introduce commercial bias, which is acknowledged in this review, it also underscores the contributions of both public and private organizations in generating evidence for informed treatment decision-making when DTx options are available.

Heterogeneity Among Included Studies

The included studies exhibited significant heterogeneity with respect to DTx intervention, type of EE, and methodology (Table 1). This review combines EEs based on both clinical trial results and decision modeling to examine DTx applications for a spectrum of diseases across various settings and for different payers. Specifically, 4 studies [33-36] did not report the clinical outcomes of the intervention, only 10 reported an ICER [37,38,40-47], and only 7 reported cost and QALYs as the outcome measures [37,38,42-45,47]. As a result of this heterogeneity, a robust meta-analysis of these data was not feasible, making it impossible to provide numerical answers regarding the cost-effectiveness of DTx interventions. The study heterogeneity also hinders the comparability and generalizability of the findings and makes the EE results difficult to interpret.

In addition to this challenge, the context-specific nature of DTx interventions is evident in a multisite RCT conducted by Piera-Jiménez et al [47], who evaluated the economic impact of the same intervention implemented in 3 different countries: the Netherlands, Spain, and Taiwan. The study found that DTx led to QALY gains in the Netherlands but not in Spain or Taiwan, whereas cost savings were observed in Spain but not in the Netherlands or Taiwan.

Methodological Characteristics of the Included Studies

With a mean CHEC score of 71% (SD 17.9%) across all 18 studies, the methodological rigor across the included studies was of moderate quality, ranging from an average of 90% (SD 8.2%) for RCT-based EE to 77% (SD 11.7%) for model-based EE to 53% (SD 6.7%) for nonrandomized study–based EE. In particular, the evaluations based on nonrandomized studies, all of which were funded by industry, adopted a payer-only perspective, which may be too narrow to broadly inform implementation decisions because it excludes direct patient out-of-pocket costs, indirect costs such as productivity loss, and other factors that can impact the long-term utility of an

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intervention. Furthermore, none of the EE based on nonrandomized studies performed an incremental analysis of costs and outcomes of the alternatives to DTx (eg, standard therapy). Finally, only 29% (2/7) of nonrandomized study–based EE performed sensitivity analysis, which is the best practice for quantifying uncertainty and testing the robustness of a study's conclusions [50].

Another methodological deficit stems from the fact that although the majority of DTx interventions were reported to have significant impacts on costs and outcomes over a patient's lifetime, most studies used a short time horizon to capture all or most clinical and economic impacts of the respective intervention. Specifically, the average time horizon of the RCT-based EE was 10.8 months, whereas that of the nonrandomized study–based EE was 17.8 months. Only 2 studies [37,45] adopted a lifetime horizon, and only 6 studies [37-39,44,45,47] included modeling decisions to extrapolate the outcome measures over time. This incongruity between the claimed lasting impacts of DTx and the limited time horizons over which they were evaluated implies that DTx should be assessed over longer periods [41,44,46,47]. In turn, determining the long-term economic effects of DTx and advancing understanding as to where their adoption may add value requires more comprehensive modeling [51].

Modeling can also ensure that trial populations reflect patient groups treated in real-world clinical practice, which is an important consideration because this review identified various biases in participant recruitment. Such biases might result in imbalances in the relevant baseline characteristics between patient groups, which can also hinder health equity considerations. As a case in point, in 11 studies [30-33,35,36,41-43,46,47], participants were required to have internet access, a smartphone or a tablet, the skills necessary to use a PC, medical insurance, or employment to participate—requirements that may limit the participation of members of marginalized groups or groups considered socioeconomically disadvantaged. In contrast, only 3 studies [32,43,46] addressed the ethical and distributional issues inherent in the implementation of digital technologies.

Across studies using the same perspective, disparities in the costs taken into account were also noted (Table 2). The importance of the time and expertise required for patient education on using and managing DTx technology [52] was only considered in 2 studies [46,47]. Similarly, only 1 study [40] factored in the ongoing maintenance costs of the DTx. Highlighting the criticality of taking stock of all costs, Lewkowicz et al [44] applied a societal perspective and reported that their model accounted for 61% of costs related to conventional treatment for low back pain when only direct costs were considered and for 81% when indirect costs were included, using a publicly available cost-of-illness study as a benchmark. Future DTx EE will therefore benefit from a more transparent, systematic, and exhaustive consideration of all the costs that implementing DTx interventions entails, including long-term health care costs that may not be directly disease- or intervention-related as per the Professional Society for Health Economics and Outcomes Research recommendations [50].

Altogether, the studied DTx interventions were found to be cost-effective in 9 (90%) of the 10 studies that performed a full EE [37,38,40-46] and cost saving in the remaining 8 studies that performed a partial EE [30-36,39]. In 5 (28%) of the 18 studies [42-45,47], the DTx interventions presented a trade-off between costs and effects (ie, intervention being more effective and more costly than the comparators). However, in 3 (60%) of these 5 studies [42,43,45], the highest ICERs obtained through sensitivity analysis fell below the willingness-to-pay threshold established in the countries in which they were performed, providing reassurance about their potential economic benefits.

The findings from this review indicate that DTx, at least in some use cases and local contexts, can be cost-effective and offer economic value to payers while simultaneously improving care for patients. However, consistent with the existing literature [49,51], qualitative deficits in methodology and significant potential biases in EE should be addressed going forward.

This review emphasizes the importance of adhering to established best practices and developing a robust, consistent methodological framework that incorporates the unique features that distinguish DTx interventions from conventional therapies or the current standard of care [49]. In the future, DTx EE analysis will need to adhere to local and international guidelines, use generalizable tools and metrics for enhanced comparability of the findings, and be both long-term focused and all-inclusive when factoring in value and cost. Such efforts are crucial for minimizing providers', payers', and patients' uncertainties surrounding the adoption of DTx interventions.

Limitations

Although we aimed to provide a comprehensive and systematic review of the economic value of clinical-grade mobile app–based DTx, there are several limitations to be acknowledged. First, only studies written in English were included. These studies were identified using a finite list of specific search terms; however, widely varying terminologies exist in the literature with reference to DTx, such as medical apps, digital therapies, or simply digital health technologies. As a result, it is possible that not all relevant studies assessing the economic impact of DTx may have been identified. Second, DTx interventions can be delivered through different modalities, including, but not limited to, virtual reality devices, mobile apps, web-based platforms, or a combination of these. To draw robust conclusions about mobile DTx as an emerging category of technologies in the clinical arena, this review focused exclusively on mobile app–based DTx and excluded multimodal DTx or those not primarily using a mobile app as the core delivery mechanism.

Conclusions

This systematic review synthesizes the available evidence on the potential economic benefits of clinical-grade mobile app–based DTx as well as some of the qualitative deficits in DTx EE methodology, which can be used to guide future research on the subject. Specific areas that can benefit from more research and would further support market access decision-making and the adoption of DTx include evaluating

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DTx interventions in more diverse populations, across a greater variety of local contexts, and over longer time horizons.

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Authors' Contributions

YS, AR, and LMC conceptualized the study. YS and XT conducted the literature searches, literature screening, study analysis, and data collection. CTAB performed the quality assessment and risk-of-bias appraisal. YS, XT, and CTAB completed the data synthesis with input from the contributors and drafted the manuscript. AR, FK, LMC, GT, AB, CLH, JY, and DH contributed to refining all sections and critically editing the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of Interest

GT is an employee of Cytel Canada Health Inc, Canada. FK is an employee of IU Internationale Hochschule GmbH, Germany, and Flying Health GmbH, Germany. CLH is an employee of Pureland Global Venture Pte Ltd, Singapore. AB and DH are coinventors of previously filed pending patents on artificial intelligence–based therapy development. YS, XT, CTAB, AR, LMC, and JY have no conflicts of interest.

Multimedia Appendix 1

Consensus Health Economic Criteria quality assessment.
[PNG File , 1567 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Risk of bias for randomized clinical trial–based economic evaluations.
[PNG File , 157 KB-Multimedia Appendix 2]

Multimedia Appendix 3

Risk of bias for nonrandomized studies–based economic evaluations.
[PNG File , 168 KB-Multimedia Appendix 3]

Multimedia Appendix 4

Risk of bias for model-based economic evaluations.
[PNG File , 111 KB-Multimedia Appendix 4]

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Abbreviations

CEA: cost-effectiveness analysis
CHEC: Consensus Health Economic Criteria
CUA: cost-utility analysis
DTx: digital therapeutics
EE: economic evaluation
ICER: incremental cost-effectiveness ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY: quality-adjusted life year
RCT: randomized controlled trial
RoB: risk of bias

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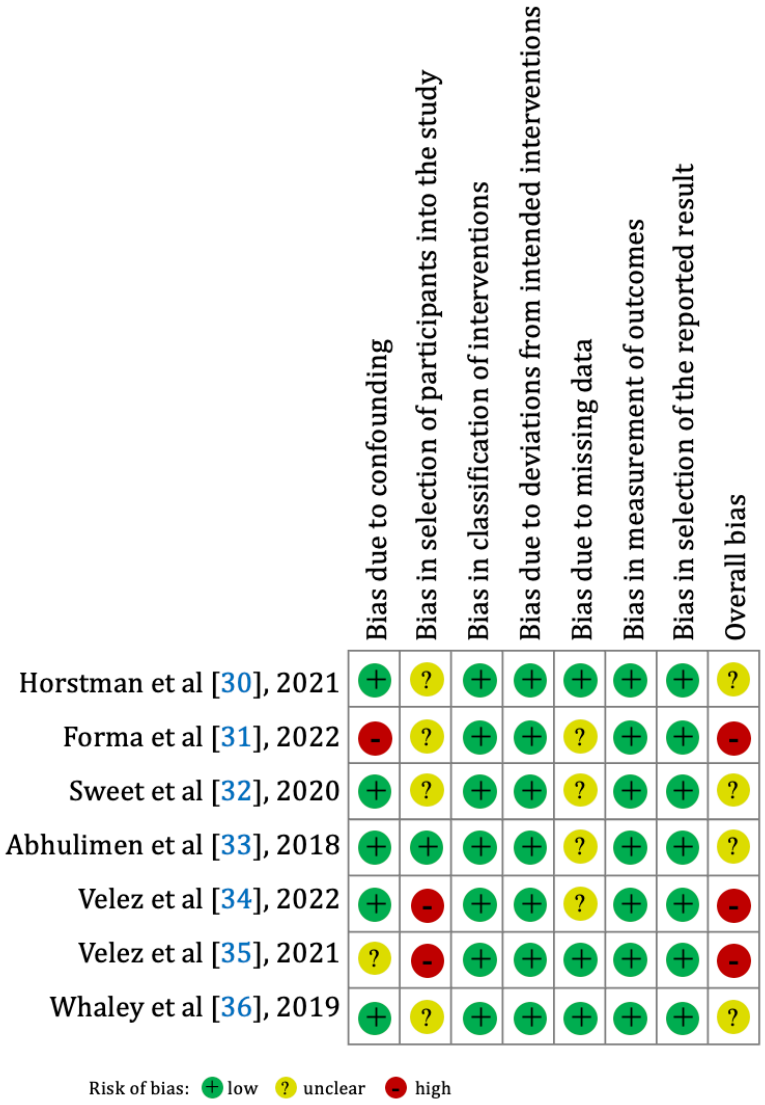
Appendix 1D. Consensus health economic criteria quality assessment

	RCT-based EE					Non-randomized studies-based EE							Model-based EE					
	Ekersund et al, 2022	Pelle et al, 2022	McManus et al, 2021	Sjöström et al, 2017	Loohuis et al, 2022	Horstman et al, 2021	Forma et al, 2022	Sweet et al, 2020	Abhulimen et al, 2018	Velez et al, 2022	Velez et al, 2021	Whaley et al, 2019	Piera-Jiménez et al, 2020	Lewkowicz et al, 2022	Nomura et al, 2022	Kumar et al, 2018	Nordyke et al, 2019	Chen et al, 2016
Is the study population clearly described?	1	1	1	1	1	1	1	1	0.5	1	0.5	1	1	1	1	0.5	1	1
Are competing alternatives clearly described?	1	1	1	1	1	0	0	1	0	1	0	0	0	1	1	0	0	0
Is a well-defined research question posed in answerable form?	0.5	1	1	1	0.5	0.5	0.5	0.5	0.5	1	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Is the economic study design appropriate to the stated objective?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Is the chosen time horizon appropriate to include relevant costs and consequences?	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
Is the actual perspective chosen appropriate?	1	0	1	1	1	0	0	0	0	0	0	0	1	1	1	1	0	0
Are all important and relevant costs for each alternative identified?	1	1	1	1	1	0.5	0	0	0	0	0	0.5	1	1	1	1	0	1
Are all costs measured appropriately in physical units?	1	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	0	1
Are costs valued appropriately?	1	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	0	1
Are all important and relevant outcomes for each alternative identified?	1	1	1	1	1	1	1	1	0.5	1	1	1	1	1	1	1	1	1
Are all outcomes measured appropriately?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are outcomes valued appropriately?	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1
Is an incremental analysis of costs and outcomes of alternatives performed?	1	1	1	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0
Are all future costs and outcomes discounted appropriately?	1	1	1	1	1	0	0	0	1	0	1	0	1	1	1	1	1	1
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	1	1	1	1	1	0	0	0	1	1	0	0	0	1	1	1	1	1
Do the conclusions follow from the data reported?	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1
Does the study discuss the generalizability of the results to other settings and patient/client groups?	1	0	1	0.5	0	0.5	0	0	0.5	1	0	0.5	0	0	1	1	0	1
Does the article indicate potential conflicts of interest of study researcher(s) and funder(s)?	1	0.5	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are ethical and distributional issues discussed appropriately?	0	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0
TOTAL SCORE	**92%**	**76%**	**100%**	**95%**	**87%**	**55%**	**39%**	**55%**	**53%**	**63%**	**50%**	**55%**	**76%**	**87%**	**92%**	**74%**	**55%**	**76%**

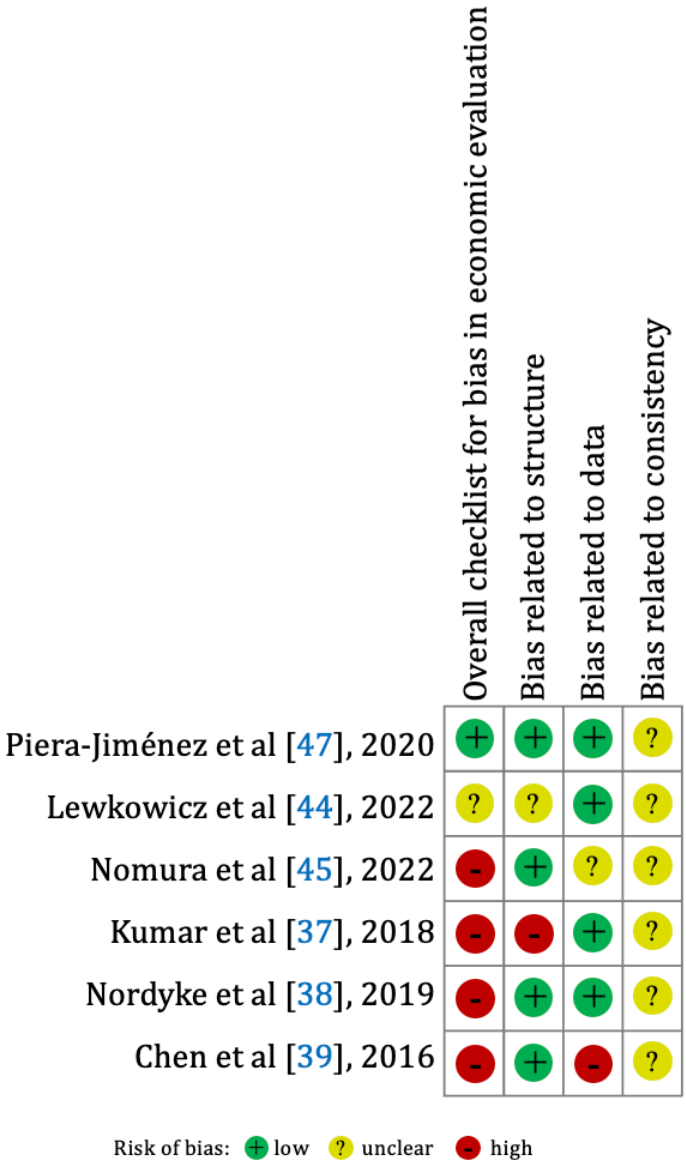
Answers to the questions: no partially yes

Appendix 1E. Risk of bias for randomized clinical trial–based economic evaluations

Appendix 1F. Risk of bias for nonrandomized studies–based economic evaluations



Appendix 1G. Risk of bias for model-based economic evaluations



PAPER 2 APPENDICES

Appendix 2A. Preprint published in Preprints with The Lancet

Stakeholder Perspectives on Factors Influencing the Economic Value of Digital Therapeutics: A Group Concept Mapping Approach

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Abstract

Background
Digital therapeutics (DTx), software as a medical device, present a promising avenue for addressing the increasing burden of a range of conditions. In a context of budgetary constraints and an enduring need for optimal resource allocation, their implementation and adoption are contingent upon their capacity to provide economic value, which remains a research gap.

Methods
Group concept mapping, a participatory and mixed method was used to delve into a comprehensive identification and understanding of the factors that are conceptualized and perceived to impact the economic value of DTx. It involved semi-structured interviews, group discussions and web-based tasks with healthcare professionals, researchers, industry and public sector representatives. Participants sorted factors by similarity (n=37), rated their importance in generating economic value and consideration in practice (n=62). Multivariate methods included nonmetric multidimensional scaling analysis and agglomerative hierarchical cluster analysis to estimate conceptual data into visual representations.

Findings
59 factors influencing the economic value of DTx were identified and grouped into eight clusters. There was broad agreement among stakeholders on the significance of the *DTx Impact on Patient Outcomes* and *DTx Implementation* as the most influential clusters affecting the economic value of DTx. The *DTx Associated Costs* and *DTx Monetization Models* clusters were reported as not receiving potentially sufficient consideration throughout the DTx development lifecycle, particularly among researchers. Consequently, a conceptual framework of priority clusters and factors potentially driving DTx economic value is proposed.

Interpretation
The results illustrate how stakeholders conceptualize, perceive, and consider factors impacting DTx economic value throughout its lifecycle. They reveal the complex interplay of multiple stakeholders and factors influencing DTx economic value, highlighting areas requiring prioritization at each stage.

Funding
None.

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Introduction

An aging population, burdened by increasing chronic and mental health conditions among others, coupled with a surge in the utilization of healthcare resources, highlights the imperative to enhance the effectiveness and efficiency of healthcare systems. All these factors have accelerated the emergence of digital therapeutics (DTx) as a new class of medical treatment. DTx are health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has a demonstrable positive therapeutic impact on a patient's health.[1,2] While these software as a medical devices are set to significantly improve the delivery of healthcare, stakeholders such as healthcare providers as well as public and private payer organizations are yet to fully embrace and realize the potential of DTx. They require a large body of evidence that demonstrates the clinical benefits and value of these solutions, including their impact on patients, such as improvements in quality of life, as well as their effect on the burden of disease and ethical and equity considerations.[3,4] Health economic data, along with considerations regarding software interoperability, data security, and privacy, are also critical factors that come into play.[5–7]

Given the context of budgetary constraints and the ongoing need for optimal resource allocation, health economic data are crucial for payment, reimbursement and adoption decisions[8], if sufficient clinical benefits and value are demonstrated. These data determine the cost-effectiveness of a DTx compared to standard treatments or alternatives, providing decision-makers with important information regarding their "value for money."[9]

Research in context

Evidence before this study

Research on the economic value of DTx remains limited. Scholars have noted a significant knowledge gap regarding DTx capacity to provide economic value, while also emphasizing the complexity of defining and assessing its value. A 2023 systematic review of clinical-grade mobile app-based DTx further underscored the challenges in reaching definitive conclusions about their economic benefits. These findings collectively highlight a critical need for more robust evidence to support market access decision-making and DTx adoption.

Added value of this study

This research contributes to the field in three ways. First, it provides a collective stakeholder approach to identify factors influencing DTx economic value. The research identified 59 such factors, aligning with the emerging literature in this field.[5–7,9–14] Second, this study provides a better understanding of the collective conceptualization of factors influencing the economic value of DTx by stakeholders involved in their development, validation, and implementation. Third, the analysis of the stakeholders' perceived relative importance and relative extent of consideration of these factors led to the development of a participatory conceptual framework of priority areas. This framework presents an interrelated and coherent set of priority clusters of potential factors driving DTx economic value.

Implications of all the available evidence

The study examines the interrelationships among factors grouped as clusters driving DTx economic value from a collective stakeholder perspective, including stakeholders such as healthcare professionals, researchers, industry, and public sector representatives. By mapping these connections, it helps gain insight into the intricate ecosystem of factors influencing the economic value of DTx. The proposed

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conceptual framework of priority factors grouped by clusters also aims to guide stakeholders in comprehensively assessing relevant factors, ensuring a methodical approach to decision-making.

This study employs a collective conceptualization stakeholder to examine factors perceived to influence the economic value of DTx, and how such factors are conceptualized by stakeholders involved in DTx from development to implementation, while also investigating how they are perceived and considered throughout the DTx lifecycle by the same stakeholders. Building on this analysis, this study aims to develop an evidence-based conceptual framework of priority areas. This framework supports a comprehensive roadmap for stakeholders, outlining considerations throughout the technology lifecycle that can ultimately influence a DTx ability to generate economic value.

Methods

To meet the objective, group concept mapping (GCM) is used to delve into potential convergences and divergences in stakeholders' perspectives and considerations on factors influencing the economic value of DTx. This mixed methods-based approach provides a structured way to synthesize complex, multifaceted concepts and associated perceptions into a coherent analytical framework.[15] The choice was motivated by GCM participatory nature and its ability to combine diverse perspectives from a broad group of participants. Napier-Raman et al. describe CGM as "particularly useful when examining complex, multifaceted issues, particularly those in public health".[16]

Initially introduced by Trochim[17], GCM engages a diverse group of stakeholders as participants in collaborative efforts to generate, structure and visualize conceptual information. It facilitates the conceptualization of abstract constructs, delving into complex social phenomena, examine relationships among factors, and compare perspectives and priorities across different participant groups.[18,19] The GCM research design transforms abstract conceptual data into visual representations or maps[16], and leads to the creation of a collective conceptual framework for comprehending a specific topic of interest.[15,17]

The GCM approach comprises five phases[17]: (1) identifying relevant stakeholders and developing the focus prompt, (2) generating factors that may impact the economic value of the DTx, (3) structuring factors through sorting and rating, (4) analyzing data and creating the visual representations, and (5) interpreting and utilizing the results.

Participants were recruited through purposive sampling and included: (1) Healthcare professionals involved in care delivery and experienced with digital health solutions, (2) Industry stakeholders often leading the commercialization efforts of DTx interventions, (3) Public stakeholders responsible for DTx-related policy and regulatory aspects, and (4) Researchers early engaged in the DTx lifecycle, that is, in the development of these technologies.

Through the GCM process, 223 potential factors[1] influencing the economic value of DTx were identified. Thematic-conceptual coding[20] was conducted to analyze the factors identified, and a list of 59 factors was established (supplementary table S2). Participants (n=37) were asked to sort the factors into virtual piles

[1] In GCM, the term "statement" is used to refer to ideas obtained from the literature, during interviews, and group discussions to denote formalized specific ideas to be included in the list for sorting and rating (phase 2). For consistency with participant terminology and to reflect the conceptual nature of these elements, this paper adopts the term "factor" at sorting and rating (phase 3) throughout, encompassing the various aspects both identified and evaluated by the participants during the GCM process.

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based on their perceived similarity in meaning. Second, participants who took part in factor sorting, along as additional ones (n=62), were tasked to rate the factors on two distinct 5-point Likert-type scales:

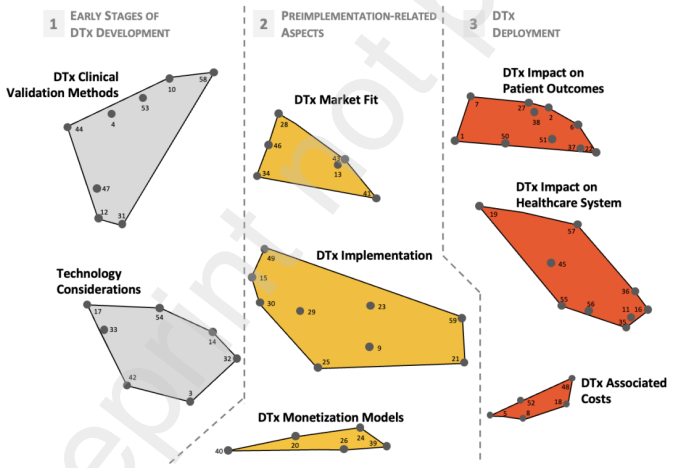
1. Importance scale: Participants rated the importance of each factor for a DTx to generate economic value based on their experience. The scale ranged from 1 (not important) to 5 (very important).
2. Extent of consideration scale: Participants assessed the extent to which each factor is considered in their field or practice regarding DTx development, clinical validation, or implementation. This scale ranged from 1 (not considered) to 5 (very considered).

Nonmetric multidimensional scaling (NMDS)[21] and agglomerative hierarchical cluster analysis (AHCA), using Ward's algorithm[22], were used to produce the conceptual model (figure 1). DTx experts (n=5) were also involved in the interpretation and external validity evaluation of the concept map and perception estimates. A detailed overview of the GCM process, analyses conducted, internal reliability indicators, and profiles of participants are provided in supplementary text S1 and figure S1.

Results

The cluster map, showcasing eight clusters, serves as a visual representation of the factors that participants have grouped together (figure 1). A dot on the map represents a single factor. The distance between the dots reflects how often participants sorted these factors into the same piles. These clusters delineate distinct themes spanning the entire DTx lifecycle, from inception to widespread deployment, with 59 factors conceptualized to influence the DTx ability to deliver economic value.

Figure 1. Cluster point map of all 59 factors perceived to influence the economic value of DTx, grouped into eight-cluster map (n=37).



The mapping of 59 factors into eight clusters reveals three main themes along a horizontal axis in the MDS map, representing a time axis that follows the traditional DTx development cycle from conception to deployment. These themes are:

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1. EARLY STAGES OF DTX DEVELOPMENT: This theme encompasses clusters of factors more pertinent to the initial phases of DTx development and clinical validation, leading toward approvals and/or market authorization by a regulatory body;
2. PREIMPLEMENTATION-RELATED ASPECTS: This theme includes clusters associated with various considerations and preparations necessary before the actual implementation of a DTx intervention; and
3. DTX DEPLOYMENT: The final theme consists of clusters containing factors pertinent to the implementation and ongoing management of DTx in a real-world environment.

Supplementary text S2 and table S2 present all 59 identified factors forming these eight clusters' contents, along with the standard deviation for each cluster and the average bridging index (ABI) for each factor, as well as for each cluster. The ABI for a cluster is the average of all the ABIs for individual factors for a cluster. Lower ABIs represent a more homogeneous cluster, while higher ABIs indicate a more heterogeneous cluster, comprising relatively diverse factors. A review of the cluster map reveals that the *Technology Considerations* cluster stands out as the sole bridging cluster, suggesting that its factors were more frequently situated in multiple clusters when sorted by participants. By contrast, all remaining clusters are non-bridging (bridging value <0·5), indicating fewer links to surrounding clusters, with factors predominantly sorted together by participants. The implication of this is the clarity in conceptualization that supports the research process.

The comparison of importance and extent of consideration ratings reveals a notable pattern (supplementary table S2). Seven out of eight clusters show higher mean ratings for importance than for extent of consideration. This suggests these clusters may be underconsidered in fields of practice relative to their perceived importance in influencing the overall DTx economic value. The sole exception is the *DTx Market Fit* cluster, where the importance rating (3·72 / 5·00) closely aligns with its extent of consideration rating (3·74 / 5·00).

In what follows, cluster results for each rating are examined, and then compared to draw broader insights. The mean ratings for importance provided by the participants for each factor and by cluster are presented in figure 2. Standard deviations (SD) are computed for each cluster to assess the degree of convergence or divergence among stakeholder responses, with a mean value of 0·13.

Figure 2. Perceived importance of the clusters of factors perceived to influence the economic value of DTx among stakeholder groups (n=62).

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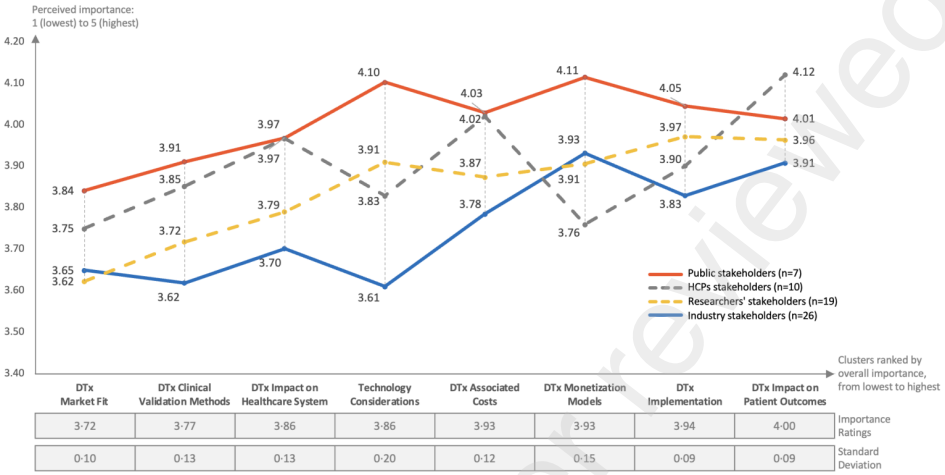

DTx Market Fit	DTx Clinical Validation Methods	DTx Impact on Healthcare System	Technology Considerations	DTx Associated Costs	DTx Monetization Models	DTx Implementation	DTx Impact on Patient Outcomes	
3·72	3·77	3·86	3·86	3·93	3·93	3·94	4·00	Importance Ratings
0·10	0·13	0·13	0·20	0·12	0·15	0·09	0·09	Standard Deviation

The two clusters of factors impacting the economic value of DTx, reported as the most important by stakeholders, are the *DTx Impact on Patient Outcomes* (rated at 4·00 / 5·00) and *DTx Implementation* (rated at 3·94 / 5·00). The SD values, of 0·09 for both clusters, indicate a narrow rating, thus a strong agreement among stakeholders.

Following closely are the *DTx Monetization Model* (rated 3·93 / 5·00) and *DTx Associated Costs* (rated 3·93 / 5·00), ranking as the third most important clusters. The *DTx Market Fit* cluster was consistently ranked lower than any other cluster by all stakeholder groups, except for Industry stakeholders, who rated it as the third lowest.

The convergence and divergence in perception among stakeholder groups merit attention. Public stakeholders consistently assigned higher importance ratings across clusters, with a mean rating of 4·00 / 5·00, compared to HCPs (with a mean rating of 3·90 / 5·00), Researchers (mean rating of 3·84 / 5·00), and Industry stakeholders (mean rating of 3·75 / 5·00). The most significant convergence of perspective is toward the importance of the *DTx Impact on Patient Outcomes*, with a SD of 0·09. However, while the *DTx Impact on Patient Outcomes* emerges as the most important cluster of factors for HCP stakeholders —an outcome most likely aligned with expectations— it ranks only fifth in importance for Public stakeholders.

The most notable divergence of perspective relates to the *Technology Considerations* influencing a DTx ability to deliver economic value, with a SD of 0·20. This cluster ranked as the second most important for Public stakeholders (with a mean rating of 4·10 / 5·00), contrasting sharply with Industry stakeholders who rated it as the least important (with a mean rating of 3·61 / 5·00). The interpretation of these convergences and divergences in perception among stakeholder groups is further examined in the discussion section.

In addition to evaluating the relative importance of clusters influencing the economic value of DTx, stakeholders were asked to rate the extent to which each factor was considered into their respective field

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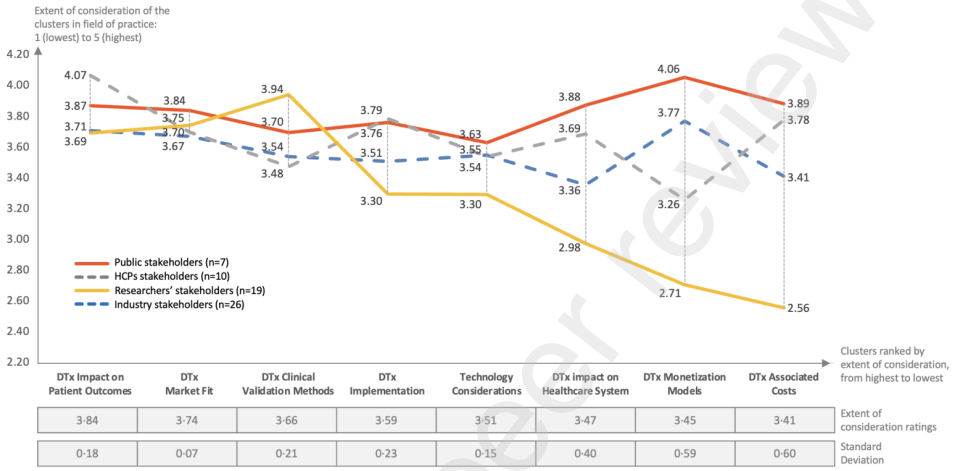
of practice (figure 3). This includes aspects like day-to-day decision-making and prioritization within their roles. The mean SD for extent of consideration across clusters is 0·30.

Figure 3. Extent of consideration of the clusters of factors perceived to influence the economic value of DTx among stakeholder groups (n=62).



Among all stakeholders, figure 3 reveals that *DTx Associated Costs* is the least considered cluster of factors (rated at 3·41 / 5·00), followed by *DTx Monetization Models* (rated 3·45 / 5·00), despite both being reported as the third most important clusters (figure 2) – results partially driven by the ratings of the group of Researchers (table 1). A strong consensus exists among stakeholders in considering *DTx Impact on Patient Outcomes* perceived as the most considered cluster (rated at 3·84 / 5·00). Once again, Public stakeholders consistently assigned higher consideration ratings across clusters with a mean rating of 3·83 / 5·00.

Table 1 compares how Researchers and other stakeholder groups reported the perception of the different clusters in their professional practice. Researchers prioritize factors related to the EARLY STAGES OF DTX DEVELOPMENT (rated 3·62 / 5·00), PREIMPLEMENTATION-RELATED ASPECTS (3·25 / 5·00), and DTX DEPLOYMENT (3·08/5·00). This aligns with Researchers' typical involvement in the early stages of the DTx lifecycle. The *DTx Associated Costs* cluster reveals a significant perception gap between Researchers and other participants. Researchers rated it considerably lower (2·56 / 5·00), while other participants gave it a higher score (3·69 / 5·00). This disparity underscores the divergent views among stakeholder groups on how factors affecting DTx economic value are considered. Notably, this cluster also shows the highest SD (0·60) across both importance and extent of consideration ratings and clusters.

Table 1. Comparison of extent of consideration ratings: Researchers vs. other stakeholder groups by cluster.

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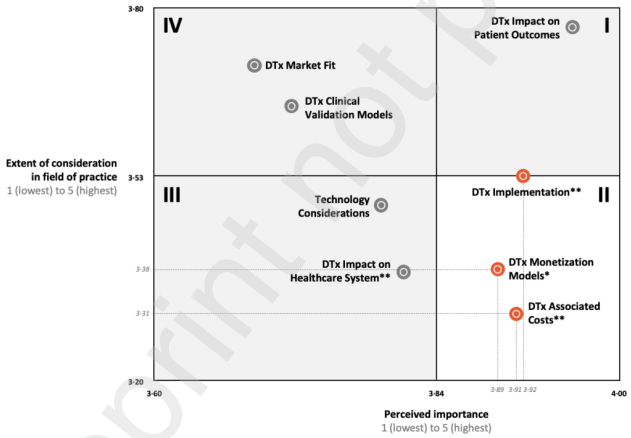
	Mean extent of consideration rating, excluding Researchers (n=43)	Mean extent of consideration rating for Researchers (n=19)	Significance
Theme 1: EARLY STAGES OF DTX DEVELOPMENT	**3·57**	**3·62**	
Technology Considerations	3·58	3.30	p > 0·05
DTx Clinical Validation Methods	3·57	3·94	p > 0·05
Theme 2: PREIMPLEMENTATION-RELATED ASPECTS	**3·71**	**3·25**	
DTx Market Fit	3·74	3·75	p > 0·05
DTx Implementation	3·69	3·30	P < 0·05
DTx Monetization Models	3·70	2·71	p < 0·005
Theme 3: DTX DEPLOYMENT	**3·74**	**3·08**	
DTx Impact on Patient Outcomes	3·88	3·69	p > 0·05
DTx Impact on Healthcare System	3·64	2·98	p < 0·005
DTx Associated Costs	3·69	2·56	p < 0·001

To further explore these results, both the ratings of importance and extent of consideration were compared not in isolation, but rather in conjunction. It led to the plotting of clusters based on stakeholders' mean ratings, resulting in an aggregate scattered bivariate plot by cluster, referred to as a go-zone graph GCM methodology (figures 4 and 5). These graphs are divided into quadrants, above and below the mean value of each factor ratings. Thus, it facilitates the overall identification of priority clusters.

Figure 4. Bivariate go-zone plot of aggregate means by cluster as perceived by stakeholders of the importance and extent of consideration in the field of practice (n=62).



**p-value<0·05; **p-value<0·005. The nonparametric Wilcoxon Rank-order test for matched pairs indicates a statistical difference (p-value < 0·05) between the relative importance and relative extent of consideration rank orderings.*

Priority quadrants are delineated based on whether clusters fall above or below the mean ratings for importance (3·84 / 5·00) and extent of consideration (3·53 / 5·00). These quadrants are defined as follows:

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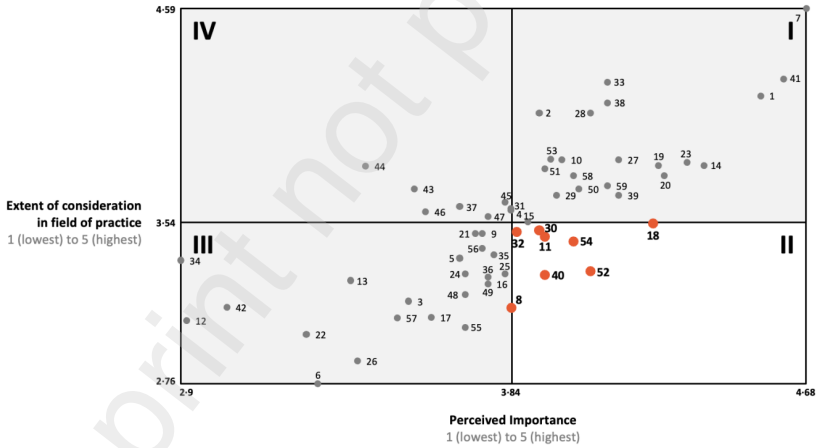
(1) Quadrant I encompasses clusters of factors perceived as important for a DTx to generate economic value and highly considered by participants in their field of practice throughout the DTx development lifecycle, (2) Quadrant II includes clusters with high importance but low consideration, (3) Quadrant III contains clusters with both low importance and low consideration, and (4) Quadrant IV comprises clusters with low importance but high consideration. This framework allows for a nuanced analysis of how various clusters of factors are perceived and prioritized in the context of DTx economic value.

The Quadrant II encompasses clusters perceived as highly important in influencing DTx economic value, yet insufficiently considered in participants' daily decision-making processes, thus indicating a potential gap. Three clusters fall within this priority quadrant: *DTx Implementation*, *DTx Monetization Models*, and *DTx Associated Costs*. These clusters are recognized by all stakeholder groups for their critical role in a DTx ability to generate economic value, as evidenced by a low mean SD rating of 0·12 across these three clusters. However, they are simultaneously acknowledged, particularly by Researchers, as potentially receiving inadequate consideration throughout the DTx development lifecycle. This discrepancy underscores a potential area of consideration for the respective stakeholders involved in DTx development and implementation strategies.

With a p-value < 0·05, the difference between the two overall scale rankings for these clusters is statistically different as reported by the nonparametric Wilcoxon rank-order test. Nevertheless, these findings should be interpreted within the context of each stakeholder group.

Figure 5. Bivariate go-zone plot of individual factors influencing the economic value of DTx perceived importance and extent of considerations in the field of practice (n=62).



An analysis of the go-zone graph at the factor level reveals eight factors (factors 8, 11, 18, 30, 32, 40, 52 and 54) positioned in Quadrant II, the priority quadrant (figure 5). These eight factors emerged as crucial for a DTx to generate economic value, with their mean importance ratings surpassing the overall mean across all 59 factors studied. Paradoxically, these same eight factors were reported as less considered by the

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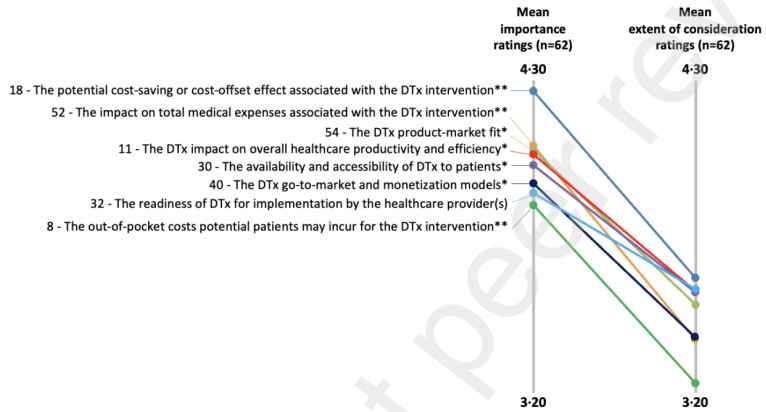
participants compared to the other factors, with their mean extent of consideration ratings falling below the overall mean.

Figure 6 illustrates the relationship between the mean rating scores for both scales. These pattern matches are valuable for detecting high-level patterns and offer a visual comparison of how stakeholders rated various factors. The descending diagonal lines indicate that each factor's importance rating is higher than its extent of consideration rating, confirming a potential lack of consideration of these factors despite their perceived importance in driving DTx economic value.

Figure 6. Pattern match of the relationship between stakeholders mean ratings: importance and extent of consideration (n=62).



**p-value<0·005; **p-value<0·001. The nonparametric Wilcoxon Rank-order test for matched pairs indicates a statistical difference (p-value < 0·01) between the relative importance and relative extent of consideration rank orderings.*

These eight priority factors (figures 5 and 6) span over five of the eight total clusters. This distribution suggests that, according to participants, no single factor or cluster should be prioritized in isolation. Instead, multiple factors across the entire DTx lifecycle may require consideration or prioritization by the relevant stakeholders at each stage.

Discussion

The study revealed both anticipated and unexpected insights, contributing to a more nuanced understanding of how different stakeholder groups influence a DTx's ability to generate economic value. Two observations merit particular attention.

The improvement of patients' clinical outcomes emerged as a primary concern across all stakeholder groups (figure 2). However, despite this broad consensus, this cluster ranked only fourth in importance for Public Stakeholders. This discrepancy may be attributed to the heterogeneous composition of this stakeholder category, encompassing individuals with diverse backgrounds in technology, clinical practice, and payer systems. Also, the complexity of decision-making regarding coverage, payment and reimbursement has intensified, with priority setting and resource allocation posing significant challenges.

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Public stakeholders are tasked with evaluating not only the clinical and financial impact of individual DTx interventions but also their broader implications for healthcare systems and populations. This evaluation must be conducted in the context of competing alternative treatments and interventions, all vying for limited funding and coverage. Therefore, while the clinical impact of these interventions is crucial, it is not the sole determining factor for final decision.

A second observation relates to Researchers appearing to give less consideration to some factors as compared to other stakeholders groups. This is particularly evident for factors within the *DTx Associated Costs*, *DTx Monetization Models*, and *DTx Healthcare System Impact* clusters, despite Researchers acknowledging the importance of these factors. This divergence potentially reflects the heterogeneous composition of this stakeholder category, as well as Researchers' primary involvement in early stages of DTx development, such as conducting research, knowledge generation, and initial clinical validation. Their priorities or mandates may differ, as they are typically not tasked with examining costs during these initial stages of technology development and clinical validation. However, failing to consider these costs impact early on could negatively impact payment, reimbursement and adoption decisions.[8] This finding underscores the critical role that all stakeholders, including researchers, play in ensuring DTx demonstrate economic value to potential payers. As innovations from research institutions often struggle to achieve commercial success[23], there exists a significant opportunity to enhance the commercialization of innovative research. A promising starting point could be fostering collaboration among major DTx stakeholder groups, such as through public-private partnerships. These collaborations should aim to integrate commercialization expertise earlier in the DTx lifecycle, ensuring that market viability is considered from the outset of development. By bridging the gap between academic research and commercial application, stakeholders can work together to overcome the challenges that currently hinder the successful translation of DTx innovations into commercially viable products.

The mixed-method approach, which involved semi-structured interviews and a group discussion with subject matter experts throughout the GCM research steps, particularly for data interpretation, contributed to confirming the external validity of the generated data and results. The external validity of the results is also reinforced by the variety of stakeholders and the wide range of settings involved. The results presented are context-specific, and it is crucial to consider context-specific external validity issues when interpreting them.

The study's sample size (n=62) and participant composition provide valuable insights within the context of the research. While the findings offer a robust and reliable foundation for understanding DTx value generation, certain limitations should be acknowledged. Building on the study's findings, future research could extend this methodology to explore factors perceived as important by specific subgroups of stakeholders, such as healthcare providers, or new groups like patients. Such investigations could be conducted across various contexts and countries to gain a more comprehensive understanding of the decision-making processes within each stakeholder group. Additionally, exploring the relationship between these perceived factors and actual economic outcomes would provide valuable insights into the real-world impact of DTx interventions.

As the field of DTx continues to evolve, ongoing research will be crucial in refining our understanding of the factors influencing economic value and adoption. By building on the insights gained from this study and expanding the scope of investigation, future research can contribute significantly to the advancement and integration of DTx in healthcare systems. This continued exploration could ultimately help inform the development of more effective, economically viable DTx interventions, benefiting both patients and healthcare systems alike.

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Contributions
YS and LMC conceptualized the study, conducted the data analysis and drafted the manuscript. YS, LMC, GT, AB, FK, DL, XT, and DH contributed to refining all sections and critically editing the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of Interest
YS, XT and DH have filed a provisional patent on data-driven behavior change. DH is coinventor of previously filed pending patents on artificial intelligence–based therapy development. GT is an employee of Cytel Canada Health Inc, Canada. AB is the founder of HAS4P, Health Access Solutions, United Arab Emirates. FK is an employee of IU Internationale Hochschule GmbH, Germany, and Flying Health GmbH, Germany. DL is an employee of PricewaterhouseCoopers Luxembourg. LMC has no conflict of interest.

Data Availability
All data generated or analysed during this study are available from the corresponding author on reasonable request.

Code Availability
No code was used in this study.

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Appendix 2B. Article published in npj Digital Medicine

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Article

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A group concept mapping study of stakeholder perspectives on digital therapeutics economic value drivers

Check for updates

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Digital therapeutics (DTx), software as a medical device, present a promising avenue for addressing the increasing burden of a range of conditions, yet their widespread implementation remains contingent upon demonstrating economic value—an understudied domain in current literature. Using a Group Concept Mapping approach, this study synthesized perspectives from healthcare professionals, researchers, industry, and public sector representatives to understand factors perceived to influence DTx economic value throughout its lifecycle. Analysis revealed 59 factors organized into eight clusters. Stakeholders consistently identified *DTx Impact on Patient Outcomes* and *DTx Implementation* as the most influential clusters affecting economic value. However, *DTx Associated Costs* and *DTx Monetization Models* clusters were reported as not receiving sufficient consideration throughout the DTx development lifecycle, particularly among researchers. Consequently, a conceptual framework of priority clusters and factors driving DTx economic value is proposed.

An aging population, burdened by increasing chronic and mental health conditions among others, coupled with a surge in the utilization of healthcare resources, highlights the imperative to enhance the effectiveness and efficiency of healthcare systems. All these factors have accelerated the emergence of digital therapeutics (DTx) as a new class of medical treatment. DTx are health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has a demonstrable positive therapeutic impact on a patient's health[1,2]. While these software as a medical devices are set to significantly improve the delivery of healthcare, stakeholders such as healthcare providers as well as public and private payer organizations are yet to fully embrace and realize the potential of DTx. They require a large body of evidence that demonstrates the clinical benefits and value of these solutions, including their impact on patients, such as improvements in quality of life, as well as their effect on the burden of disease and ethical and equity considerations[3,4]. Health economic data, along with considerations regarding software interoperability, data security, and privacy, are also critical factors that come into play[5–7].

Given the context of budgetary constraints and the ongoing need for optimal resource allocation, health economic data are crucial for payment, reimbursement and adoption decisions[8], if sufficient clinical benefits and value are demonstrated. These data determine the cost-effectiveness of a DTx compared to standard treatments or alternatives, providing decision-makers with important information regarding their "value for money."[9]

However, research on the economic value of DTx remains limited. In 2021, Kario et al.[8] noted that little is known about DTx capacity to provide economic value, while Gomes et al.[9] emphasized the complexity of defining and assessing this value. A 2023 systematic review of clinical-grade mobile app-based DTx further underscored the challenges in reaching definitive conclusions about their economic benefits, largely due to heterogeneous study methods and data collection processes[6]. These findings highlight a critical need for more robust evidence to support market access decision-making and DTx adoption[5,7].

It is also crucial to recognize that the development, clinical validation, and implementation of DTx involve numerous stakeholders, including researchers, software developers, engineers, clinicians, care providers,

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patients, regulatory agencies, and payers, among others. Each stakeholder decisions—from designing user interfaces to prioritizing specific features—are interrelated and influence the potential clinical value and economic benefits of DTx for the healthcare system, providers, and patients.

Given that economic impacts are crucial in supporting health budget allocation, reimbursement decisions, and the eventual mass adoption and use of DTx, a significant research gap exists. There is a pressing need to address the following research question: How do diverse stakeholders involved throughout the DTx lifecycle collectively conceptualize and perceive the prioritization of factors influencing DTx economic value? It is essential to comprehend how various stakeholders contribute to and shape DTx economic value generation, while also providing a deeper understanding of the complex decision-making processes that impact DTx economic outcomes throughout its lifecycle.

To address the identified research gap, this study employs a collective conceptualization stakeholder approach to examine factors which influence the economic value of DTx. It aims to explore how these factors are conceptualized by stakeholders involved in DTx from development to implementation, while also investigating how they are perceived and considered throughout the DTx lifecycle by the same stakeholders. Building on this analysis, this study aims to develop an evidence-based conceptual framework of priority areas. This framework will provide a comprehensive roadmap for stakeholders, outlining considerations throughout the technology lifecycle that can ultimately influence a DTx ability to generate economic value.

Results

The cluster map, showcasing eight clusters, serves as a visual representation of the factors that participants have grouped together (Fig. 1). A dot on the map represents a single factor. The distance between the dots reflects how frequently participants sorted these factors into the same piles. These clusters delineate distinct themes spanning the entire DTx lifecycle, from inception to widespread deployment, with 59 factors conceptualized to influence the DTx ability to deliver economic value.

The mapping of 59 factors into eight clusters reveals three main themes along a horizontal axis in the nonmetric multidimensional scaling analysis (NMDS) map, representing a time axis that follows the traditional DTx development cycle from conception to deployment. These themes, detailed in Supplementary Note 1, are:

1. EARLY STAGES OF DTX DEVELOPMENT: This theme encompasses clusters of factors more pertinent to the initial phases of DTx development and clinical validation, leading toward approvals and/or market authorization by a regulatory body;
2. PREIMPLEMENTATION-RELATED ASPECTS: This theme includes clusters associated with various considerations and preparations necessary before the actual implementation of a DTx intervention; and
3. DTX DEPLOYMENT: The final theme consists of clusters containing factors pertinent to the implementation and ongoing management of DTx in a real-world environment.

Supplementary Table 1 presents all 59 identified factors forming these eight clusters' contents, along with the standard deviation for each cluster and the average anchoring and bridging index (ABI) for each factor, as well as for each cluster. The ABI for a cluster is the average of all the ABIs for individual factors for a cluster. Lower ABIs represent a more homogeneous cluster, while higher ABIs indicate a more heterogeneous cluster, comprising relatively diverse factors. A review of the cluster map reveals that the *Technology Considerations* cluster stands out as the sole bridging

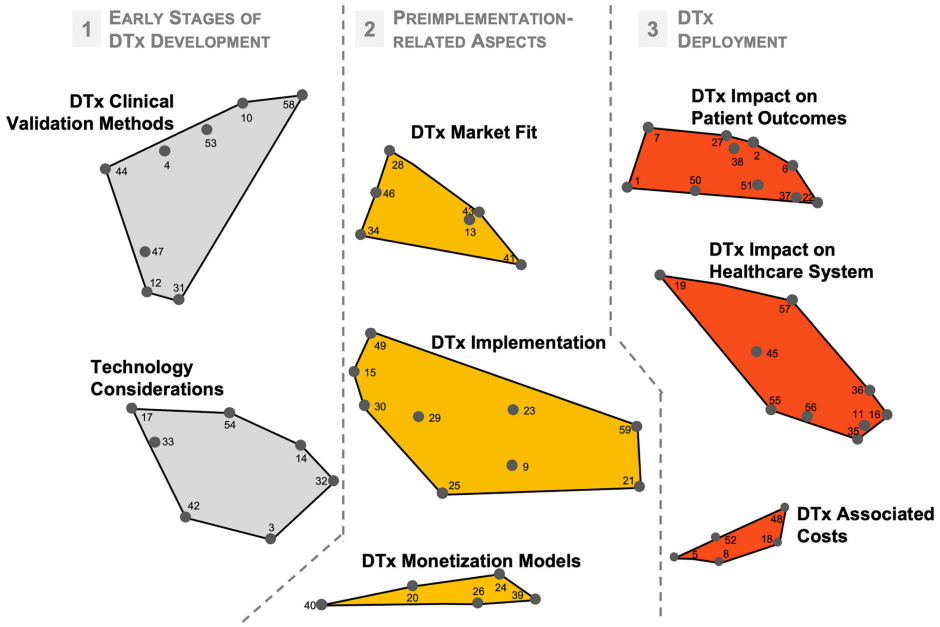

Fig. 1 | Cluster point map of all 59 factors perceived to influence the economic value of DTx, grouped into eight-cluster map ($n = 37$). The cluster point map reveals the interconnected nature of 59 factors that contribute to the economic value of DTx, organized into eight non-overlapping clusters, as shown by the polygons, where each one represents a key aspect of DTx development and implementation. Through spatial conceptual relationships, the map illustrates how participants consistently grouped certain factors together, with closer proximity represented within the perimeter of each polygon to indicate stronger association among them.

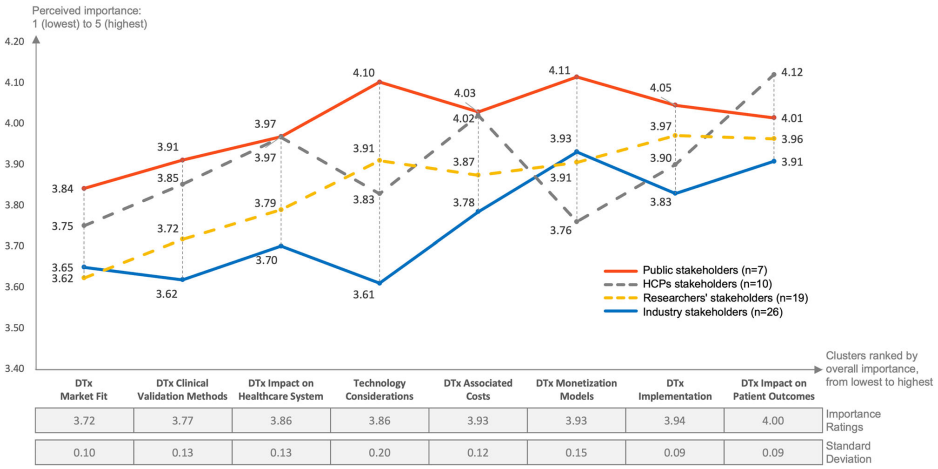

Fig. 2 | Perceived importance of the clusters of factors perceived to influence the economic value of DTx among stakeholder groups ($n = 62$). The figure shows how different stakeholder groups - Healthcare Professionals (HCPs), Industry, Public, and Researchers - rated the importance of each cluster. *DTx Impact on Patient Outcomes* and *DTx Implementation* emerged as the most important clusters overall, with mean ratings of 4.00/5.00 and 3.94/5.00, respectively. Public stakeholders consistently gave higher importance ratings across clusters compared to other groups.

cluster, suggesting that its factors were more frequently situated in multiple clusters when sorted by participants. By contrast, all remaining clusters are non-bridging (bridging value < 0.5), indicating fewer links to surrounding clusters, with factors predominantly sorted together by participants. The implication of this is the clarity in conceptualization that supports the research process.

The comparison of importance and extent of consideration ratings reveals a notable pattern (Supplementary Table 1). Seven out of eight clusters show higher mean ratings for importance than for extent of consideration. This suggests these clusters may be underconsidered in fields of practice relative to their perceived importance in influencing the overall DTx economic value. The sole exception is the *DTx Market Fit* cluster, where the importance rating (3.72/5.00) closely aligns with its extent of consideration rating (3.74/5.00).

In what follows, cluster results for each rating are examined, and then compared to draw broader insights. The mean ratings for importance provided by the participants for each factor and by cluster are presented in Fig. 2. Standard deviations (SD) are computed for each cluster to assess the degree of convergence or divergence among stakeholder responses, with a mean value of 0.13.

The two clusters of factors impacting the economic value of DTx, reported as the most important by stakeholders, are the *DTx Impact on Patient Outcomes* (rated at 4.00/5.00) and *DTx Implementation* (rated at 3.94/5.00). The SD values, of 0.09 for both clusters, indicate a narrow rating, thus a strong agreement among stakeholders.

Following closely are the *DTx Monetization Model* (rated 3.93/5.00) and *DTx Associated Costs* (rated 3.93/5.00), ranking as the third most important clusters. The *DTx Market Fit* cluster was consistently ranked lower than any other cluster by all stakeholder groups, except for Industry stakeholders, who rated it as the third lowest.

The convergence and divergence in perception among stakeholder groups merit attention. Public stakeholders consistently assigned higher importance ratings across clusters, with a mean rating of 4.00/5.00, compared to HCPs (with a mean rating of 3.90/5.00), Researchers (mean rating of 3.84/5.00), and Industry stakeholders (mean rating of 3.75/5.00).

The most significant convergence of perspective is toward the importance of the *DTx Impact on Patient Outcomes*, with a SD of 0.09. However, while the *DTx Impact on Patient Outcomes* emerges as the most important cluster of factors for HCP stakeholders —an outcome most likely aligned with expectations— it ranks only fifth in importance for Public stakeholders.

The most notable divergence of perspective relates to the *Technology Considerations* influencing a DTx ability to deliver economic value, with a SD of 0.20. This cluster ranked as the second most important for Public stakeholders (with a mean rating of 4.10/5.00), contrasting sharply with Industry stakeholders who rated it as the least important (with a mean rating of 3.61/5.00). The interpretation of these convergences and divergences in perception among stakeholder groups is further examined in the discussion section.

In addition to evaluating the relative importance of clusters influencing the economic value of DTx, stakeholders were asked to rate the extent to which each factor was considered into their respective field of practice (Fig. 3). This includes aspects like day-to-day decision-making and prioritization within their roles. The mean SD for extent of consideration across clusters is 0.30.

Among all stakeholders, Fig. 3 reveals that *DTx Associated Costs* is the least considered cluster of factors (rated at 3.41/5.00), followed by *DTx Monetization Models* (rated 3.45/5.00), despite both being reported as the third most important clusters (Fig. 2) – results partially driven by the ratings of the group of Researchers (Table 1). A strong consensus exists among stakeholders in considering *DTx Impact on Patient Outcomes* perceived as the most considered cluster (rated at 3.84/5.00). Once again, Public stakeholders consistently assigned higher consideration ratings across clusters with a mean rating of 3.83/5.00.

Table 1 compares how Researchers and other stakeholder groups reported the perception of the different clusters in their professional practice. Researchers prioritize factors related to the EARLY STAGES OF DTX DEVELOPMENT (rated 3.62/5.00), PREIMPLEMENTATION-RELATED ASPECTS (3.25/5.00), and DTX DEPLOYMENT (3.08/5.00). This aligns with Researchers' typical involvement in the early stages of the DTx lifecycle. The *DTx Associated Costs* cluster reveals a significant perception gap between Researchers and

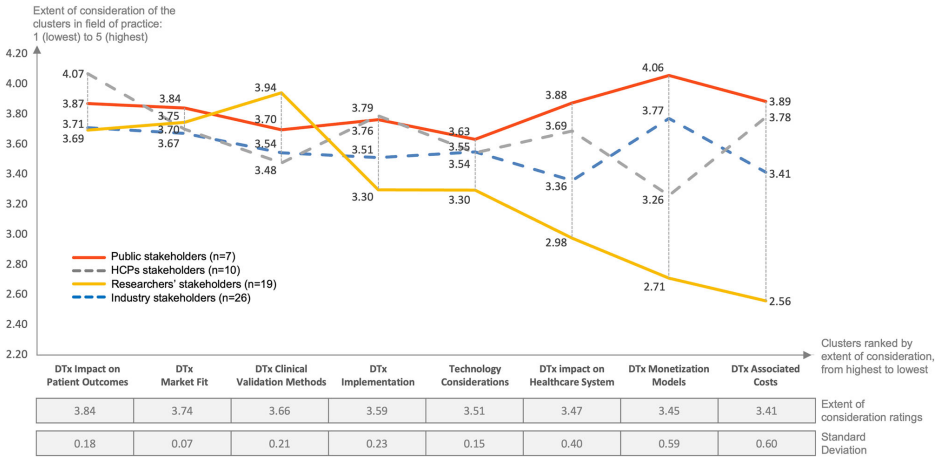

Fig. 3 | Extent of consideration of the clusters of factors perceived to influence the economic value of DTx among stakeholder groups ($n = 62$). The figure illustrates the extent to which each stakeholder group rated these clusters in their practice. *DTx Associated Costs* was the least considered cluster (3.41/5.00), followed by *DTx Monetization Models* (3.45/5.00), despite their high importance ratings. *DTx Impact on Patient Outcomes* was reported as the most considered cluster (3.84/5.00).

Table 1 | Comparison of extent of consideration ratings: Researchers vs. other stakeholder groups by cluster

	Mean extent of consideration rating, excluding Researchers ($n = 43$)	Mean extent of consideration rating for Researchers ($n = 19$)	Significance
Theme 1: Early stages of DTx Development	**3.57**	**3.62**	
Technology Considerations	3.58	3.30	$p > 0.05$
DTx Clinical Validation Methods	3.57	3.94	$p > 0.05$
Theme 2: Preimplementation-related Aspects	**3.71**	**3.25**	
DTx Market Fit	3.74	3.75	$p > 0.05$
DTx Implementation	3.69	3.30	$p < 0.05$
DTx Monetization Models	3.70	2.71	$p < 0.005$
Theme 3: DTx Deployment	**3.74**	**3.08**	
DTx Impact on Patient Outcomes	3.88	3.69	$p > 0.05$
DTx Impact on Healthcare System	3.64	2.98	$p < 0.005$
DTx Associated Costs	3.69	2.56	$p < 0.001$

other participants. Researchers rated it considerably lower (2.56/5.00), while other participants gave it a higher score (3.69/5.00). This disparity underscores the divergent views among stakeholder groups on how factors affecting DTx economic value are considered. Notably, this cluster also shows the highest SD (0.60) across both importance and extent of consideration ratings and clusters.

To further explore these results, both the ratings of importance and extent of consideration were compared not in isolation, but rather in conjunction. It led to the plotting of clusters based on stakeholders' mean ratings, resulting in an aggregate scattered bivariate plot by cluster, referred to as a go-zone graph in group concept mapping (GCM) analysis (Figs. 4 and 5). These graphs are divided into quadrants, above and below the mean value of each factor ratings. Thus, it facilitates the overall identification of priority clusters.

Priority quadrants are delineated based on whether clusters fall above or below the mean ratings for importance (3.84/5.00) and extent of consideration (3.53/5.00). These quadrants are defined as follows: (1) Quadrant I encompasses clusters of factors perceived as important for a DTx to generate economic value and highly considered by participants in their field of practice throughout the DTx development lifecycle, (2) Quadrant II includes clusters with high importance but low consideration, (3) Quadrant III contains clusters with both low importance and low consideration, and (4) Quadrant IV comprises clusters with low importance but high consideration. This framework allows for a nuanced analysis of how various clusters of factors are perceived and prioritized in the context of DTx economic value.

The Quadrant II encompasses clusters perceived as highly important in influencing DTx economic value, yet insufficiently considered in participants' daily decision-making processes, thus indicating a potential gap. Three clusters fall within this priority quadrant: *DTx Implementation*, *DTx Monetization Models*, and *DTx Associated Costs*. These clusters are recognized by all stakeholder groups for their critical role in a DTx ability to generate economic value, as evidenced by a low mean SD rating of 0.12 across these three clusters. However, they are simultaneously acknowledged, particularly by Researchers, as potentially receiving inadequate consideration throughout the DTx development lifecycle. This discrepancy

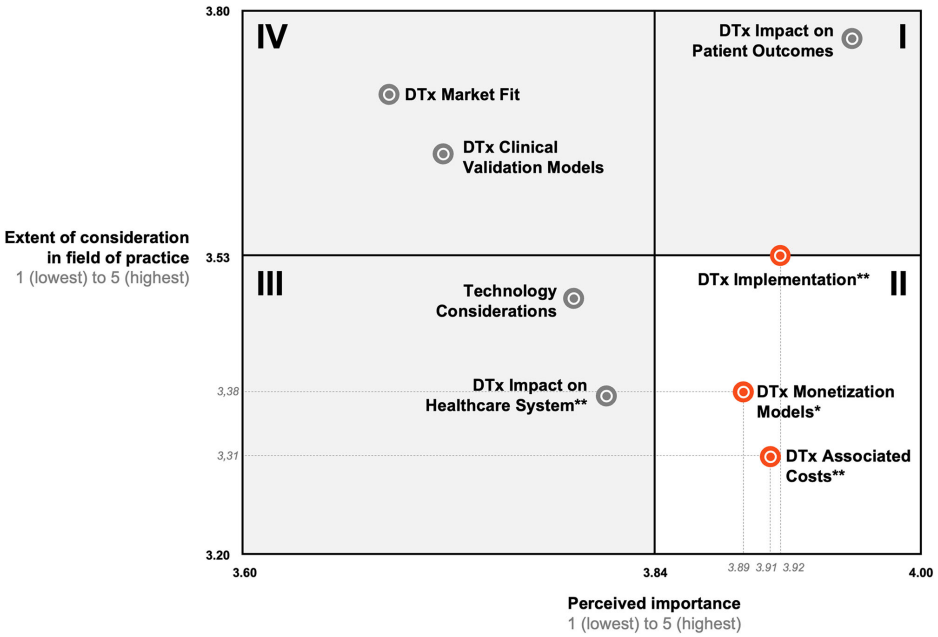

Fig. 4 | Bivariate go-zone plot of aggregate means by cluster as perceived by stakeholders of the importance and extent of consideration in the field of practice ($n = 62$). This quadrant analysis plots clusters based on the importance (x-axis) versus the extent of consideration (y-axis). The scattered plot identifies three priority clusters that are highly important but receive insufficient consideration (Quadrant II), these are, *DTx Implementation*, *DTx Monetization Models*, and *DTx Associated Costs*. A single asterisk (*) indicates a $p < 0.05$, and double asterisks (**) indicate a $p < 0.001$. The nonparametric Wilcoxon Rank-order test for matched pairs indicates a statistical difference ($p < 0.05$) between the relative importance and the extent of consideration rank orderings.

underscores a potential area of consideration for the respective stakeholders involved in DTx development and implementation strategies.

With a $p < 0.05$, the difference between the two overall scale rankings for these clusters is statistically different as reported by the nonparametric Wilcoxon rank-order test. Nevertheless, these findings should be interpreted within the context of each stakeholder group.

An analysis of the go-zone graph at the factor level reveals eight factors (factors 8, 11, 18, 30, 32, 40, 52, and 54) positioned in Quadrant II, the priority quadrant (Fig. 5). These eight factors emerged as crucial for a DTx to generate economic value, with their mean importance ratings surpassing the overall mean across all 59 factors studied. Paradoxically, these same eight factors were reported as less considered by the participants compared to the other factors, with their mean extent of consideration ratings falling below the overall mean.

These eight priority factors (Figs. 5 and 6) span over five of the eight total clusters. This distribution suggests that, according to participants, no single factor or cluster should be prioritized in isolation. Instead, multiple factors across the entire DTx lifecycle may require consideration or prioritization by the relevant stakeholders at each stage.

Discussion

The results of this study illustrate the benefits of GCM methodology as a participatory approach in creating a collective conceptual framework for understanding a specific topic of interest[10]. The approach elucidates stakeholders' shared perspectives, while also revealing how both collective and individual stakeholders contribute to and influence this economic value. This research contributes to the field in three ways.

First, it provides a collective stakeholder approach to identify factors influencing DTx economic value. The research identified 59 such factors, aligning with the emerging literature in this field[9,11–15]. Notably, this study highlights several factors that are inconsistently considered in economic evaluations of DTx and are simultaneously recognized as barriers to the widespread adoption of these technologies[5–7]. These include factors such as the time and expertise needed for patient education in using DTx technology (factor 5), ongoing maintenance costs (factor 26), direct patient out-of-pocket expenses (factor 8), indirect costs (factor 48), and the local context as a significant source of uncertainty (factor 13).

Second, this study provides a better understanding of the collective conceptualization of factors influencing the economic value of DTx by stakeholders involved in their development, validation, and implementation. It examines the interrelationships between clusters and factors driving DTx economic value from a collective stakeholder perspective. By mapping these connections, it helps gain insight into the intricate ecosystem of factors influencing the economic value of DTx.

Third, the analysis of the stakeholders' perceived relative importance and relative extent of consideration of these factors led to the development of a conceptual framework of priority areas. This framework, illustrated in Figs. 4 and 5 and detailed in Supplementary Table 1, presents a grouped and coherent set of potential priority clusters and factors for driving DTx economic value. It aims to guide stakeholders in comprehensively assessing relevant factors, ensuring a methodical approach to decision-making. It is recommended that each stakeholder group interpret this framework meticulously to comprehensively assess relevant clusters and factors derived from the study findings.

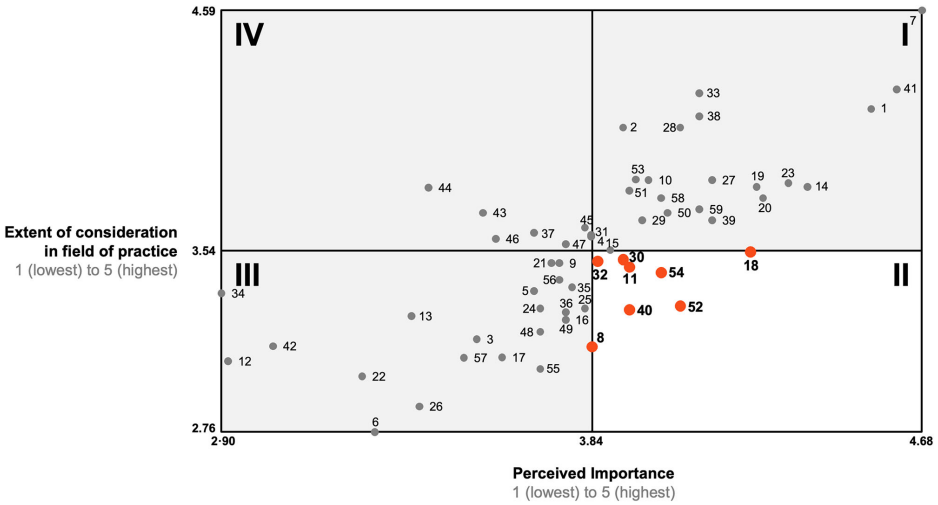

Fig. 5 | Bivariate go-zone plot of individual factors influencing the economic value of DTx perceived importance and extent of considerations in the field of practice ($n = 62$). This quadrant analysis plots individual factors based on their importance (x-axis) versus extent of consideration (y-axis). The scattered plot identifies eight specific factors that fall into the priority quadrant (Quadrant II)—meaning they are considered highly important but receive insufficient consideration in practice.

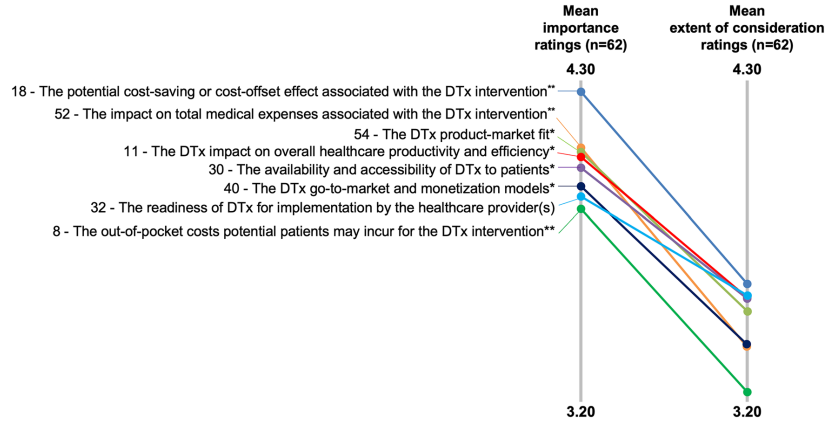

Fig. 6 | Pattern match of the relationship between stakeholders' mean factors in Quadrant II: higher importance and lower extent of consideration ($n = 62$). The figure illustrates the relationship between the mean factor ratings for both scales. These pattern matches for the factors identified in Quadrant II are valuable for detecting high-level patterns and offer a visual comparison of how stakeholders rated these factors. The descending diagonal lines indicate that each factor's importance rating is higher than its corresponding extent of consideration rating, confirming a potential lack of consideration of these factors despite their perceived importance in driving DTx economic value. A single asterisk (*) indicates a $p < 0.005$, and double asterisks (**) indicate a $p < 0.001$. The nonparametric Wilcoxon Rank-order test for matched pairs indicates a statistical difference ($p < 0.01$) between the relative importance and the relative extent of consideration rank orderings.

The study revealed both anticipated and unexpected insights, contributing to a more nuanced understanding of how different stakeholder groups influence a DTx ability to generate economic value. Two observations merit particular attention.

The improvement of patients' clinical outcomes emerged as a primary concern across all stakeholder groups (Fig. 2). However, despite this broad consensus, this cluster ranked only fourth in importance for Public Stakeholders. This discrepancy may be attributed to the heterogeneous composition of this stakeholder category, encompassing individuals with diverse backgrounds in technology, clinical practice, and payer systems. Also, the complexity of decision-making regarding coverage, payment and reimbursement has intensified, with priority setting and resource allocation posing significant challenges. Public stakeholders are tasked with evaluating not only the clinical and financial impact of individual DTx interventions

but also their broader implications for healthcare systems and populations. This evaluation must be conducted in the context of competing alternative treatments and interventions, all vying for limited funding and coverage. Therefore, while the clinical impact of these interventions is crucial, it is not the sole determining factor for final decision.

A second observation relates to Researchers appearing to give less consideration to some factors as compared to other stakeholders groups. This is particularly evident for factors within the *DTx Associated Costs*, *DTx Monetization Models*, and *DTx Healthcare System Impact* clusters, despite Researchers acknowledging the importance of these factors. This divergence potentially reflects the heterogeneous composition of this stakeholder category, as well as Researchers' primary involvement in early stages of DTx development, such as conducting research, knowledge generation, and initial clinical validation. Their priorities or mandates may differ, as they are typically not tasked with examining costs during these initial stages of technology development and clinical validation. However, failing to consider these costs impact early on could negatively impact payment, reimbursement and adoption decisions[8]. This finding underscores the critical role that all stakeholders, including researchers, play in ensuring DTx demonstrate economic value to potential payers. As innovations from research institutions often struggle to achieve commercial success[16], there exists a significant opportunity to enhance the commercialization of innovative research. A promising starting point could be fostering collaboration among major DTx stakeholder groups, such as through public-private partnerships. These collaborations should aim to integrate commercialization expertise earlier in the DTx lifecycle, ensuring that market viability is considered from the outset of development. By bridging the gap between academic research and commercial application, stakeholders can work together to overcome the challenges that currently hinder the successful translation of DTx innovations into commercially viable products.

The mixed-method approach, which involved semi-structured interviews (Supplementary Note 2) and a group discussion with subject matter experts throughout the GCM research steps (Supplementary Note 3), particularly for data interpretation, contributed to confirming the external validity of the generated data and results. The external validity of the results is also reinforced by the variety of stakeholders and the wide range of settings involved. The results presented are context-specific, and it is crucial to consider context-specific external validity issues when interpreting them.

The study's sample size ($n = 62$) and participant composition provide valuable insights within the context of the research. While the findings offer a robust and reliable foundation for understanding DTx value generation, certain limitations should be acknowledged. Building on the study's findings, future research could extend this methodology to explore factors perceived as important by specific subgroups of stakeholders, such as healthcare providers, or new groups like patients. Such investigations could be conducted across various contexts and countries to gain a more comprehensive understanding of the decision-making processes within each stakeholder group. Additionally, exploring the relationship between these perceived factors and actual economic outcomes would provide valuable insights into the real-world impact of DTx interventions.

As the field of DTx continues to evolve, ongoing research will be crucial in refining our understanding of the factors influencing economic value and adoption. By building on the insights gained from this study and expanding the scope of investigation, future research can contribute significantly to the advancement and integration of DTx in healthcare systems. This continued exploration could ultimately help inform the development of more effective, economically viable DTx interventions, benefiting both patients and healthcare systems alike.

Methods

Study design

To meet the objective, GCM is used to delve into potential convergences and divergences in stakeholders' perspectives and considerations on factors influencing the economic value of DTx. This mixed methods-based approach provides a structured way to synthesize complex, multifaceted concepts and associated conceptualisations and perceptions into a coherent analytical framework[17]. The choice was motivated by GCM participatory nature and its ability to combine diverse perspectives from a broad group of participants. Napier-Raman et al. describe CGM as "particularly useful when examining complex, multifaceted issues, particularly those in public health."[18]

Initially introduced by Trochim[19], GCM engages a diverse group of stakeholders as participants in collaborative efforts to generate, structure and visualize conceptual information. It facilitates the conceptualization of abstract constructs, delving into complex social phenomena, examine relationships among factors, and compare perspectives and priorities across different participant groups[20,21]. The GCM research design transforms abstract conceptual data into visual representations or maps, and leads to the creation of a collective conceptual framework for comprehending a specific topic of interest[17,19].

The study received approval from the Ethics Boards of the National University of Singapore (certificate number: NUS-IRB-2023-399) and the University of Quebec in Montreal (certificate number: UQAM-CIEREH-2024-6028). Participants provided written informed consent to engage in either face-to-face sessions, group discussions, or web-based tasks described below. The Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist was used to guide the reporting of this study (Supplementary Table 2)[22].

The study was conducted between March 2023 and August 2024. Data collection occurred from September 2023 to February 2024, with analysis, interpretation, external validation, and manuscript preparation conducted from February to August 2024.

Overview of group concept mapping process

The GCM approach comprises five phases[19]: (1) identifying relevant stakeholders and developing the focus prompt, (2) generating factors that may impact the economic value of the DTx, (3) structuring factors through sorting and rating, (4) analyzing data and creating the visual representations, and (5) interpreting and utilizing the results (Supplementary Fig. 1).

Phase 1: Preparation. The preparation phase includes all aspects of planning, including ethics review board approvals and participants' recruitment, and focus prompt definition and interview guides (Supplementary Note 3). Participants were recruited through purposive sampling based on their relevant experience according to three inclusion criteria: (1) experience in DTx development, clinical validation and/or implementation; (2) geographic diversity to ensure broader perspectives; and (3) fluency in English or French. Participants were identified through the research team's professional network. The final participant pool comprised four key stakeholder groups: (1) Healthcare professionals involved in care delivery and experienced with digital health solutions, (2) Industry stakeholders often leading the commercialization efforts of DTx interventions, (3) Public stakeholders responsible for DTx-related policy and regulatory aspects, and (4) Researchers early engaged in the DTx lifecycle, that is, in the development of these technologies (i.e., biomedical engineers, clinical researchers, healthcare management and economics researchers, behavioral scientists, and regulatory scientists). To provide context, a sociodemographic questionnaire was used to collect non-personal information, including demographic and professional information from participants (Supplementary Table 3).

Phase 2: Factors generation. Factors influencing the DTx economic impact were initially extracted from the literature[6,9,11–15]. Subsequently, four in-depth face-to-face semi-structured interviews were conducted with DTx experts (Supplementary Note 2), defined as individuals having at least 5 years of experience in DTx development and/or implementation, and a group discussion was conducted with six additional DTx experts (Supplementary Note 3). The purpose of the interviews and group discussions was to identify and exchange ideas related to a central prompt question: "*What factors may impact the ability of digital*

therapeutics to provide economic value or benefits?" In total, 223 potential factors influencing the economic value of DTx were identified. In GCM, the term "statement" is used to refer to ideas obtained from the literature, during interviews, and group discussions to denote formalized specific ideas to be included in the list for sorting and rating (phase 2). For consistency with participant terminology and to reflect the conceptual nature of these elements, this paper adopts the term "factor", encompassing the various aspects both identified and evaluated by the participants during the GCM process.

Thematic-conceptual coding[23] was conducted to analyze the factors identified and a list of 59 factors was established (Supplementary Table 1), which was pretested by two additional DTx experts independently. For example, the factors "The degree of contextualization and personalization in the intervention," "The level of personalization in interventions delivered to the patients," and "The use of real-world data to personalize the therapeutic intervention" were synthesized into "The degree of personalization of the DTx intervention at the individual patient level." Each factor was randomly placed in the list and an identifying number was attributed for the traceability of empirical results.

Phase 3: Factors sorting and rating. At this phase, participants were invited to engage in three key activities through groupwisdom™, a web-based platform for GCM data collection, analysis, and results visualization[24]. First, participants ($n = 37$) were asked to sort the factors at Phase 2 into virtual piles based on their perceived similarity in meaning and to assign a name to each one. Second, participants who took part in factor sorting, along as additional ones ($n = 62$), were tasked to rate the factors on two distinct 5-point Likert-type scales:

1. Importance scale: Participants rated the importance of each factor for a DTx to generate economic value, based on their experience. The scale ranged from 1 (not important) to 5 (very important).
2. Extent of consideration scale: Participants assessed the extent to which each factor is considered in their field or practice regarding DTx development, clinical validation, or implementation. This scale ranged from 1 (not considered) to 5 (very considered).

A total of 91 potential participants were initially contacted for this Phase 2, primarily via email between November 2023 and February 2024. Of these, 62 individuals completed the study, while 24 did not respond, 3 declined to participate, and 2 agreed but did not complete the required tasks. Supplementary Table 3 presents a comprehensive overview of participants' professional profiles, international geographic zones, and experience across the DTx lifecycle. Notably, 77% of participants reported at least 5 years of experience in their respective fields, thus ensuring a high level of expertise among participants.

Phase 4: Data analysis. The sorting results of the sorters ($n = 37$) were analyzed using NMDS to produce a point map[25]. This map displays the individual factors in two-dimensional (x, y) space. Factors frequently sorted together into piles by participants are plotted in Euclidean proximity on the point map, while factors not frequently sorted together into piles are spatially positioned farther away. The estimated stress value (SV) for this study stands at $[0.27 < 0.276 < 0.29;\ p < 0.05]$, and falls within the 95% confidence interval for internal statistical reliability from meta-analytic studies in GCM[26]. Similarly, test results obtained for SV for sample split-half-1 $[0.27 < 0.288 < 0.29; p < 0{\cdot}05]$ and SV for sample split-half-2 $[0.27 < 0.290 \le 0.29;\ p < 0.05]$. This "goodness-of-fit" statistic confirms a strong fit between the sort data (i.e., collected data) and the results of the estimated point map (i.e., processed data)[26]. Subsequently, agglomerative hierarchical cluster analysis (AHCA), using Ward's algorithm[27] was employed with the NMDS-estimated x-y coordinates of each factor used as an input. This spatially groups factors in polygons on a cluster map that are closest and non-overlapping. From NMDS estimates, anchoring and bridging Index (ABI) values are in the interval [0,1] and generated for each factor and their mean values calculated for each cluster[10,17]. The mean ABI provides insight into how factors within a cluster relate to each other and to factors in other clusters. Lower ABI values (toward "0") indicate that factors were more frequently sorted together by participants, thus they are more tightly associated within their cluster and reflect agreement among participants, while higher values (toward "1") suggest factors may serve as bridges to other clusters, and less agreement as to their spatial location on the concept map.

To determine the optimal number of clusters, i.e., the number of clusters which define the concept map solution, the study team systematically evaluated each cluster solution, ranging from 12 to 8 clusters. Each step involved examining which factors were grouped together as informed by the AHCA, and ABI values for consideration, to decide the best conceptual fit for the concept map, related to the intended purposes of the study[26,28]. The result was a final configuration of eight clusters (Fig. 1, Supplementary Note 1 and Supplementary Table 1), each containing between 5 and 10 factors. There is no single a priori correct number of clusters or statistical method to determine the single best cluster solution[26,28,29], an examination of data found the mean number of sorted piles by participants is 7.91 (standard deviation: 2.14) and the median is 8. Regarding scale ratings, the 'importance' and 'extent of consideration' ratings were averaged for each factor and by cluster. To establish the internal reliability of rating consistency, the inter-rater reliability test estimate of participants obtained using the Pearson-Brown Prophecy formula[30] for the importance of the factor for generating DTx economic value $[0.91 < 0.92, p < 0.05]$ and for the extent of consideration of the factor in the DTx field of practice $[0.84 < 0.90 \le 0.90, p < 0.05]$ provide quite strong internal reliable and valid scale evaluation results with the 95% confidence interval or higher based on the criteria established in GCM meta-analyses on reliability[26].

Phase 5: Data interpretation. At this final stage, semi-structured interviews/discussions involving five DTx experts were organized to interpret the findings. These experts, each with at least 5 years of experience, represented diverse profiles covering all aspects of DTx development, clinical validation, and implementation. These sessions involved a comprehensive review of the point map, point cluster map, as well as the ratings for importance and extent of consideration. These ratings for each factor and cluster, both within and among each group of stakeholders, were thoroughly examined and compared to comprehend potential convergence and divergence among factors. The goal was to interpret these variances and derive meaningful findings.

Data availability

All data generated or analyzed during this study are available from the corresponding author on reasonable request.

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Author contributions

Y.S. and L.M.C. conceptualized the study, conducted the data analysis and drafted the manuscript. Y.S., L.M.C., G.T., A.B., F.K., D.L., X.T., and D.H. contributed to refining all sections and critically editing the manuscript. All authors contributed to and have approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41746-025-01600-7.

Correspondence and requests for materials should be addressed to Yoann Sapanel.

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Appendix 2C. IRB approvals

The IRB approvals for this research, including the second and third papers, are presented below, with the first approval issued by the National University of Singapore (certification number: NUS-IRB-2023-399), followed by the IRB approval from the University of Quebec in Montreal (certification number: 2024-6028).

Office of the Deputy President (Research and Technology)
Institutional Review Board

NUS National University of Singapore

NUS-IRB Reference Code: NUS-IRB-2023-399

2 June 2023

Mr Yoann Sapanel
Head, Health Innovation at the Institute for Digital Medicine (WisDM)
The N.1 Institute for Health
National University of Singapore

Dear Mr Sapanel,

EXEMPTION FROM NUS INSTITUTIONAL REVIEW BOARD (NUS-IRB) REVIEW

Protocol Title: Comprehending the Economic Value Drivers for Digital Therapeutics

Principal Investigator: Mr Yoann Sapanel
Co-Investigators: Prof Dean Ho, Dr Smrithi Vijayakumar, Prof Cloutier Martin

Source of Funding: Nil

We are pleased to inform you that the NUS Institutional Review Board (NUS-IRB) has reviewed and approved the ethical aspects of your above-mentioned research based on your declaration and the IRB Application Form submitted.

We note that your research only involves human participants as stated in the following category:

(7B) Research involving benign behavioural interventions where disclosure of subjects' responses outside research would not reasonably place the subjects at risk.

The exemption shall remain valid until such time the research is completed, unless the research is terminated earlier for any reason whatsoever.

The NUS-IRB has reviewed the IRB application form and the following documents for the purpose of granting the exemption from NUS-IRB review: -

Documents:

1. Phase 1_Focus Group Guide_01062023.docx
2. Phase 3_Focus Group Guide_01062023.docx
3. Focus Group Participant Demographics.docx

1 of 2

Please note that:

1. The Principal Investigator should inform the NUS-IRB within two (2) working days if any significant deviations from the information submitted in this application arise.

2. The Principal Investigator should apply for IRB approval if s/he decides to include any other human participants in the research at a later point in time.

3. The Principal Investigator should submit the Closure submission via iRIMS-IRB within 3 months after the completion of the research.

4. The Principal Investigator is responsible to inform the NUS-IRB should s/he tender resignation from NUS and notify us of any changes to the study status, e.g. change in Principal Investigator or study termination. Otherwise, the IRB approval will lapse 3 months from the date of your official departure from NUS.

5. All applicable forms/reports can be completed and submitted via the online system (iRIMS-IRB).

Thank you.

Yours sincerely,

Mrs Jenny Bong
Deputy Co-Chair, Institutional Review Board
National University of Singapore

Cc: Organisational Approver (iRIMS-IRB), The N.1 Institute for Health, NUS

This is a system generated approval letter. No signature is required.

Block MD 11, #05-09, 10 Medical Drive, Singapore 117597
Tel: 65-6516 4311
Website: http://www.nus.edu.sg/research/irb
Company Registration No: 200604346E

UQÀM | CIEREH
Comité institutionnel d'éthique de la recherche avec des êtres humains

CERTIFICAT D'APPROBATION ÉTHIQUE

No. de certificat : 2024-6028
Date : 06 juillet 2023

Le Comité d'éthique de la recherche avec des êtres humains (CIEREH) a examiné le projet de recherche suivant et le juge conforme aux pratiques habituelles ainsi qu'aux normes établies par la *Politique No 54 sur l'éthique de la recherche avec des êtres humains* (janvier 2020) de l'UQAM.

Protocole de recherche

Chercheur principal : Martin Cloutier
Unité de rattachement : Département d'analytique, opérations et technologies de l'information
Titre du protocole de recherche : Comprendre les facteurs de la valeur économique des traitements thérapeutiques fondés sur les applications numériques (DTx)
Source de financement (le cas échéant) : s.o.
Date prévue de fin de projet : 2024-03-31

Équipe de recherche
Cochercheurs externes (National University of Singapore) : Yoann Sapanel; Dean Ho; Smrithi Vijayakumar

Modalités d'application

Le présent certificat est valide pour le projet tel qu'approuvé par le CIEREH. Les modifications importantes pouvant être apportées au protocole de recherche en cours de réalisation doivent être communiqués rapidement au comité.

Tout évènement ou renseignement pouvant affecter l'intégrité ou l'éthicité de la recherche doit être communiquée au comité. Toute suspension ou cessation du protocole (temporaire ou définitive) doit être communiquée au comité dans les meilleurs délais.

Le présent certificat est valide jusqu'au **06 juillet 2024**. Selon les normes de l'Université en vigueur, un suivi annuel est minimalement exigé pour maintenir la validité de la présente approbation éthique. Le rapport d'avancement de projet (renouvellement annuel ou fin de projet) est requis dans les trois mois qui précèdent la date d'échéance du certificat.

Gabrielle Lebeau
Coordonnatrice du CIEREH

Pour Julie Cloutier
Julie Cloutier, Ph.D.
Professeure
Vice-présidente

Signé le 2023-07-06 à 15:54

Exporté le 2023-07-06 15:54 par Lebeau, Gabrielle --- CODE DE VALIDATION NAGANO: uqam-54ba1b22-6694-4f07-8f32-7b37ca3ce04ehttps://uqam.nagano.ca/verification/uqam-54ba1b22-6694-4f07-8f32-7b37ca3ce04e

Appendix 2D. Consent form to participate in a research study (GCM Step 1)

NUS National University of Singapore

GUIDELINES ON PARTICIPANT INFORMATION SHEET & CONSENT FORM
(For Social, Behavioural and Educational Research studies)

1. **Protocol title**
Comprehending the Economic Value Drivers for Digital Therapeutics

2. **Principal Investigator and co-investigator(s), if any, with the contact number and organization:**

Principal Investigator:
Professor Dean Ho, (+65) 6601 7515, The Institute for Digital Medicine (WisDM), National University of Singapore

Co-Principal Investigator:
Yoann Sapanel, (+65) 96 48 49 62, The Institute for Digital Medicine (WisDM), National University of Singapore

Collaborator's Co-Principal Investigator:
Professor Martin Cloutier, (+1) 514 987 3000, Université du Québec à Montréal (UQAM), Canada.

3. **What is the purpose of this research?**
You are invited to participate in a research study. This information sheet provides you with information about the research study. Professor Dean Ho's team representative will also describe this research to you and answer all of your questions. Read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Digital therapeutics (DTx), also known as evidence-based therapeutic treatments powered by high-quality software, are expected to influence health care delivery and its consumption across the globe. DTx are said to be the "next paradigm" of modern health care. There is indeed emerging clinical evidence that DTx can prevent, manage, or treat a spectrum of medical disorders and diseases. However, their capacity to provide economic value is not well established, an important consideration in payers' reimbursement and pricing decisions resulting in an important knowledge gap. The factors driving the DTx economic value have also not been thoroughly researched, neither in terms of what are they nor how they should be considered.

In keeping with this gap in understanding, in this research study, we examine how various factors driving the DTx economic value, are considered and perceived among stakeholders involved in the DTx development, evaluation and commercialization.

4. Who can participate in the research? What is the expected duration of my participation? What is the duration of this research?

All stakeholders involved in the DTx development, evaluation and commercialization, especially engineers, clinicians, commercialization leaders, health technology assessment experts and payers. Participation will comprise a 60-minute discussion.

5. What is the approximate number of research participants involved?

10-20 participants, including NUS and WisDM staff.

6. What will be done if I take part in this research study?

Upon recruitment, a member from our study team will approach you to invite you to a scheduled focus group discussion, or to an in-depth interview. The discussion will begin with a welcoming brief overview of the research and its objectives. A sociodemographic questionnaire will be used to collect non personal information, including demographic and professional background information from participants. You will then be invited to share ideas around the following focus prompt question: "*What are the factors that might influence the digital therapeutics' ability to deliver economic value or benefits?".*

The group discussions serve to share ideas among participants in a flexible manner and provide an open forum for a free-flowing discussion among participants. Everyone speaks voluntarily and the role of the facilitators is to ensure that the discussion is orderly, and that it allows for exchanges around follow-up questions as the discussion progresses. The ideas collected during the group discussions will be used to structure a set of 50-60 potential DTx economic value drivers.

With your permission, the researchers would like to make an audio recording of the group discussion and of the in-depth interviews. The purpose of this recording is to allow the verbatim transcription. We ask that you do not identify yourself during the recording of the group discussion. Once the audio transcript has been made, the audio recording will be destroyed. However, the transcript will not identify you. Participation in this group discussion implies that you commit to respecting the confidentiality of what is shared by the other participants, not to identify by name people with whom you are in contact, nor to share information that would allow the group members to identify them. It is important to remember that the data collection relates to your experiences and perspectives in the development, clinical validation and commercialization of DTx, not to any work in at particular business or personal data.

You may decline to participate/withdraw from the study at any point. You do not have to answer any question you are not comfortable with. Transcripts and notes from the focus group discussions or in-depth interviews will be made available for review upon request.

7. If biological samples are taken, what will be done with my samples? *(Please include this only if applicable. Please provide details, such as amount of saliva/ tissues and type of tissues or secretions, etc.)*

N.A.

8. How will my privacy and the confidentiality of my research records be protected?

NUS researchers and our collaborator at Université du Québec à Montréal (UQAM), Canada, will be involved in data collection, transcription and de-identification, having access to personal data (i.e., names and contact information).

Personal data will only be collected for the purpose of obtaining consent as required in this form, for transcript review, and to provide you with information after participation, but not to be used in a publication or presentation. All data collected will be kept in accordance to the University's Research Data Management Policy.

To protect your identity and the confidentiality of your data, you will always be identified by an alphanumeric code. This code associated with your name will only be known to the project leader and team members. No publication or conference presentation about the research (including the theses and dissertations of student members of the team, as the case may be) will contain any information that could identify you unless you give your explicit consent.

The research data from this study will be kept for a minimum duration of five (5) years or the minimum of duration of retention period as specified by the IRB, whichever longer. Personal data will be discarded upon the completion of the research.

9. What are the possible discomforts and risks for participants?
None.

10. What is the compensation for any injury?
No study-related injury or compensation are expected. However, if you follow the directions of the PI in charge of this research study and you are physically injured, the NUS will pay the medical expenses for the treatment of that injury. By giving your consent, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

11. Will there be reimbursement for participation?
No remuneration or compensation is offered at the end of your participation in the project.

12. What are the possible benefits to me and to others?
There is no direct benefit to you by participating in this research study. However, the knowledge gained may benefit the public in the future.

13. Can I refuse to participate in this research?
Yes, you can. Your decision to participate in this research study is voluntary and completely up to you.

In the event that you have decided not to participate in this research, your prior or on-going involvement with our study team in other studies will not be affected.

14. Whom should I call if I have any questions or problems?
Please contact the Principal Investigator, Co-Principal Investigator or a member of the study team for all research-related matters and in the event of research-related injuries.

For an independent opinion regarding the research and the rights of research participants, you may contact a staff member of the National University of Singapore Institutional Review Board (Attn: Dr Chan Tuck Wai, at telephone (+65) 6516 1234 or email at irb@nus.edu.sg).

Consent Form

Protocol title: Comprehending the Economic Value Drivers for Digital Therapeutics

Principal Investigator with the contact number and organization:
Professor Dean Ho, (+65) 6601 7515, The N.1 Institute of Health, NUS

Co-Principal Investigator with the contact number and organization:
Yoann Sapanel, (+65) 96 48 49 62, The Institute for Digital Medicine (WisDM), National University of Singapore

Collaborator's Co-Principal Investigator:
Professor Martin Cloutier, (+1) 514 987 3000, Université du Québec à Montréal (UQAM), Canada.

I hereby acknowledge that:

1. I have agreed to take part in the above research.
2. I have received a copy of this information sheet that explains the use of my data in this research. I understand its contents and agree to donate my data for the use of this research.
3. I can withdraw from the research at any point in time by informing the Principal Investigator. If I am taking part in a group interview, and if I am to withdraw my participation, my data will not be discarded as it would disrupt the flow of the data content collected as part of the discussion. However, the same privacy and confidentiality ethical dimensions will be maintained for the collected data I will have provided.
4. I will not have any financial benefits that result from the commercial development of this research.
5. I agree to the audio-recording of my participation in the research.

Name and Signature (Participant) Date

Name and Signature (Consent Taker) Date

Appendix 2E. Consent form to participate in a research study (GCM Step 2)

INFORMATION AND CONSENT FORM

Research project title
Comprehending the Economic Value Drivers for Digital Therapeutics

Research leader
Martin CLOUTIER, Professor, Université du Québec à Montréal (UQAM)

Research team members
Professor Dean HO, (+65) 6601 7515, The Institute for Digital Medicine (WisDM), National University of Singapore

Yoann SAPANEL, (+65) 96 48 49 62, The Institute for Digital Medicine (WisDM), National University of Singapore

Dr Smrithi VIJAYAKUMAR, (+65) 83 42 02 05, The N.1 Institute for Health, National University of Singapore

Funding agency: Nil

Preamble

We invite you to participate to a research project.

Before accepting to participate in this project, please take the time to understand and carefully consider the information that follows. This information and consent form explains the purpose of the study, the procedures, the benefits, the risks and disadvantages as well as the individual resources to contact if necessary. If there are any words or sections that you do not understand or that do not seem clear, please do not hesitate to ask us questions or to contact the project leader or research coordinator.

Project Description and Objectives

Digital therapeutics (DTx), also known as evidence-based therapeutic treatments powered by high-quality software, are expected to influence health care delivery and its consumption across the globe. DTx are said to be the "next paradigm" of modern health care. There is indeed emerging clinical evidence that DTx can prevent, manage, or treat a spectrum of medical disorders and diseases. However, their capacity to provide economic value is not well established, an important consideration in payers' reimbursement and pricing decisions resulting in an important knowledge gap. The factors driving the DTx economic value have also not been thoroughly researched, neither in terms of what are they nor how they should be considered.

In keeping with this gap in understanding, in this research study, we examine how various factors driving the DTx economic value, are considered and perceived among stakeholders

involved in the DTx development, evaluation and commercialization.

Nature and Duration of Your Participation

Participation in the written and individual data collection step of the research consists of three tasks on an online portal that you will access through a secure link. Upon recruitment, a member from our study team will approach you to provide you with access to the online specialised and encrypted portal (Groupwisdom). (Total time approximately 60 minutes):

Task 1. A sociodemographic questionnaire will be used to collect non personal information, including demographic and professional background information from participants. (takes approximately 5 minutes).

Task 2. Sort into virtual piles a series of numbered items following specific instructions. This will be anonymous, digitally coded (takes approximately 30 minutes).

Task 3. Rate the same items as for Task 2, for two scales (relative importance; relative indication as to the use of these factors are considered). This form will be digitally coded (duration approximately 25 minutes).

It is important to remember that the data collections relate to your experiences and perspectives, and not to any work at a company or any personal data.

Advantages

You will not personally benefit from participating in this study. However, you will have contributed to the advancement of scientific knowledge regarding the economic dimensions of DTx. The research results and practical findings that emerge after the study is completed may help to advance your thinking in relation to the study topic.

Risks and Inconveniences

There are no risks or inconveniences in participating in this research.

Compensation

No remuneration or compensation is offered at the end of your participation in the project.

Confidentiality

It is understood that all information collected is confidential. Only the research team members (Martin Cloutier; Dean Ho; Yoann Sapanel, and Smrithi Vijayakumar) will have access to it. Your research data and consent form will be stored separately at the office of the project leader or on a secure UQAM institutional server for the duration of the project. To protect your identity and the confidentiality of your data, you will always be identified by an alphanumeric code. This code associated with your name will only be known to the project leader and team members. No publication or conference presentation about the research (including the theses and dissertations of student members of the team, as the case may be) will contain any information that could identify you unless you give your explicit consent. All material that is no longer required for the conduct of other projects will be securely destroyed. Research data will be destroyed five (5) years after the last scientific publication.

Voluntary Participation and Right to Withdraw

Your participation in this project is voluntary. This means that you agree to participate in the project without any external coercion or pressure. It also means that you are free to terminate your participation at any time during the course of this research, without prejudice of any kind, and without having to justify your decision. In this case, and unless you have given verbal or written instructions to the contrary, the documents, information and data concerning you will be destroyed.

If you decide to withdraw from the study, your decision will not affect the quality of the services to which you are entitled in the context of your activities at National University of Singapore or the Université du Québec à Montréal.

The project leader may terminate your participation, without your consent, if he or she believes that your well-being or that of other participants is compromised or if you do not comply with the project's guidelines.

Secondary Use of Data

Your research data will be anonymised and kept for five (5) years after the last scientific publication at the end of the project. We may wish to use it in other similar research projects. These research projects will be evaluated and approved by a Research Ethics Board at UQAM before they are completed. Research data will be stored in a secure place. In order to preserve your identity and the confidentiality of the research data, you will be identified by a code number. You are free to refuse this secondary use.

☐ I agree that my data may be used in other research projects
☐ I do not want my data to be used in other research projects

Questions Concerning the Research Project?

If you have any further questions concerning your participation or the study itself, you may contact the team members responsible for the project:

Martin Cloutier, Ph.D., Professor ESG UQAM; Email: cloutier.martin@uam.ca
Yoann Sapanel, Head, Innovation, The Institute for Digital Medicine (WisDM), NUS,
Email: yoann@nus.edu.sg

The research ethics review committee involving human subjects (CIEREH) has approved this research project in which you are involved. If you have any ethical concerns or complaints about your participation in this study, and want to speak to someone who is not on the research team, please contact the coordinator of CEIREH at UQAM: ciereh@uqam.ca or 001 (514) 987-3000, extension 7753.

If you have any questions about your rights as a participant in this research project or if you have any complaints, you can contact the University Ombudsperson's office at UQAM; ombudsman@uqam.ca or: 001 (514) 987-3151.

Acknowledgements

Your collaboration is essential to the realisation of our project and the research team wishes

to thank you. If you would like a written summary of the main findings of this research, please add your details below.

Informed Consent

I acknowledge having read about and understood the present research project, including the nature and extent of my participation as well as the potential risks and disadvantages to which I will be exposed, as indicated in this consent form. I have had the opportunity to ask questions concerning the various aspects of the study and to receive answers to my satisfaction.

I, the undersigned, voluntarily consent to participate in this study. I understand that I can withdraw at any time without prejudice of any kind. I certify that I have been given the time needed to make my decision.

I would like to receive a summary of the project results: YES ☐ NO ☐

A signed copy of this consent form will be given to me.

_____
First Name, Last Name

_____
Signature

_____
Date

Declaration by the Researcher

I, the undersigned, hereby declare that:
(a) I have explained the terms of this form to the signatory;
(b) I have answered the questions he has asked me in this regard;
(c) I have clearly indicated to him that he is free to terminate his participation in the research project at any time, as described above;
(d) I will give him a copy of this form, signed and dated.

_____
First Name, Last Name

_____
Signature

_____
Date

Appendix 2F. Consent form to participate in a research study (GCM Step 3)

NUS Institutional Review Board (IRB)

GUIDELINES ON PARTICIPANT INFORMATION SHEET & CONSENT FORM
(For Social, Behavioural and Educational Research studies)

1. Protocol title
Comprehending the Economic Value Drivers for Digital Therapeutics

2. Principal Investigator and co-investigator(s), if any, with the contact number and organization:

Principal Investigator:
Professor Dean Ho, (+65) 6601 7515, The Institute for Digital Medicine (WisDM), National University of Singapore

Co-Principal Investigator:
Yoann Sapanel, (+65) 96 48 49 62, The Institute for Digital Medicine (WisDM), National University of Singapore

Co-Investigator:
Dr Smrithi Vijayakumar, (+65) 83 42 02 05, The N.1 Institute for Health, National University of Singapore

Collaborator's Co-Principal Investigator:
Professor Martin Cloutier, (+1) 514 987 3000, Université du Québec à Montréal (UQAM), Canada.

3. What is the purpose of this research?

You are invited to participate in a research study. This information sheet provides you with information about the research study. Professor Dean Ho's team representative will also describe this research to you and answer all of your questions. Read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Digital therapeutics (DTx), also known as evidence-based therapeutic treatments powered by high-quality software, are expected to influence health care delivery and its consumption across the globe. DTx are said to be the "next paradigm" of modern health care. There is indeed emerging clinical evidence that DTx can prevent, manage, or treat a spectrum of medical disorders and diseases. However, their capacity to provide economic value is not well established, an important consideration in payers' reimbursement and pricing decisions resulting in an important knowledge gap. The factors driving the DTx economic value have also not been thoroughly researched, neither in terms of what are they nor how they should be considered.

In keeping with this gap in understanding, in this research study, we examine how various factors driving the DTx economic value, are considered and perceived among stakeholders involved in the DTx development, evaluation and commercialization.

4. Who can participate in the research? What is the expected duration of my participation? What is the duration of this research?

All stakeholders involved in the DTx development, evaluation and commercialization, especially engineers, clinicians, commercialization leaders, health technology assessment experts and payers. Participation will comprise a 60-minute focus group discussion.

5. What is the approximate number of research participants involved?

15-20 participants, including NUS and WisDM staff.

6. What will be done if I take part in this research study?

Upon recruitment, a member from our study team will approach you to invite you to a scheduled focus group discussion. The group discussion will begin with a welcoming brief overview of the research and its objectives. A sociodemographic questionnaire will be used to collect non personal information, including demographic and professional background information from participants.

You will be invited to a debriefing of the study results, which refers to the data collection and analysis of potential factors that may influence the economic profile of digital therapeutics by the study team. You will be invited to share your thoughts on these findings and to engage in a discussion with other participants. These discussions will help establish the external validity of results.

With your permission, the researchers would like to make an audio recording of the group discussion. The purpose of this recording is to allow the verbatim transcription. We ask that you do not identify yourself during the recording of the group discussion. Once the audio transcript has been made, the audio recording will be destroyed. However, the transcript will not identify you. Participation in this group discussion implies that you commit to respecting the confidentiality of what is shared by the other participants, not to identify by name people with whom you are in contact, nor to share information that would allow the group members to identify them. It is important to remember that the data collection relates to your experiences and perspectives in the development, clinical validation and commercialization of DTx, not to any work in at particular business or personal data.

The group discussions serve to share ideas among participants in a flexible manner and provide an open forum for a free-flowing discussion among participants. Everyone speaks voluntarily and the role of the facilitators is to ensure that the discussion is orderly, and that it allows for exchanges around follow-up questions as the discussion progresses.

You may decline to participate/withdraw from the study at any point. You do not have to answer any question you are not comfortable with. Transcripts and notes from the focus group discussions will be made available for review upon request.

7. If biological samples are taken, what will be done with my samples? *(Please include this only if applicable. Please provide details, such as amount of saliva/ tissues and type of tissues or secretions, etc.)*
N.A.

8. How will my privacy and the confidentiality of my research records be protected?
NUS researchers and our collaborator at Université du Québec à Montréal (UQAM), Canada, will be involved in data collection, transcription and de-identification, having access to personal data (i.e., names and contact information).

Personal data will only be collected for the purpose of obtaining consent as required in this form, for transcript review, to provide you with information after participation, but not to be used in a publication or presentation. All data collected will be kept in accordance to the University's Research Data Management Policy.

To protect your identity and the confidentiality of your data, you will always be identified by an alphanumeric code. This code associated with your name will only be known to the project leader and team members. No publication or conference presentation about the research (including the theses and dissertations of student members of the team, as the case may be) will contain any information that could identify you unless you give your explicit consent.

The research data from this study will be kept for a minimum duration of five (5) years or the minimum of duration of retention period as specified by the IRB, whichever longer. Personal data will be discarded upon the completion of the research.

9. What are the possible discomforts and risks for participants?
None.

10. What is the compensation for any injury?
No study-related injury or compensation are expected. However, if you follow the directions of the PI in charge of this research study and you are physically injured, the NUS will pay the medical expenses for the treatment of that injury. By giving your consent, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

11. Will there be reimbursement for participation?
No remuneration or compensation is offered at the end of your participation in the project.

12. What are the possible benefits to me and to others?
There is no direct benefit to you by participating in this research study. However, the knowledge gained may benefit the public in the future.

13. Can I refuse to participate in this research?
Yes, you can. Your decision to participate in this research study is voluntary and completely up to you.

In the event that you have decided not to participate in this research, your prior or on-going involvement with our study team in other studies will not be affected.

14. Whom should I call if I have any questions or problems?

Please contact the Principal Investigator, Co-Principal Investigator or a member of the study team for all research-related matters and in the event of research-related injuries.

For an independent opinion regarding the research and the rights of research participants, you may contact a staff member of the National University of Singapore Institutional Review Board (Attn: Dr Chan Tuck Wai, at telephone (+65) 6516 1234 or email at irb@nus.edu.sg).

Consent Form

Protocol title: Comprehending the Economic Value Drivers for Digital Therapeutics

Principal Investigator with the contact number and organization:
Professor Dean Ho, (+65) 6601 7515, The N.1 Institute of Health, NUS

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I hereby acknowledge that:

1. I have agreed to take part in the above research.
2. I have received a copy of this information sheet that explains the use of my data in this research. I understand its contents and agree to donate my data for the use of this research.
3. I can withdraw from the research at any point in time by informing the Principal Investigator. Given that I am taking part in a group interview, if I am to withdraw my participation, my data will not be discarded as it would disrupt the flow of the data content collected as part of the discussion. However, the same privacy and confidentiality ethical dimensions will be maintained for the collected data I will have provided.
4. I will not have any financial benefits that result from the commercial development of this research.
5. I *agree / do not agree** to the audio-recording of my participation in the research.

**please delete as appropriate*

Name and Signature (Participant) Date

Name and Signature (Consent Taker) Date

Appendix 2G. Semi-structured interview guide

Hi! Thank you for joining us to discuss DTx and the factors that influence their potential economic benefits. My name is Yoann Sapanel, and I am from the National University of Singapore. Part of the research study team, we also have Dr Smrithi, part of the National University of Singapore and Prof. Cloutier, from the University of Quebec in Montreal.

You've been invited based on your experience in developing, clinically validating, or implementing digital health technologies, particularly DTx. Today's discussion focuses on factors influencing the economic benefits of DTx.

Informed consent: Before we begin, let's review the ethical aspects of this research. You received the Information Sheet and Consent Form via email. We want to review the importance of the contents from the Information Sheet and Consent Form. We want to ensure that you understand the purpose of the research, the protection of your privacy and the confidentiality of the research records, that there are no possible discomforts and risks, that there is no remuneration or compensation for participating, that benefits are indirect for taking part in the research for the advancement of knowledge; that the interview will be audio recorded only; and that you can withdraw from the research at any point in time by informing the Principal investigator.

Note: Ensure participant comprehension of the Information Sheet and Consent Form.

Please note that we are audio recording the session to ensure that we do not miss any of your comments. We will be on a first name basis today, and we won't use any names in our reports. You may be assured of complete confidentiality. So, let's get started!

To provide a bit of context, the current technology development process involves a large number of individuals, including researchers, engineers, clinicians, and health technology assessment experts, to name a few. Numerous factors at each stage of this tech. development process, may have an impact on how the technology delivers value, particularly economic value, when it reaches the hands of end users, often the patients.

As a result, we'd like to solicit your feedback today on the factors that, in your opinion, may impact DTx ability to deliver economic value at each stage of development. It involves factors that can affect costs, resources, and the clinical efficacy of the solution.

There are no wrong answers but rather differing points of view. Keep in mind that we are equally interested in factors that might have a negative or positive impact on the economic benefits of DTx. The discussion will assist us in filling a research gap by describing all key factors driving DTx economic value across the DTx development life cycle.

Opening Question

1. Based on your experience, what are the factors that might influence digital health technologies' ability to deliver economic benefits from inception, development, clinical validation and implementation?

Note: Ask participants if they need more context and/or clarification. If so: the economic benefits of any solution are mostly determined by two aspects: firstly, the solution's ability to improve clinical outcomes for patients, and secondly, the potential costs linked to its implementation. That's why we should consider factors that can impact both the solution's effectiveness in delivering clinical outcomes and the costs involved in achieving those results. Ultimately, these factors can be either enablers or barriers for DTx in delivering economic benefits.

Follow-up Questions

We are going now to look at specific factors at each step of the DTx development process, from inception, clinical validation to implementation.

Note: Clarify the key distinctions between digital health solutions/technologies and DTx. Note that this study considers all DTx applications, spanning all therapeutic areas and delivery mechanisms (e.g., mobile apps, web-based systems, and virtual reality platforms).

a. Phase 1 – DTx inception and development: if we only consider the inception and development phases of a DTx, what early factors could either enable or hinder its ability to deliver economic benefits? What might be some overlooked factors during the DTx inception and development phases and that you feel could be opportunities?

b. Phase 2 – DTx clinical validation: if we only consider the clinical validation stage of a DTx, what factors at this stage could either enable or hinder its ability to deliver economic benefits? What might be some overlooked factors during the clinical validation stage that you feel could be opportunities?

c. Phase 3 – DTx implementation: if we only consider the implementation of a DTx, what factors at this stage could either enable or hinder its ability to deliver economic benefits? What might be some overlooked factors during the implementation of a DTx and that you feel could be opportunities?

2. What factors are unique to DTx compared to other digital health solutions?

3. Of all the factors or potential drivers of economic value, we've talked about, what are the most important to you? and why?

Ending Questions

4. What advice would you offer to someone who begins their DH solution building and/or implementing journey?

5. Have we missed anything? Are there additional considerations or factors that could impact the economic profile of digital health technologies, and/or DTx? Is there anything else you would like to emphasize or mention on this topic?

Wrap up, thank you and next steps.

Appendix 2H. Semi-structured interview transcripts

PARTICIPANT: #1

Topic: GCM DTx Study
Interview date: Sep. 19th 2023
Location: SFAH Auditorium, Singapore
Time: 12pm
Interview type: Face-to-face in-depth interview
Participant Profile: Engineer involved in DTx development and validation, with close to 10 years of experience

Data	Insights
Yoann: Let's start with a general overview of what's your experience across the different phases of the DTx development (from inception, development, clinical validation to implementation). Participant: Okay, so from the engineering perspective, there is still not a structured way on how to look for real unmet needs, and how to incorporate the challenges that are coming up. You know, so at the innovation stage is really kind of free for all you can do whatever you want, unless there is a you know, look at the issues that you know, are even personal interests, unless there is a clear mandate from the top. I can see only the influences that are coming you know from the grants, but overall there's not a good, and to some extent it's not a negative thing, to some extent, this is how you want your innovation to happen, a little bit of a bottom up, but it also means that there's a lot of innovation that is not a good match for further development, or maybe it is fine for further development, but it fails in the market. So that's definitely something that I can see. I can start with that. Yoann: So just to explore further, to what extent do you think that this maybe lack of clear validation upfront, might impact the overall ability of your solutions, being a digital health solutions or DTx, to potentially deliver economic benefits down the road? Participant: Yeah, for sure, definitely. I think one of the reasons is that there is no clear mandate. I mean, there are mixed KPIs for the current team. One of them is to continue foundational research towards manuscripts, publications and even our ideas that are supposed to address unmet needs and reach the markets, on the way there, they are still have to fulfil the academic KPIs, which is publications, publications, publications, grants, presentations, things like that which are, they add slightly a bit of a skewness to how things are being developed and maybe that is very, you know, specific to the profile of the of the current team, in particular. I also mentioned that there are no clear frameworks for how to include this downstream elements	Yellow= potential economic driver factor Green= other consideration ability to address an unmet needs [a real one], and validating early that you are addressing an unmet needs external influences early in the process

in the early innovation, but there are actually, I've just read the paper or part of the paper that mentioned that there are over 150 frameworks for digital health implementation, 150!! So it's not the lack of frameworks, per se, but maybe this is the frameworks are not appropriate or frameworks are not implemented. Maybe there's not enough knowledge about that. I would say if you have 150 they cannot all, you know all of them talk about the original elements, they must overlap. So clearly, even for the people that were developing those frameworks, and they were not aware of the others or they chose not to include them and so the problem might be somewhere else….	Follow an evidence-based theories for the DTx development, and using the right framework
Yoann: And on this framework, let's focus on the inception of initial DTx, are you using any specific framework that may be out there, that maybe helps you guide the teams towards the right kind of solution to address the unmet needs, or that you consider as a best practice.	Tech development key principles, such as co-creation, how patients are involved in the development,
Participant: We don't use a specific framework, but we are guided by several principles. One of them is to co-create so include both the physicians and patients in the technology development. So either do behavioural research with the patients, either research the physicians and physicians, include them in the discussion and even not only the co-creation of the solution, but later on in the operations of the solutions. So including this, this co-creation itself takes different forms. It's been evolving in how we approach it. So far we have not included patients as a developer, so the technology we have been more we've been looking at more kind of insights as to their attitudes, etc. But they have not been on board of co-creating which might change in the future. That's kind of a big trend... And it's who knows, how it's gonna pan out long term, but this is again, thanks to the academic character that gives us a lot of time to even do this pre-development, or this inception stage, sensemaking of the of the context. So that's there will be two big principles, other principles that are salient, but also more present is where the funding is and what are the interests of the funding agencies which in parts represent the implementation, well, downstream implementation interests and can support the downstream implementation in that sense. So that's another one. And then obviously, what it's technically possible, there's definitely a pursue of technical frontier but that is only one of the considerations…	How funding drives the interest and shape the development and priorities of the team/ the tec. Tech complexity and possibility, close to the tech. frontier
Yoann: Maybe now if we again, if we take a step back, from your experience, have you seen any factors that might contribute in one way or the other, more as an enabler or, as a potential buyer, might contribute to the ability of digital health solutions to deliver economic values?	How tech. light is the solution Interoperability
Participant: I believe that technology doesn't have to be complex, and actually keeping technology light might help with its providing economic value because the cost of rolling it out, you know the change management might be lower if the technology is designed in a way that is interoperable, adaptable, and if it doesn't cause major changes or it's not disruptive to current workflows and processes. Despite disruptive innovation, something so appealing, it does not seem to be the easiest model for healthcare… And quite often this initial induction cost is too high for it to provide economic benefits. So yeah, keeping it light keeping the flexible, technology, adaptable, in this kind of	Level of disruption to current workflow, protocols and processes. initial induction cost alignment with tech. standards especially in healthcare

bigger level. And then looking more into the different stages, I think it's quite important to develop the technology in the technical standards that are already or will be supported to avoid the redevelopment, which definitely can be quite costly. And there are a couple of standards in healthcare, unfortunately, there's not only one for data interoperability. And kind of the same with the privacy by design, and getting get ready for the regulatory oversight. So that's kind of more from the development perspective, maybe savings for the developers. But for the for the payers and it would be also addressing the real bottlenecks. And yeah, which at times might not be in, from the patient perspective, it's quite often in the operations, which might steer away from the DTX per se, but there will be areas that are more ready for DTx addressing real bottlenecks, and there will be areas that the bottlenecks are in a very different places, it's about identifying which spaces are more ready for DTx.	(privacy by design, regulatory, security, etc.) absence of standards and guidance on data interoperability DTx addressing real bottlenecks
Yoann: So just to summarize what you just mentioned, one is about the tech complexity as one of the elements that will have further down different implications, one is good tech complexity, two is the integration of the tech to existing standards and systems, and three, privacy and data aspects that might influence it economic benefits, and last one about the market readiness, I guess?	market fit (indication is ripped for DTx) degree of optimization of current operations
Participant: I would say market fit, and at that one can be also broken down in a couple of more things. One is the witch disease indication spaces is ripped for DTx to be rolled out in, and which, actually, this cost benefits might come from, from optimization of the operations or any other type of activity in that particular area, it can be pharmaceutical solution, you know, it can be a lot of other stuff. And another factor would be where the DTx can offer have healthcare economic benefits is where there is no alternatives. So, if there are no alternative treatments, and DTx is the only one, obviously, then that needs to be also put against the QALYs and what not. But perhaps that's the way to think about it.	absence of alternatives/ the comparator QALYs improvement and impact
Yoann: So, market fit will be the fourth element. So I have the tech. complexity, the overall tech interoperability, the privacy aspects, market fit as the fourth one.	right solution to solve the right problems
Participant: I mean, we can also throw in any regulatory framework, but I mean, that's from kind of cost effectiveness for the developers, as soon as you can align with what your solution will need to satisfy anyway, then that's the better but from the healthcare system, I can think about like, just speaking the right solution to solve the right problems.	
Yoann: Out of the elements mentioned, do you see additional factors that clinicians that might consider?	
Participant: In terms of the costs?	
Yoann:	trial design

From the clinician perspective, are they considering the same or different factors? Participant: you mean for them to adopt the technology? For them, when they are thinking about the cost effectiveness of the DTx? Yoann: For them when they are thinking about DTx validation, such as the trial design you mentioned, do you think that they have the same five factors in mind, or different ones? Participant: I've been trying to think about the cost dimension, but from the physicians perspective, it's definitely cost in the sense of the time and during the whole time HCP time, the clinics time, and you know, avoiding additional complexities in the service that they provide to the patients if they are to use additional technologies. So I think the time and the utility that might be on top of the minds. And the second thing would be, what do they actually do with any analytics provided about the patients? So if the DTx is set to improve ABC, is ABC also what the physicians are interested in from the clinical perspective? Is it something that they can act on or is it something that is not really relevant and sometimes it's also about the volume of information, but they don't have necessarily use for. Yoann: How the profiles and characteristics of the patients also influence DTx ability to deliver economic value? Participant: If the patient's perceived value in the DTx or treatment, any other treatment even, they will adhere to it. I think that's one of the principles and if they don't, there will be quite a high attrition. So you will have individuals that are generally more receptive and more open and ready to perceive value in these solutions. And you will have individuals that may try but are going to drop and that it can be affected by a lot of things. So I don't want to put it only on you know, their personas or their openness to the solution or not because how you know our willingness to pay so called a willingness to adhere. It's going to relate or a lot of different factors, both of the solution and of the individuals but yeah, there's a lot of variation that's for sure. Yoann: I would want to try to look these factors, phase by phase and see if based on your experience, if there are any additional specific factors that you have seen that are maybe already considered or that may be overlooked. So as I was saying earlier, I look at typically the first phase, as the inception phase, as well as the issue of development that might be more engineering driven, then the phase two will be about the clinical trials and clinical validation, … Participant: Okay, let's go phase by phase. Yoann:	HCP and clinic times (in short HRU) Perceived utility Relevant of the solution patient's perceived value Adherence/ high attrition Patient's readiness or willingness to a DTx [willingness to adhere] designing for implementation how is the technical solution developed, and considering the different costs elements,

Let's go on to the first one. So if we only consider this initial inception and development phase or phases of a DTX, what are some of the early factors that could be potential enabler or barriers in the ability of a DTx to deliver economic value?	such as computational power, data storage, infra., etc. implementation factors
Participant: So definitely designing for implementation that can improve the cost benefit ratio later on. Another factor would be how is the technical solution developed, is it developed with the cost in mind? So for example, you know, the computational power required for the solution, the data that is that are required for the solution and the storage of the data. So is it big data? It's big data, things are gonna add up in terms of the costs. And this is also something that is not very well controlled by the developers in the future, so if there, you know, you're basically touching a little bit on some micro economic developments, potentially where you are semiconductor struggles, etc for example. So, yeah, so to some extent, we cannot assume that things will only get cheaper over time in terms of the cost, data, network, etc. So yeah, so those two things for sure. At the inception, yeah, the implementation factors and technological complexity.	technological complexity Nature and complexity of the development costs, solution architecture
Yoann: You didn't want to influence you too much, but when you mentioned the role of patients involved early on, and I know knowing you, and how this is important to you, and your wish probably of wanting to do more, is this like one of the potential overlooked factors by the community and the importance of adding patients individually?	Participation and involment of patients through the DTx development
Participant: I mean, yes. Or no, I think in terms of the implementation factors, yes. But at the time of the inception, yes, you also want to find the right problems to solve. And I think for that patients are very useful. But there's also a cost to involving patients. So your development costs are going up. If you want to get the patients involved at that stage, especially as for example, in Singapore, there is very little patient advocacy. So you're basically on your own, trying to reach to the community, and fishing for insights! So involving patients, overall it's a good idea, but how much of the cost benefit it will provide, I'm not entirely sure at that stage, I'm not entirely sure maybe there is room to do some pivots later on…	Implementation factors can be a category on itself Agile development and ability to MVP, iterate and pivot
Yoann: In this room, this is one of your whenever can I eliminate anything else that you see in this initial conceptions and the different stages or phases that might be overlooked? That could be done differently, or…	
Participant: I mean, you also have your…you know, including the physicians, but I still put it under the implementation factors. This is something that you need to do throughout, you know, and again, you can come up with some sort of MVP first and then get your physicians and patients involved. So to me this inception and development stage, it's a little bit more focused on technical capabilities and designing your solution architecture and this is where you can make some decisions that will make things cheaper or more expensive and you can manoeuvre some of those trade-offs, or balance.	Study design + quality of the study/ information collected Level of participation from the physicians
Yoann:	

If we move on to the next phase of a clinical trial equalizations again, this if we only consider this space and see any unique and specific factors that might play a role in future ability of a DTx to deliver value?	Early feasibility validation/ fit to a potential workflow and environment [agile approach?]
Participant: Yeah, for sure. So one is your study design. How insightful how much of the information can you get from the dollar amount and number of patients that join. That's one, how just literally, like, almost quantity wise. The other one would be quality wise, what type of information I can get how well it's aligned with the regulatory expectations and the market expectations to avoid "You're not invented here", for example. The third thing is including the physicians, trying to also gauge some of the implantation factors. So get, as you know, we do a lot of feasibility testing first to even see if this is going to fit into the workflow. So again, your implementation factors are quite big, but at the same time, we tried to collect also some early efficacy information and things like that, relatively small trials and collect a lot of insights and not necessarily on the efficacy yet.	Early small trials, step by step approach, collect information of quality/ insights Gauge early the potential interoperability
But you can already get so much information both from the in terms of the interoperability in terms of patients thoughts, physician thoughts, here you can really get a lot of stuff from these stakeholders within this public system or that are already you know, it's not as a product at the market, but as the medical solution [at the market].	Ability/ impact of real world evidence and real word data?
Yoann: Anything that you wish we could do differently? That the clinical team could do differently?	Representativeness of the recruited participants in trials to the population?
Participant: Well, there's also the real world evidence and real world data which we don't really do much so that's, you know, moving from your clinical trials to the validation with people in the community, so it's something that we touched on with some of the solutions that don't have the medical designation, and, you know, those trials also allow to incorporate a bit more of the context, also the studies.	
Another thing that I can add for both real world evidence and for clinical trials is to be very intentional about the recruited populations and the representation in those populations because they should represent the individuals that the solution is designed for. So again, get more of that insights from the actual target group rather than your "perfect patients."	Validation of the solution among a heterogeneous profile of participants who are representative of the population the solution is designed for
Yoann: Is this something you consider currently as best practice in a way in the committee? Or is it something that more likely to emerge much better in terms of like this representations of participants in our trials and studies?	
Participant: So far, I think it's a good mix in the representation that we have integrate in CURATE.AI trials, I cannot speak for the others. We are a recruitment criteria. We usually start with quite broad recruitment criteria and we may narrow down but it is part of the factors and it's part of the conversation on how to, again balance, you know, getting your results and insights about the technology from relatively homogeneous group that allows us to make conclusions about the technologies and efficacy and also have the most	

representative group of patients that the solution is designed for, which is much more heterogeneous. Yoann And this is for kind for your team. What about the rest, from what you have seen across markets? US or in Europe, and research groups overseas. Participant: So it really depends it varies from group to group, but, for example, for solutions that are entering Asian markets there are requirement to do the population study in Asia, and even the teams that pride themselves in having extensive research behind their solution, they are not necessarily tested out in the Asian population. DTx is actually context is so important. And that's part of the regulatory requirements, so for example, to market a product in the US you have to have 50% of the patients, from the US. It's not 50%...But this is a stipulated number of patients that are from the US that's what should be included in the trial. So that's very different setup and in that sense, I think particularly for DTx, validating with the local community is quite important before rolling out. Having said that, validation can also be done post market entry if that's your real world data, we will evidence that different ways about it, trying to understand a bit more at that stage, the kind of trial validation stage. Yoann One more question on this phase of validation. How long does it take to clinically validate a DTx, what does it take in terms of preparations and of time? Participant: There are a lot of strategies on how to do the trials and how to do them effectively and fast and that really depends on the resources that the company wants to put in. And there is a lot of innovations around trial management, actually think a lot of digital health companies either pivot to that area, they pivot out of that space. Platform solutions for remote data collection and remote trials, having your digital twins in clinical trials to serve as control so a lot of things happening in this space. I think the bottom line is how fast you can recruit your participants. That is something that can that can make it more or less cost effective if you have to recruit your participants, if it takes months, and that's a very tangible cost, and also it's quite an insight about you know, it's a little bit of your market validation... if there are recruitment issues. Yoann: let's move to the last phase, of implementation. Did you see any additional factors that might be specific to this stage? Participant: Yeah, so touching a little bit on implementation science here, but it's about finding your KOLs and the community leaders that can champion your solution and support others in adopting, taking up your DTx and that's also where you know all your prior work then for these on the alignments with the regulatory, with privacy, with policies is going to show up because that also will be required. Yoann:	Validation in the local context of implementation (pre or post market -> real world data) Cost effective trials? -> Effective trials, from a management perspective, effective participant recruitment, from a resources, IT perspective, etc. such as with remote data collection, etc. KOLs and the community leaders that can champion the solution and support others in adopting [support network?] Having key endorsers Degree of stakeholders buy-in right product market fit on the policy levels

[…] based on your own experience, what are the different aspects that can contribute to the readiness for implementations? Participant: Thing that stakeholders buy-in is the biggest one. If you want to roll out something in a public health, you need to get your public health officer or endorser to be involved and aligned and invite, involved I mean, doesn't simply mean that they were involved in a development but they perhaps were involved in setting up expectations and a checklist for your solution to you know, what, what their expectations are from any solution that they would adopt in and if they are aware about your developments that might help align it to the expectations early and also just develop a rapport with those key endorsers. I think it's also about finding the right product market fit on the policy levels, different governments have different long term plans for their countries or regions or constituencies and the more you can align with that means that you might get more support in rolling out your solution. Yoann You want to touch briefly on patient side and user side and what from their perspective, could be defined as their “readiness for implementation”? Participant: So I mean that's what I meant kind of by engaging with the community, community representatives can serve as the middle kind of layer and help with the implementation, that's quite important. The other authority that you may see for these individuals, sometimes it’s just the doctors, then it will be a different approach than looking at the community leaders. Sometimes it's you know, it's just the head of the family or you know, it's the different ways to think about it. And the other one is obviously the interface, the more difficult the solution is, the less likely people will stick to using it, and it shows up as one of the key patient expectations in Singapore and beyond from digital health, the other one is data security and privacy. Again, the work you put at the earliest stage now benefits developers. Obviously it's going to be also adjusted at the later stage, but it's just overhauling, sometimes the technical solutions architecture that can be very, very costly. Yoann We frequently stress the importance of a multi-stakeholder and multidisciplinary approach when developing, validating, and implementing digital health solutions. But to what extent are we assessing the efficiency of this ecosystem or how effectively DTx manufacturers are leveraging and engaging with the various stakeholders required throughout this process? Participant: Yeah, so one way it can contribute is to set up those guidelines for development early on and best practices. One of the issues though, is that sometimes those guidelines are not very transparent or they're not very easy to find. So you know, there is in Singapore quite a lot of ecosystem support for innovation, innovation in digital health, but it's not very clear, who are the players how is the government involved or not, what to do at what stage, even in terms of how you classify your solution from the regulatory perspective, so our ecosystem is definitely can make the journey easier and more cost-effective or making it also faster, but the more players then, a new challenge shows up which is how to navigate this… Yoann	Figure of authority, such as the doctor, community representatives, etc. Interface simplicity Security and privacy thinking early about these aspects and requirements A supportive and efficient ecosystem of…

if you take like two identical countries and teams developed the same DTx, but one in a very efficient environment, and the other one in a less efficient environment. Do you think that the cost benefits from this “efficient ecosystem” can be just marginal or really important and potentially driving new potential economic benefits?	Level of existing healthcare infrastructure
Participant: It’s a good question, I'm not entirely sure to be honest, because if you I mean, I obviously would like to say that it's the efficient ecosystem is more supportive, but it also means that there's less modes and there's more competition, for a less efficient ecosystem, there usually, you know, less guidance, but there might be unofficial sources of advice or unofficial alignments with the with the parties that are governing the space. It's very volatile though, this type of setup. So overall, it's always better if there are some clear policies of ease in terms of the regulatory, in terms of data, and then it depends from solution to solution if they also require infrastructure. Because we've seen a lot of really interesting digital solutions, digital health solutions, but digital solutions in SEA and in countries that don't have infrastructure, but these solutions are quite effective and offer value.	
Yoann So, to make sure on this last point, about infrastructure, are you saying that the level of existing infrastructure might play a role? It can be in both ways basically. You have countries like the developing markets, that might not have the right infrastructure, but because of elements, factors, etc. some of the solutions can deliver economic benefits.	
Participant: Yeah, exactly. But it really depends from solution to solution about what are the requirements. So we have Reach52, it's not exactly your DTx, but, you know, they have their offline first solution that they rely basically on the fact that there is no other way to access these patients. And then if DTx is rolled out as an OTC, again it can serve as an alternative to you know, I'm not talking about technical infrastructure, but let's say lack of healthcare infrastructure and if someone cannot reach the hospital, or go for regular clinic check-ups, healthcare access, the traditional healthcare access, this is what this type of solutions can offer more value than they would have offered in a well-developed country. Well, if someone waits at the end of the day, they will see your psychologist or psychiatrist, looking specifically at mental health.	Efficient in your evidence solution and trials design User interface Support patient engagement and adherence (e.g. behavioural nudges) therapeutic effectiveness
Yoann: You mentioned a lot of factors, right? Do you see factors that might be unique to a DTx versus a digital health solutions?	value to the physician health care system
Participant: There are two things. DTx needs evidence! So you want to be efficient in your evidence collection, and to make that evidence as relevant as possible. So that's your second stage, so the clinical validation of DTx, validation, and that is quite unique to DTX compared to some other solutions and or healthcare apps. And the other one is that DTx are patient facing. So if they are patient facing it's really means they have to offer really good service in terms of the user interface, in terms of your behavioural nudges. So they the customer can be quite demanding and DTx have to fulfil that because their effectiveness relies on it. So not only you know their cost effectiveness, but the therapeutic effectiveness relies	solution architecture degree of patient centricity interface

on it so it's important to a good job. I'm actually going later today to [name of company] digital health events and I was chatting to [name of the contact] how [name of the company] evolved and of course it's their marketing and behavioural insights that allow them to now offer a services, kind of consultancy services in the healthcare space, because that's the part that is so fundamental for DTx. And then obviously, DTx still needs to offer value to the physician health care system, etc. But maybe that is slightly less unique about DTx… Yoann: Second last questions, out of the factors we discussed, if you have to pick and choose the two or three, are the most critical from your experience? Participant: Okay, so as an engineer, I think the solution architecture is critical. Like if you get this one wrong, it's going to be so difficult to provide your service at cost. And obviously, there are caveats because it depends was the WTP but maybe even have huge margin but of course you always wanted as big margin as possible and that requires the solution to be designed in a smart way, I mean efficient from a technical standpoint, efficient way. And then the second thing is the patient centricity. So this perceived economic value that the patients see in the solution, that's the game changer. How do you achieve that is it through amazing interface and your social media campaigns or is it you know, going by physician endorsement and the healthcare system endorsement. You know, what is the model? Is it OTC or is it reimbursement. At the end of the day even if it's for public or any other insurance reimbursement if patients don't perceive value they are going to stop using it. So that's going to that's going to escalate into healthcare system also not wanting to pay for something that is not effective. So patients and then you're keeping your solution architecture, light, smart, whatever that means future proof! Yoann: so yes, we've covered quite a lot! And again, thanks a lot for your time and spending time I'm sorry, I don't have drinks or anything to offer you but anything else but we have not discussed or not touched on, anything else that you want to share? Participant: I think there's one thing that we didn't touch on is that there's a lot of volatility, how the DTx field is changing and what are the expectations so there's still no clear regulatory frameworks in many of the geographies which might make all of these recommendations very difficult to implement in practice and also the customer preferences keep on changing and they have new digital interfaces, different kinds of capabilities, different type of digital habits. You know, social media, yes, it's still big, but it's changing how we interact with it. So is this the right channel? So yeah, this overall volatility, and it's not so easy to pivot and it's not very easy to follow trends for these healthcare solutions. So I think there's, there's one of the ways I tried to solve it is to keep a lot of flexibility at the deployment, while the kind of core offering is fixed so that's one of the thoughts. Then, part of this volatility is also that we have a lot of new players and non-traditional healthcare players. You have NTUC, OCBC, Ogilvie, etc. and they are all, where they are in this value chain, they can both parties that purchase these solutions, they can be channels for the solutions, but they can also be competitors and they can also be parties that are, you know, common	social media campaigns, reach out to patients, educate and convince them patient's perceived value of the DTx Absence of regulatory frameworks Solution agility to adapt to constant customer preferences or habit change

with less understanding of healthcare, they can in a way spoil the market with, you know, lesser quality, less well aligned solutions, and that's not only the new players, but just kind of the plethora of players that are in this space and trying to do stuff. I think overall volatility. Players from all the different corners of tech and medical and pharma and they're all trying to do something. And so, your customers experiences and preferences are also affected by that. [end]	

PARTICIPANT: #2

Topic: GCM DTx Study
Interview date: Sep. 19th 2023
Location: Online
Time: 2pm
Interview type: In-depth interview over Zoom
Participant Profile: HTA Expert with >15 years of experience in MedTech field

Data	Insights
Yoann: What are the factors that comes into your mind about factors that you have seen that might influence the ability of a DTx to basically deliver economic benefits? Participant: Um, yeah, in terms of factor that affects I think if you go into understanding what is the economic value, I think that for me, it's really about how much of that technology can demonstrate effectiveness. And what I mean by effectiveness is really not just demonstrating the efficacy that the technology works, but it really makes actual impact on patient outcomes. And that works matters from economic standpoint, because first of all, you have to ensure that there is a clinical impact from the patient perspective, and then how does that translate into economic value? So, I think that's the really very first factor that needs to be really very clear in terms of articulating the economic value of the technology. The second point would be on whether we are addressing an actual, medical and clinical needs. And that follows the first point, because if there is a small or medical needs, that is actually not being a priority for the, let's say, the segments that you're targeting, then the economy value itself would be very much minimal and would not be well understood. And then the third point, is really how it is going to be used in the and how it is going to be integrated in the overall clinical practice and looking at the wider ecosystem that the technology is going to impact. Yoann: What was your second point again?	Technology efficacy and effectiveness how much of that technology can demonstrate effectiveness. Real clinical impact on patient outcomes (effectiveness), and how does it translate into economic value. addressing an actual, medical and clinical needs. (real need) of priority to the patients and clinicians community integration to the clinical practice and workflow meeting the needs of the specific population that you're targeting

Participant: So I think it's really about the clinical needs. So I would say, so it's a little bit like the PICO framework, right? So it's the population right and whether how it is actually meeting the needs of the specific population that you're targeting. Yoann: So on that just maybe a follow up question, you know, sometimes it's not because there is a kind of a clinical need or unmet need, that there is a market opportunity, right? And so how do you take this into consideration so how should we early on, you know, in developing DTx, how can we validate or how should we take into considerations that, ensuring that there is maybe a clinical need? An unmet need from a patient standpoint, a clinical need but there is also a financial opportunity? Participant: It's a really important question that it's not always easy to answer. But I would say like an example that typically is being that I already see in my experience, so let's say orthopaedic surgery or knee surgery, that in the US one of the medical gap is that you know, it's very expensive to stay at the hospital and technology wise, you can actually have it done as ambulatory and therefore, that you have all these patient support programs or apps that really help the hospital to discharge the patient, just after the day of the surgery and follow up the patient thereafter, so it has a significant economic value, in terms of shortening the hospital stay and therefore cost. The patient is very happy because they don't want to stay at the hospital pay the big bill and they have the you know the comfort of their home. But if you bring the same solution in Japan, it's still a you know medical needs, but culturally patients want to stay at the hospital. They don't have anyone at home to care for them and they are not comfortable to be by themselves and they need you know, a support here, team or people behind to help them go through that journey. And the incentives that so the reimbursement actually does not encourage early discharge either. So for all these reasons then we'll although there is a gap and there is a need and that really makes sense, there is a lot of healthcare expenditure that is significant in Japan, but then if you really understand what is your target population here, you're talking about elderly patients, they don't want to be discharged early. Whereas if you are in your 40s and you have to have your knee surgery for a sports injury, for example, you would want to be discharged early than a Japanese person. So it's about understanding and defining very well what is the population that you're targeting. So not just saying that it's patients undergoing knee surgery, it's about defining exactly so maybe this is, working patients undergoing knee surgery between 30 and 60, something like that. So that's what I mean. Yoann To your point it's about not only understanding the kind of target of targeted user, but also their profiles and the context, the cultural context, it's the sum of different factors that should be very well defined or understood, right? Participant: Yes, absolutely. And the lifestyle that goes with it. Yoann	HRU and bed utilization Reimbursement level Degree of inefficiencies of the health care market (with often high health care expenditures) Comprehension of the target groups/ patients and needs, their context and profiles/ personas, lifestyle, for which the solution is developed for

So maybe now if we said this was more than understanding the overall factors, but the kind of drivers economic value DTx, I would want now to zoom in each of the kind of men three phases that you haven't already checked development. So first one is the inceptions and initial MVPs, I guess, then you have a clinical trial, and the third phase is more on the implementation deployment. So now if we focus purely on the Phase One on the inception, the initial MVPs that you have DTx and it's a phase that maybe tends to be a bit more engineering driven, typically, are there any factors that that you have seen might impact later the ability of DTx to provide economic value? Or are there factors that you wish could be more or less considered by these initial teams that are working on these initial concepts and MVPs? Participant: Yeah, no, I think that there are two things that I have seen at that early stage, that have not always has been defined. First is what is the value proposition? To whom, who's going to benefit it and clearly define it. And then the second one for me would be the comparator. And it has to be really clearly defined, even at that stage. It might not stay the same comparators throughout the development stages because things change, you know, new competition comes in in the marketplace, so it doesn't mean that it will be static. But if you don't think about your comparator early on, that is going to be very difficult later on because one of the fundamental aspects of economic value and if you're looking at the payers, is really they are making a funding or spending decision and it is always they will be funding A versus B. There is always a comparison. So you have to really position yourself and ask yourself, what is the right comparator? Is that the standard of care right now how is being done and this is your comparator, or is it a technology that is similar to yours? People don't necessarily think through very in detail, but I think it's a missed opportunity because it's going to drive exactly how it's going to be your value proposition. How would you differentiate yourself with that specific comparator? Because then you're how to demonstrate value and a significant value versus that comparator. Yoann If we move to the second phase of a clinical trial with clinical validations, it's quite an interesting to hear from you, that the point about the comparator is a point that you wish for teams might have defined super well even before going to the clinical trial. Are there any additional factors that you see at this stage of trials and clinical validations ? Obviously any factors that are maybe at least specific to this target, that can be overlooked or missed opportunities or could be opportunities to drive the economic value? Participant: Yes. So just to clarify, the clinical validation is really that you're piloting the technology to make sure that it's working in the real world, working with the clinicians in place, right? Yoann: Correct Participant: I think that this is one of the missed opportunity is probably to look at the bigger picture. It's not only about validating that your technology works and you know, demonstrates the outcomes that it is supposed to demonstrate. I think something maybe to consider is looking at the impact of the usage of	What's the alternative and comparator, TBD early (understand the current SoC). How to demonstrate value and a significant value versus that comparator. Clinical outcomes at the patient level + impact of the usage of the technology within the healthcare system. (degree of disruption and of impact of the DTx positively or negatively) HRU: healthcare resources for the clinician, for the staff, for the hospital, for the patient

the technology within the healthcare system. So because using that technology is going to disrupt the clinical routine clinical practice, you're introducing a new technology, a new way of doing this, I don't know like a surgery or a procedure. So there is going to be a disruption and how much technology is going to impact negatively or positively. Economic Value is looking at how it impacts positively and how it is going to help in terms of saving healthcare resources for the clinician, for the staff, for the hospital, for the patient. So how much of that is actually going to deliver economic value? And that is something that, again, people think afterwards when they think about the patient care path, which is defined maybe at a much later stage, and they have to look at the economic value, but it is actually a very good opportunity to already gather insights and maybe some early economic endpoints or data that is will be useful for you in the later stage of the development. I think that's certainly something that not easy to do. And then just taking some examples of robotic solution, it's going to require space within the clinic, so how much space will it required? If it's mobile, could you go transfer it from one room to another, maybe that could be a feature, thinking about the development that might be useful and delivering economic value.	collect early economic endpoints or data that is will be useful for you in the later stage of the development.
Yoann: So if we move to the next and last stage where last might have deployment implementations in a clinical practice of patients and individuals to use such Digital Health Solutions, DTx at home I guess, in the communities, are there any specific and unit unique factors at the stage that you have seen it from your experience that are going to drive basically up or down the economic benefits of the DTx?	Degree of patient adherence and retention, Usage of the solution
Participant: One of the biggest one is what you mentioned earlier is really about adherence and retention. So it's not enough just to get the doctor to prescribe it and tell the patient to use it, you have to make sure that the patient actually use it. From personal experience also, I have seen that there are a lot of digital solutions that are not used by the patient. And they are some really nice ideas in terms of features and development of capturing patient feedback, for example, but if you have a questionnaire that is 30 questions, and that's going to take 15 minutes for the patient to enter every week or every day, you know, it's not going to work. That's first, would really drive usage and the effectiveness of your technology. Taking into account again, the lifestyle and the profile of your patients, how they're going to use it. Are they digital literate enough to use your technology or do they need support. So that is something that you also have to think about and deal with in your business model accordingly, but that would significantly impact economic value would be perceived. And it's very interesting that the payers are also very interested in that. Some countries are asking, what is your usage?	Profile of the patients, are they digital literate? Support needed?
Yoann: In France like they are asking DTx each organization to share back that up with a friend a good friend, whenever they use it have a solution. So it's not like just like giving reimbursement and approvals. But it's like, you have to share back basically the adherence, usage adherence to the solutions, which is kind of really interesting because when you think about drug, you know, you prescribe a drug, but nobody's going to ask any pharma you know, what's the adherence to whatever drug that you have in the market?	readiness for implementation

Right. So it's an additional requirements, but it's definitely an important point. You know, one of the one of the factors I will say also, but has seen quite a bit in the literature is what we call this “readiness for implementations”, right, but could be from a physician standpoint, patients or at the infrastructure level, etc. It’s a contextual factors that might drive the ability of DTx solutions to deliver economic value, and I wanted to get your thoughts on whatever some of the sub-elements that you see are important when we are considering this “readiness for implementation” of any organizations. How would you define it? Participant: Yeah, so you mean how an organization is ready to deploy a digital technology? Yoann: Yes. What would be the different factors that might be relevant to assess the readiness of any organizations to be ready year for implementing a DTx? Participant: Wow, that's a very good question. So I think firstly, we'll think about the infrastructure systems, in terms of the system, in terms of technologies, whether they have the structure to actually integrate that to show technology inside the organization, so infrastructure, I will think about the resources and human resources on who would be able to use these, integrate them, how digitally savvy they would be to integrate this solution. And to what extent are they going to be able to use this and change, let’s say, the clinical protocols within this new technology? And that requires agility flexibility from that organization to change completely the protocol, to integrate new technology. So, I would say the key three factors that I have, that I have in mind. The last one, I think would be the, what one would call the interoperability. But not just technology wise, but also the how the different users of that technology would interact with each other, not just the hospital staff, but also the patient and then even also the carers. So the people who are supporting the patient like family and friends who can be involved in this digital technology. And let's not forget, also that, you know, funding is an important part also the ecosystem. So anything that the payer or the decision maker payment would require from the usage of that technology. Yoann Yeah, another important point on the funding aspect. I have a question, back to our earlier conversations we had earlier about the efficiency of the ecosystem. And I wanted to get your thoughts on that, you know, we have some ecosystems that are more or less efficient in a way on how the different stakeholders we do work and collaborate together, having access to patients, to physicians and researchers and so on. And I wanted to get your thoughts on how, how do you see this efficiency of ecosystems playing a role in DTx ability to deliver economic value? So if I take an example, let's say you have maybe Singapore as a super-efficient ecosystem, where everything is smooth, and the opposite extreme, I'm not going to mention any specific country, but you have a super	Interoperability broadly speaking (how the different users of that technology would interact with each other, not just the hospital staff, but also the patient and then even also the carers) Funding (part of a supportive ecosystem?) Relative efficiency of the healthcare provider and system in general, to benefit from any cost or time savings from the DTx, and or any gains (e.g. cost, time, etc.) might be

inefficient ecosystem in a different country. To what extent do you think it's going to translate into potential additional or less ability to drive the economic benefits of a DTx?	translated into economic benefits or value.
Participant: Yeah. So you're talking about how the efficiency of the ecosystem might impact the economic value? Yes. Yeah, no, absolutely. I think it's a super important and that, you know, links to what I was trying to say with my "interoperability", which might not be the right word, but that's what I'm trying to say is that how the different players interoperate with each other. Because if you're, let's say a decision making digital solution that can maybe save 10 minutes or the overall episode of care, if these 10 minutes are not used by hospital staff and say to no schedule another case for example, then these are 10 minutes I will be wasted and then the upcoming value will be void. Right so efficiency is absolutely critical of the efficiency of the ecosystem is absolutely critical. And even more than a clinical value, I would say because clinical value is that you actually is making an impact on the patient health but the economy value depends very much on the efficiency. And efficiency actually is one of the key factors for economy. So if you're, if your system is not efficient, then you might have the risk of voiding it. And one of the reason for that is that things are being siloed when different teams for example, are not working with each other. So when whatever is being saved in 10 or 15 minutes or let's say even 30 minutes, but if it's not translated by savings from or efficiency to another team or by the same team, then it is an economic value that is lost. And the other thing that I was thinking also in terms of efficiency and optimizing operational efficiency is on the importance of data. And that's one of the key issue in healthcare is that data is very fragmented, and because of the precautions and we are really good reasons, they are privacy laws to protect patient data. It also is a barrier to operational efficiency because without data and access to the right data, you will not be able to fully optimize your operations and again, that will have a significant impact on the economic value.	optimizing operational efficiency barrier to operational efficiency (lack of data, or access to it). Existence and impact of privacy laws to protect patient data Data availability, governance, access, etc from current healthcare organisations, and system
Yoann It's basically back to the earlier point, which is a readiness for implementations of a system, or an organisation, right? The overall efficiency might be an element to the overall readiness of any organizations to implement or to deploy DTx. Is it fair to say that? Participant: Yes, absolutely. I think that, you know, access to data and all that data is connected with the other data sources. And how does also the organization uses that data, because in many of the organization I have observed that they are sitting on the data without actually drawing insights into the data that they already have. And that can really help them to be way more efficient and cost effective…	
Yoann: You mentioned quite a lot of different factors and considerations that might influence the economic kind of profile of a DTx, and we tend to use on a day to day basis, digital health solutions, DTx, wellness type of solutions, etc.	RWE or RCT as primary source of evidence?

Do you see some factors that are unique and specific to DTx versus digital health solutions? Participant: Yeah. So I think the key difference for me between DTx and other digital solutions is about the evidence and the evidence requirements, because of choosing the category of DTx, the strategy is really going towards a medical claim and because of that medical claim, there is s a requirement to demonstrate clinical impact, so real patient clinical impact. So it would require clinical studies as well, as economic studies if the technology is also seeking funding. So that is a key difference between the DTx and other digital health solutions, which does not have that requirement. But then at the same time, they cannot make medical claims. So the key difference for me is that evidence requirement. I would say also another note is that so you did mention a lot on RWE, but I wanted to clarify is that for DTx, although let's say that there is a lot of advocacy to make RWE being accepted as a source of evidence, the reality is that still there are many countries across the world that are still not recognized, RWE, and it's as an acceptable source, that's why I was talking about clinical and obviously RCT as being still the standard of default type of evidence to be generated, both for regulatory and payers, funding perspective. So I think there has been more openness nowadays, for RWE for regulatory approvals, but when it comes to funding decisions, RWE is till only accepted as complementary and cannot be as primary source of evidence. But that's quite something again, that faces an additional burden for DTx as compared to digital health solutions. Yoann You mentioned quite a lot of different factors, when you do you your HTA, what is the 80/20 and the most important factors which you have seen that will drive economic value up or down basically? Participant: Yeah. I think the most critical one is really clinical outcomes. If you cannot demonstrate a significant clinical benefit versus the comparator, so that is, you know, the very important point that I had early on, then you can forget about the very good recommendation. The requirement is first to have a clinical outcome. So I do have a lot of technologies that coming my way where they have just similar clinical outcomes, but then hoping that with economic value, they will be able to get a good reimbursement. Unfortunately, again, funding decisions is always a choice between technology A and technology B. So they will always prioritize the technologies that demonstrate better clinical outcomes before they look at economic outcomes. So look then you look at the economic value, what are the different factors that are taken into account and unfortunately, I can't say for sure these are the criteria, but it will depend on different markets. So let's say for example, Japan for a very long time, healthcare resources have never been an important economic factor for them. But recently, there has been a little bit more of openness especially after the pandemic, if you can demonstrate that your technology can reduce the burden or workload, hospital staff, then you might have more positive look at your technology benefits. So obviously, that would be one example. So really, around the local context and the market that prioritize which of the different economic value, you should look at in general, I think that if you look at now specifically for digital health technologies, a key benefit is going to be the	Ability to demonstrate a significant clinical benefit versus the comparator Context and markets in which the solution will be deployed / implemented Engagement with continuous feedback loop with key decisions makers through the tech development/ deployment, gathering insights, market reality Well defined value proposition

user and most of the time, patient and the quality of life and being able to articulate what is the benefit of quality of life, it will help you in terms of the adoption. Not specially for funding, as quality of life is still not that high, but in terms of adoption, that will help.

Yoann:
Now, that's quite a lot of insights and elements to be considered. Maybe last questions is, you have been in this field for some time, what would be your advice to someone, who is about to develop or implement digital health solutions or DTx?

Participant:
Well, I think, yeah, the advice I would have is really to reach out early to really understand the market that these technologies is trying to address in terms of challenges, because obviously, you know, the idea is always to address a problem. And you might be more surprised to the willingness of the different, some key decision makers in terms of helping you think through on what value your technology can bring for them. So I think mapping that out early on and seeking feedback would be very useful. My earlier career has been in regulatory, I was actually in a very small unit that was supporting startups because the regulatory agencies don't want to be taken by surprise when new technology shows up at the door, they want to be prepared because it takes them a long time to make a decision. So they actually would welcome that early discussion, and that will actually give you a lot of insights on how you would develop your technology. The second point is really around defining well the value proposition. I can't stress that enough. Because it's not what you think is the value proposition of your technology, but actually, what is the value proposition of your technology versus the different stakeholders that you will need to demonstrate that value, whether it's the user or the payer or the regulator or the clinician, the prescriber? So these are this is not an easy task definitely and it is probably changing throughout the development stages of the technology…

Yoann
Is there anything that we have not discussed covered on this topic of economic value, and some of the factors that might impact in the DTx ability to deliver such economic benefits? Is there anything else that you would want to mention?

Participant
Yeah, so I do want to mention something, which is that when we're talking about the current value, it's quite broad. So the current value to whom and then also the economic value for what purpose because in terms of where do you use the current value, so obviously, most of the time it is to get funding or that to show that your technology is going to be paid for so that it is value for money. You want to demonstrate that your tech. is value for money, but then there are different ways to look at the value or the funding because typically, people would fall down to the default which the reimbursement but it is a very wrong way to think of it. And it's actually quite easy in the sense because you establish agency that is so also task is to look and evaluate their economic value for reimbursement purposes. But that's only one of the funding mechanisms. You also have out of pocket, so you know the technology that is directly for the patients and paid for them or the employer to pay for them, and for them, they would have different economic value. So that's why I was referring back to that value proposition and clearly having that perspective in mind, because when you define that

value proposition, you have to think about who would be your stakeholder and therefore, also potentially in the down the road, they might be your payers. And if you have defined your economic value well in advance, it will help you tremendously, because along the way, I do hope that you only have collected data to support that value proposition. Yoann I agree. I think the complexity is, is the level of granularity that we should go through in some of these conversations. You're obviously expert in your field so we can go much deeper, but when we have these conversations with the engineering teams, or clinicians, they may have slightly different understanding of perspective on the concept of economic value, what does it mean basically to them. In some of the interviews, I might need to clarify upfront and define the concept of economic value. It will help to provide some context. Participant: Yeah, so when we're talking about funding, it would also be about adoption, which impacts the economic value. Yoann: Exactly. Totally. Thanks a lot. And let me just stop the recording.	

PARTICIPANT: #3

Topic: GCM DTx Study
Interview date: Oct. 2nd 2023
Location: Online
Time: 11am
Interview type: In-depth interview over Zoom
Participant Profile: Clinical + Digital Health Expert with >20 years of experience in clinical/ advisory and business angel capacity.

Data	Insights
Yoann: So maybe it's the first question. And this is more like a high level general question, but from your experience, what are the factors that you have seen, but my influence be digital health technologies, ability to deliver economic value across the full cycle of inception, development and implementation? Participant: Yeah, I think the first thing that comes to mind when you ask that right, it's probably two things in my head, and then mindset and acceptance. I'm just thinking back we had a really good panel session last week. I'm just kind of extracting what I what we discussed that. When I say “mindset”, it's the mindset of all the stakeholders, especially the stakeholders, who are	Level of understanding and of awareness/ education about the importance of economic value, and how it is important to any organisation and or individual

potentially going to pay for this, whether it's the insurer, whether it's a government, whether it's a user or a private entity, right. So the mindset that right now and this is my personal opinion, that mindset isn't there of looking at the economic benefits and understanding that, hey, actually, the economic benefits are related to me, regardless of who I am. So let's take a simple example if I as an employer, right, what are the economic benefits to me? If it doesn't digital therapeutic benefits? an end user, it might be more productive employee, less off days, happier staff, you know, all these things that then obviously, impact our business, right? If you're a government or a payer, it's the same thing. Right? I think the mindset today is we think of just the immediate implication or consequence of something right, that return on investment is very narrow the definition whereas we have to realize, okay, these are broader things that ultimately do affect me and the acceptance when I said mindset and acceptance. I think it's the acceptance of that, what is the value of need to have an economic benefit? And what does that what impact does that have on me?	Understanding the ROI, from a narrow to a broader and longer term perspective.
Yoann And so maybe to make sure I understand your first point, about mindset, would you say that the same DTx, let's say in Singapore versus let's say, in Germany, and in the US, that the same solution might deliver different economic value to different set of stakeholders because of the "mindset" being different in these countries?	
Participant: No, I don't think the economic value will be different. But I think the ability to get to the point to deliver that economic value is different. So, in country X, this DTx is reimbursed and approved, right, and is used, it's going to deliver the economic benefits associated with it. But in country Y, it's not even given the opportunity. It cannot deliver that economic benefit. I don't think the economic benefits will vary. Maybe I'm wrong.	
Yoann: Let's say we are in Singapore, what are some of the factors you know, it is always the 20% of factors that might deliver 80% of the economic value…so when you look at these digital health solutions, what are some of the critical factors that you have seen that might impact or deliver higher economic value from a DTx?	Right problem statement
Participant: Yeah, I would say, and maybe I'm biased, but this goes to the report that we just published, but I think the biggest factor is whether or not the right problem has been identified. First of all, because if the right problem hasn't been identified, you can forget about it. I don't think it's going to deliver any value, right. The second point apart from the right problem being identified, I was going to say that the level at which you're certain of this affecting an actual behavioral change. I personally have seen very few solutions globally so few that I can't even name an example off the top of my head that actually show a quantified benefit. So I think the second thing is whether it's theoretical or not, you must be able to show a quantifiable benefit or improved outcome, even if it's theoretical. And I think if you cover these two things, in my opinion, I think you're almost at this, the majority of it [the solutions], will ultimately be delivering that economic benefit. Does that make sense?	Modification in affecting an actual behavioral change Demonstrable quantifiable benefit or improved outcomes
Yoann:	

I mean, I totally agree with you. And because you're like a clinician/ business leader, , how would clinicians define economic value versus the entrepreneurs? Participant: I actually think both are really poor at it. And clinicians are probably worse. As clinicians, we are not taught to think about economic value, right? As clinicians, we just want our patient to get better. So at the end, of the day, what ever is available in the terms of tools and solutions, we don't care how much it costs. We don't care whether there's economic value societal in, you know. At the end of the day, all we care about is if this going to make my patient better in this particular instance. So I think that's the biggest gap right? And so clinicians have no idea about it, they're not aware of it and are educated about it. Entrepreneurs, I think that probably a little bit more aware just because from the entrepreneur and angle you have to commercialize, right. So part of that journey is okay, to commercialize. What do I need, and everyone knows or reimbursement is a big part. Well, how can you potentially get reimbursed even more easily, right? Oh, show that there is an economic impact show that there's economic benefit, etc. So I think entrepreneurs are a little bit better, but clinicians, they don't quantify it at all… Yoann Do you see this as a gap in terms of awareness and maybe knowledge gap? Do you see this as an opportunity? From an ecosystem standpoint, I don't know if "educated" is the right terminology, but should we educate entrepreneurs as well as clinicians on basically this concept of economic value or maybe just the importance of delivering at some point some economic benefits, being to the patients, to the [healthcare] system, or the healthcare providers? Participant: I absolutely think that that is the role you guys should play or someone should play at least right. And in fact, I would take it a step further, and say it's not even clinicians, or entrepreneurs, we need to go way back even earlier. And in fact, you guys are in a perfect position. I actually think it should be in medical school, right, to raise this awareness and educate people. If you look at only medical school I know is my friend Shafi Ahmed Bart's in London, where he actually changed the curriculum and you should look it up bots, X medicine, where they actually teach about technology modules, finance modules, entrepreneurial modules, etc. I think it's super important. And it's a very simple thing, right? I think you need to explain to people that when we talk about economic benefits, or you know, when we do an economic analysis, what are the costs associated with this, What are the benefits, right, and Joanne broke it down really nicely. You need to think about it as direct costs. And indirect costs are probably the only one that doctors are aware of either, right? Direct Costs, indirect costs, societal costs, and opportunity cost. Right? I think these four other even if you don't teach in depth or make people aware, I think people need to understand that, , these are the four that exists and you do need to think about it.	societal economic value Reimbursement possibility Ability to impact the direct costs? Ability to impact the indirect costs? Ability to impact the societal costs? What's the opportunity costs?

Yoann And just to make sure I understand the “opportunity cost”? Participant: Depending on who you are, the opportunity cost to me or to my organization, spending time and money on this solution, versus potentially doing something else. And whether that's something else is associated with that same disease or problem I'm trying to solve or not. That's the opportunity costs or potentially spending time I'm doing something bigger, something major. Yoann I see. You know, one of the factor I think we are particularly blessed in Singapore as the ecosystem is kind of quite efficient, compared to some of the ecosystems out there. Participant: I know it's right. Yoann: It could be much better, but I think maybe compared to some of the ecosystems is quite okay, quite efficient. Participant: I wouldn't say efficient, I would say is comprehensive is has all the solutions, but we're not efficient. Yoann: So, okay, so could you define this “efficiency” of what might be missing to have an efficient ecosystem? Participant: A very simple answer, and you might laugh at me on this, right? I think it's the lack of an independent central entity that an orchestrator. There is no single orchestrator in our ecosystem. Yoann: I see. And one of the assumption that I wanted to check with you is how the degree of efficiency of the ecosystem might impact DTx entrepreneurs to deliver value economic value down the road? Do you see this ecosystem efficiency as one of the potential factor that might influence the DTx ability to deliver economic value? Participant: Not that I see, but I know it for a fact because we can take examples in the health tech space over the last five or six years, where a certain startup or company work with a certain group of people or an organization who helps make that journey efficient, versus all the others that are just going through the system as in when as in when they know how to write in an inefficient manner. You can see the clear parts which succeed which don't how fast they take to get to point B versus how fast this company takes so it's not a we know that right. Yoann If you look at the evidence or in the literature, the “readiness for implementation”, of your ecosystem, healthcare providers, etc. would play a	How structured is the ecosystem and supportive body (such as having an independent central entity that an orchestrator)

critical role in DTx to implemented, deployed and you know, adopted. How will you define what are the sub-components of this readiness for implementation, or how would you define it? What are some of the factors that you will want to consider?	
Participant: That's a tough one. So you're saying essentially, what kind of whether it's a framework or what kind of questions would be asked to determine and define whether an individual as a clinician or a provider as an organization is ready to implement?	Structure and governance of the organisation, the kind of capabilities they might have, leadership level
Yoann: Right so if, for example, you do a benchmark or a comparison between two healthcare providers, and you want to assess which one is ready to adopt a DTx, what are the 5-10 factors that you would want to assess?	
Participant: So I think, again, I'm just thinking off the top of my head there, whether or not there is a dedicated "innovation office" or "digital therapeutics" office, etc. That's one parameter okay. If there is or if there is not, but there is a wish to have one in the future, whether or not the right capabilities exist within the past so I won't mention names but I know some provider groups that have set up these kinds of offices but absolutely with the wrong kind of people, right. So I think ensuring that the right resources and right capabilities exist within that that's another like data point, right. Also the general mindset and acceptance I mentioned that at the start of this call, right? Does even that mindset and exit acceptance exists at a leadership level. Okay, both on the ground and the leadership level, but it's especially at the leadership level, right. Is there an initiative, you know, is it put out there that the leadership of this provider group are advocating this, right? And then it's some very simple yes or no questions to me. And again, you might laugh, right? Are you as an organization agreeable to test and pilot and implement these solutions? But just a very simple yes or no? And if you say yes, then obviously you need to ask the questions... Okay. What do you have in place today, that will allow that? Do you have a process? Do you have a team? Do you have the environment to actually test this?	
Yoann When you look at each stage of the tech. development process, do you see that they are maybe some factors that might be over considered or overlooked? And that you know, as your role as a mentor, providing guidance to these startups, at the inception, please really consider these factors because you know in 18 months down the road, they are going to help deliver value, etc.. So overall, if you look at these different phases of tech development, validation, and implementation, what are the factors that you think are overlooked, and that could be an opportunity?	Representation of trials participants to the targeted population in real life?
Participant: Yes, hold on. I want to I'm just looking for a quote that I read last week, one second, okay. Up here, okay. So before I give you the quote, my answer would be the same answer as we did for clinical adoption of health technologies. I think there's no difference when it comes to DTx. And that's the earlier what I said, have you identified the right problem and have you clinically validated it, but have you clinically validated it with the right people? So the identification of the problem statement and the clinical validation of it by the right people, but also the clinical validation by the right	Presence of IP Think about regulatory pathway, early enough Early economic analysis

people of the proposed solution. That's the first thing. The second thing is then have you thought about the actual IP behind this? And the value and strategy is it legit, is it not? And also, I think people get very caught up often they have IP and they think that it's great, but it doesn't mean anything. Often you don't have IP, but it can be very valuable anyway. The thought is at least thinking through the regulatory pathway, early enough, right. And the last is the economic analysis itself, which should be done early, which is anyway the purpose of this study, right? But what I would add is this quote by an orthopedic surgeon in the US, he's posted the biggest barrier to adoption and threat to the future of digital health question mark, and his answer is one word. reimbursement. So at the end of the day, who's going to pay for it price? And I think, in my head anyway, what I do when I even as an angel investor, or when I review these different technologies, right for grants, when I look at the problem, right, and the first question I asked myself, and I think entrepreneurs should ask themselves is, okay, is this a common problem, or is this something niche, right? If it's a common problem, the reimbursement and economic analysis becomes a lot easier to do. Right? And you don't have to worry about it so much. If it's a niche problem, then you need to spend a little bit more time even thinking about, okay, is this a rare disease? You know, why is this niche who would pay for it and it becomes a little bit more tricky. And so before going further ahead, I'd say spend a lot more time figuring out in that situation, who might potentially pay for it. And is there even an economic benefit? Because if there's not I think it's going to be a struggle.. Yoann: I agree. One more question. So, on the economic value, you know, at the later stage of the process, if you're a DTx or if you're a digital health solutions, you will need to demonstrate at some point, its value to a potential payer. Do you see specific and unique challenges that a DTx might have in demonstrating and in assessing the economic value that it might deliver versus a digital health solution? Do you see any specific challenges in DTx demonstrating economic value versus a more general digital health solutions? Participant: I think defining the economic value is extremely important. And you haven't shared with me what you all are defining as economic value? So I would love to know what you define as economic value because that could vary between stakeholders.. But that aside, I think the main difference is, I mean, when you talk about DTx versus digital health solutions, the big difference, you're seeing that this is a therapeutic. And when anything is therapeutic, there is always a way you must be able to quantify that therapy, whereas with many digital health solutions out there, especially the ones in like the wellbeing space, right, it's very vague…And so, I think the uniqueness is, if you can't quantify it, game over. Yeah. Yoann Which is basically back to the evidence, your earlier point of having the clinical evidence, and the need to demonstrate a clinical benefit and how and what are the costs associated to it… Participant: The other point, I suppose, again, from a clinician perspective, I think when you're doing a DTx, you must accept that the timeline is going to be longer	Common problem vs niche problem you are trying to address Timeline (or period required), being development timeline, clinical trials timeline, etc. Convenience of the solution

than a general digital health solution. Because by definition, if you're a therapeutic, you're going to need a period of treatment and then a period of follow up, review and quantify. So I think that's also a little bit different. Whereas other digital health solutions that focus on convenience or you know, other things that end users want. That timeline is a little bit of a lot faster. Yoann: No, I mean, totally agree with you, and, and maybe on that, as you said, you're an angel investor, so, what are the role of investors, broadly speaking, and how do they shift such timeline, or impact it? What's the role of investors in this overall journey in defining this timeline from maybe expectations and requirements standpoint? Participant: That it's very good question, I think the first thing I would say is that there is no such category as investor. I think you need to break that category of investor into into groups, right. And I'll tell you what I mean, right. So, first of all, by stage right, you know, early stage versus mid versus later stage. There are very few early stage investors in this part of the world true early stage investors, there are many who claim there, but there are very few true early stage investors. I think the other category that needs to be broken down within the Investment Group is the impact or non-impact type of investors, right? Are investors looking for true impact? And when I say impact, I mean, clinical impact, right, versus just monitoring returns. And then it goes back to my earlier point on I think when we look at problems, right, actually, whose responsibility is it and that there's no straight answer, right. So the first question is in a common problem, is it a niche problem or rare problem, right? It my personal belief is that if it is a niche or rapid problem, my personal opinion is that governments need to focus on that more, because it's going to be difficult. Even if you find an impact investor, it's going to be difficult, right? So if I had a magic wand, I'd say Okay, anything rare and niche, government focus, anything public or big if government wants to find but it's more of a private play because there's a chance to make money right. So I think the role of investors is very important, but finding the right investors and is the challenge essentially, and I think the I mean, investors are also "private equity" right? Investors, of any many, many years ago, about a decade ago, a very senior cardiothoracic surgeon told me, I think there should be in Singapore and in healthcare in general, there should be three legislations: 1.) One is that doctors can't make money from kickbacks and referrals and things like that, 2.) Doctors should not make money from the selling of medicines and putting margins on it; 3.) and three, this is the interesting one, no healthcare entity should be allowed to be listed. And, you know, I thought about that a lot for a lot over the years. And it comes back to that investor mentality. Role of investors important to get things funded and off the ground. But then the question is, it's a very slippery slope right at the end of the day, is the investor just in it to make money? And I think that's the difficult thing to do the difficult problem to solve… Yoann: It's complex. It's the same conversations about schools right? Should schools be for private or nonprofit type of organizations, right. […] At the end of the day, you need to deliver the right impact at the right cost, which	a niche problem or rare problem, right? investor mentality, role and impact over the course of the DTx development cultural nuances, cultural practices and beliefs

is basically back to your earlier point about what's the definition of economic value. So, the way we are looking at this is basically the economic benefit of a DTx will be defined by two things: 1) One is the degree of impact that the DTx might have on the clinical outcomes, right? It's looking at the efficacy, effectiveness. So any factors that might influence one way or the other being enablers, or a barriers, such clinical impact. Then you have the cost side, it's basically whatever resources, infrastructure, etc. that might be required, so you are looking at additional cost but could be cost savings also, that might be required to deliver such clinical value. So any factors, any enablers any barriers, basically, that might influence one way of the over the clinical impact, and financial impact? […] Is there anything else that you would want to mention any potential enablers, barriers, factors, dimensions, whatever you call it, that might influence or impact a DTx ability to deliver economic value? <u>Participant:</u> We didn't talk about cultural nuances. I think cultural nuances would probably play a big role too. I mean, we can talk about it in in a bit more details… Yeah, just cultural practices and beliefs are often not thought about in, in solutions. I remember one solution I came across a few years ago, when I was the company asked me that like, just through the interface, right. And one of the questions was, in terms of what race are you and they were very quite granular, right? And I asked, why you're asking this? And they said, actually, the flow of the app and the interface changes, depending on what you select. I was like, oh, that's interesting. So in the Singapore context, been Malay or Chinese, the actual interaction and user interface would be different. I find that I found that very interesting. I was like, that's, that's important. <u>Yoann</u> I love what you said because I have not seen this yet. […]It's not about just changing the language, the icons, the colors, the font, but it's maybe just the overall experience with flow. <u>Participant:</u> We are not anywhere near [this degree of personalization] in digital therapeutics or digital health today… <u>Yoann:</u> No, I agree. And it's quite unfortunate... Anyway, I don't want to take too much of your time, is there anything on this topic of economic value that we have not discussed that you would want to mention? <u>Participant</u> I guess the challenge and I'm sure many people will say this is actually accessing the right data to actually determine the economic value. That's, I think, still a huge, huge challenge. What else can I think of? We've already talked about the importance of defining economic value in the first place. Do you all have a definition yet? Actually, all you haven't. <u>Yoann</u> So the definition that we are using? It's a bit complex because if you are engineers or clinicians or if you're like an HTA experts, such as Joanne, we might all have a different level of understanding and we don't want to be too specific in defining specific aspects of for example, is it economic value, but	Degree of contextualisation and of personalization Data access

for whom is it for you and highest potential patients? Is it for the health care system, is it for physicians? Is it for a potential payer, because then the definitions might be quite different. So we don't want to go to this level of granularity. Participant The definition of economic value cannot be different. The definition of value might be different. So the definition of economic value shouldn't be different. Yoann Right, it's the perceived, basically, economic value and to what extent some of the factors might be more or less important. So if you're like a, for example, the end user and you are in a out-of-pocket type of market, your understanding and expectations from an economic value, might be different. Let's say in Singapore patient's priorities might be quite different… […] Anyway, we covered a lot in like one hour, so thanks a lot for your time. If there's anything else later, obviously, you have my whatsapp, you could always like send me articles or any additional points that you will want to share basically for the study. [end of the recording]	

PARTICIPANT: #4

Topic: GCM DTx Study
Interview date: Oct. 3rd 2023
Location: Online
Time: 3pm
Interview type: In-depth interview over Zoom
Participant Profile: HTA expert with >20 years of experience

Data	Codes
Yoann [Yoann providing some context] Do you have do you have like any questions or clarifications on that before we start? Participant It's clear, and I just went through your paper this morning to refresh a little bit. Yoann On what would be a typical DTx development, could you please share your experience and your understanding and like what are the different stages in the DTx development cycle or life cycle - it will be a good way to start maybe. Participant	

I published a paper last year about patient engagement in the different phases of human centered design, and I believe that human centered design the five cycles starting from identifying the unmet need, and going through the requirements, the prototyping the testing, and having the users embedded in each of those cycles is in my view, one of the best approaches to design so starting with the unmet need, rather than starting with which technology is sexy like 90% of the cases is in my view, where we should be starting, starting with the users and users here are not only the patient, but also the clinicians, healthcare institution management payers, pharma companies, like the 360 view of who can be part of this journey from the very early beginning. It's also about ensuring that we're talking to people that are not only experts, but also we're talking to people who are lay audiences, so talking to the "least capable" of patients, not only patient experts that are renowned for their project management and development capabilities, but also people who might not be that familiar with technology because a good design should be usable for unfavored populations because they are most likely the ones that need it most. So I think this is where we should start with the unmet needs, identifying the unmet needs and doing the ground research to start there. Then, starting with translating this into a list of requirements that then goes into a prototype that we can then test and then you go into hyper care mode, and start maybe with a beta version, where you're really looking closely into the metrics and what's going on how is it fitting into the context like one of your key findings, some of the values show in one context completely differently to another for the same tool, right? So understanding this fit this this this, how does it work as a part of the whole is also a very important part in design and keeping this iterative approach. So that constant development cycles that keep going, it's not out in the market, product delivered. It's only the start of the journey. So this is how I see it. I don't know if that's what you're looking for or am I going in a different direction?	Translating end user needs into tech requirements. Fit into the context Iterative approach, with constant development cycles
Yoann It's perfect! There's no right or wrong answer but yeah, I'm with you. So you know in the in the kind of like the different steps and kind of old development cycle you just mentioned, from your experience, what are some of the key factors that you have seen, or that you know, that might influence one way or the other, the ability to deliver economic value?	
Participant I think one of the issues that I see quite often is that people neglect this unmet need and requirement, collection phase and they go directly with prototyping. They find a sexy technology, they have a good idea, and then they come with a scenario for those users to test. And what I advise the people I work with is go there with an open mind. Don't give them a prototype and tell them does this make sense? Start with a blank page because you might get blindsided if you don't start there. And that's what I see quite often happening. It's identifying this real unmet need, because if you give people a list of features or a prototype or a demo, they become very targeted to evaluate whatever you gave them, but they don't look outside that framework, right? They don't look beyond but if you go with a blank page, and listen, some of the ideas might not be realistic. Some of the ideas will be you know, dreams that cannot come through today. So you need some expectation management as well. So you can tell them, hey, we want to listen today might not be able to deliver everything, but we want to really hear what you need. And I think this is where the discussion needs to start. Rather than going with an idea. Quite often we see startups that have not like they come with a with their minimum viable product before even talking to one single patient.	Technology looking for a problem vs a problem looking for a tech. Clinicians engagement and involvement throughout the design and validation

Ask them have you did you talk to the patient? I mean, it's easier to involve clinicians because the regulatory hurdles fair and the ethical considerations are far less. They're professionals and you can involve them they're not the vulnerable population like patients are sometimes it's more difficult for startups to include patients from the beginning to better understand whether that makes sense at all for them. So I think this is probably one of the key gaps that I see where they fail to deliver value because they might come up for instance with a really strong solution that's capable of delivering clinical outcomes. But it's not user friendly enough. It's too complicated for a patient might work for the clinician, but for the patient, they're not going to use it every day. So coming back to your point of adherence, you lose them there.	User friendliness of the solution and its interface,
Or maybe it's not that difficult but it doesn't have the behavioral change element in the design enough incentivization and enough personalization, for instance. So all these things are super important. And I don't know about your experience there. But in my experience, so many startups fail to talk to patients or fail to include them in the journey from the very beginning. So I think it's a bit tricky to only on to mostly focus on technology and what technology is capable of be for looking at what is the unmet need and does this worked for the people who it is intended for? Right? And there are studies coming out every now and again, saying that the most vulnerable populations that need those the key X's do not have access to them or are not capable of using them. So I think that's also one of the key areas where we're failing to deliver value. So is it really working for the people that need them? are we testing it with them? Or are you testing it with your capable developer who's above average when it comes to technology use right?	vulnerable populations and access related issues, not be able to use DTx (literacy)
Does that make sense? To me? Does it match your experience?	
Yoann Yeah, I totally agree with you. So to back to the initial questions about some of the factors you mentioned about the unmet needs and the ensuring that you address an unmet needs. You mentioned about the overall experience of the patience of the end user on the solutions in terms of user friendliness, adherence personalization and is there anything you would want to add?	
Participant What is value and how do you measure it? And of course, this may be impacted as you also mentioned in your introduction by the payer system in a specific context is it fee for service is it value based healthcare. And we see the challenges with value based healthcare and all the challenges of objectively measuring some of the things that lead to better quality of life, for instance, because it's very subjective, and some of the metrics are not even included. As one of the metrics like the level of fatigue for chronic patients, for instance, and here I can talk as a patient I have autoimmune disease. So fatigue is one of the issues that I struggle with every day in the morning. I have to start and say okay, I have 10 things to do today. I know I'm only going to be able to do three or four of them. So where do I start? That's my daily struggle. But there isn't one metric that measures my fatigue. Right. So this leads to what to my GP basically prescribing things like muscle relaxants, instead of giving magnesium for my tight muscles. Even though my quality of life with the muscle relaxants is horrible. I'm like a zombie. Why can I not do anything with muscle relaxant? That's fine for a 65 year old on pension. But for me in my early 40s. That's a real problem for quality of life and that is not measured. And to give you an example of how this really plays into how we perceive value, I've been part of a	Ability to measure objectively what matters to patient

jury that that is defining which of some of the startups would get grants and go to the next funding level or a funding round? And one of the startups was working on an objective fatigue measurement, which has some real gap today, as only a patient with chronic fatigue would understand that and to understand where they're coming from because the two researchers behind it, one was diagnosed with MS, the other with long COVID-19. So they know what they're talking about. I was with a group of experts of eight people and I was the only one that saw value in this because seven others do not have chronic fatigue. They don't know what it means. And if I go to my rheumatologist, I tell him fatigue, he looks at me and he knows he has no measure. And he has no solution. So if I can have a digital tool that actually helps me measure this in an objective manner, and we can see the different impacts of different treatment pathways on this, my quality of life would look very different. Not only me but actually all people with autoimmune disease with where fatigue is one of the key things that they suffer from, but no one's measuring it. No one's looking at it. And no one's looking at clinical trials with control groups where they can see yes, this way leads to less fatigue. For instance, I think our definition of value and the challenge that comes afterwards, which is an objective way of measuring those types of value in in a value based healthcare approach are also issues with assessing what type of value does specific DTx bring?

Capturing and assessing the perceived value of the DTx

Ability to measure what matters to patients, and the system

Because simply, they can be a revolutionary like the startup I'm talking about, in my view as a patient, that would be a lifesaver, right? Because in today's world that's not even measured. The value might be completely overlooked. So we need a bit of a mindset shift to welcome this new world of opportunities that we might be overlooking because we're still judging it with the old ways of judging therapies. Does that make sense?

Yoann
I totally agree with you there. But I was thinking, you know, back to your earlier point about ensuring that you address an unmet need, you know, but what's the market readiness, including the physician readiness to consider a DTx, or the right level of knowledge, understanding and awareness. How do we ensure that we are addressing the right unmet needs?

Participant
I think that it's trying to find a way to quantify and objectively measure and I think those guys, they did that in a way because they were trying to find a scientific way to measure fatigue, which is something that was not that did not exist before their idea they barely made it made it to the next round. So I'm glad to say that they did and their approach to monetization was working with pharma companies to try and prove that some medication can have enhancing fatigue as one of the outcomes. That's the big proving value and accordingly reimbursement and you know, superiority of specific treatment and so on. So that's their current approach. Of course, in a world where we don't have the pharma lobby in place, we can also look into things like physical treatment, like physiotherapy like natural treatments like magnesium versus muscle relaxant, like the example I gave you. Unfortunately, in the world today, the power dynamics do not support this for monetization. So talking from a patient perspective, in an ideal world, the driver would be really looking at how does the patient look at the end, but because the current setup does not put the power in patient hands because it's in the payer hands or in the pharma lobbies hands because they are the ones that are funding research, then those tools must always find something that would be attractive for payers, the ones with the big money that are making that machine work, and keep going. So in that case, that that specific case that I'm bringing, they were smart of saying we're

quantify and objectively measure the solution's key outcomes

superiority of specific treatment

the power dynamics in the DTx ecosystem, among the decision makers

going to work with pharma companies to show that the treatments actually work. So this can show the superiority of one drug over the other. So it's a little beyond the pill approach, where you're doing things that have not been measurable before, and you're saying Okay, so with this, we can actually sometimes I think there's a new law that even enables pharma companies to prolong their patents, like their patent protection now, if they can prove superior value. So such real world data can really help. That's another additional type of value creation that we did not have before. Those tools were in our hands. So I think there are possibilities but they aren't by challenging and there must be some willingness from the system really in a top down approach to say, we are moving towards a value based healthcare. I think the real playground for DTx is in a value based healthcare approach rather than a fee for service that mostly focuses on cutting cost, which is the case in the majority of contexts. Yoann Yeah, no, I agree with you on this shift towards value based healthcare. You mentioned also about the pharma and the established player. I would be keen to understand from your perspective on how this existing incumbent player, the large pharmas and medtech. How do you see their role in influencing the DTx ability to deliver economic value in one way or the other, right? Participant I think some of the pharma companies are doing this pretty well. Like if you look at Roche, for instance, and the amount of partnerships and acquisitions that they have in the digital health space is amazing. Sometimes they develop their own things sometimes they acquire or they partner with companies. And they do of course with funding studies that prove value that's one part of facilitating the sort of the scientific proof of digital therapeutics value. Of course, that has to always be tied back to their medication in one way to another or another, that's the downside of it. Right? And some of them would say if I don't have exclusivity, I'm not going to do it. So why would I help you? You know, develop your tool further if you're gonna give it to my competitor next. So I think there are commercial limitations or commercial challenges. That come to play when it comes to partnering with pharma. We see that there are some major players that are playing a very good role in partnering with startups and co-developing. What I see works well, one of the studies that I've been involved in between Roche and kaiku health for example, a DTx for digital patient monitoring for oncology patients, is that for instance, we could develop a specific module that becomes proprietary or that becomes exclusive. So rather than binding the whole company or the whole tool to them, they say well, we're going to co-develop this piece with you for our specific line of drug and that becomes something that we work on together rather than just you know, make it available to everyone. So that was one of the setups that I have seen work well and I think they managed like the legal and contractual side of it to be a win win in this case. So of course, funding the study and showing the proof is something that pharma can really support with because most of those startups they don't get funding for the for that type of activities, or it's really challenging to get funding for that type of activities. So partnering with pharma can be a good win because it's in their benefit to work with those beyond the pill type of approaches and generating real world evidence. That was not possible before that we were bound to the data that we generate in a clinical trial setting. But going beyond that, and really collecting data from people's daily lives that are completely engaged, that's a complete game changer for those companies as well. So it's a good win win approach for pharma and for med tech to work together in partnership to prove value to fund those studies. Of course, always paired in with a medication in this case or with a pill	Ability to prove superior value (clinical and economic) Presence or ability to generate and leverage real world data to demonstrate value, personalise the intervention, etc. Ability to play in a value based healthcare approach versus in a fee for services (that mostly focuses on cutting cost) Ability to co-develop part of the solutions with potential commercial partners (a pharma) Level of support from an established pharma/ medtech organisations, funding studies, etc. Ability to generate real world evidence

Yoann On the need for evidence, like clinical evidence, being in a clinical trial, we will what evidence what might be just good enough, from your perspective, you know, it's always like, you know, should have like 10 RCTs, or one is enough. From your perspective, what kind of data might be good enough?	
Participant I think there's no one size fits all approach, because if we compare something that's almost pandemic like diabetes to a rare disease, where only I don't know 0.1% of the population gets, what good looks like can be very different. It's very contextual. And it has to do with the larger population, so like I was working with a company with a rare disease drug where they had like 25 patients over Switzerland that have this this disease and only 10 of them are on the drug. So how would good look like in this context, compared to a study on hypertension or mental health or diabetes? Sorry, that I'm not able to give you a straightforward response here, but it's really very contextual and we have to really look into the overall population, the diversity in that population. Does the sample reflect the scene? Like, is it representative of that overall population or not? We have issues with minorities and with the under-represented groups in many clinical trials, right. Historically, clinical trials have been male, white, so even women were not allowed to be part clinical trials until the 90s because we were deemed unstable because of our hormones, that sort of representation needs to change, right? We need to reflect all those un-represented groups in those studies, depending on the context and the overall population, so that that would be in an ideal world, that would be the way to go to have a balanced result at the end.	Larger to smaller population or niche population Trials participants representative of that overall population
Yoann How long does it take or could it take for them to deliver clinical impact and obviously, economic value from the day one, the initial inception to the ability to really deliver economic value and to demonstrate and to quantify what Yes, I could deliver economic value.	
Participant There is a confidential study, but a couple of years back and I interviewed some senior leaders in the field and the general agreement was that especially in the case of the DTx it's about four to five years until you see first results, because it does take time until you get the regulatory approvals. It's not a wellness tool. It's something that really needs to go through a rigorous regulatory review and certification process and that takes time. So the general agreement again, it will depend, of course, on the disease area that we're talking about how easy is it to collect the data and to sort of prove safety and stuff like that, again, if it's a rare disease, it might be more difficult to find users to test it and so on, but the general agreement was that it would be four to five years.	Speed to obtain regulatory approvals Facilite a collecter des datas sur les targets populations
Yoann And by four to five years, you mean value, from a clinical or financial perspective? Or both?	
Participant It depends on the context. In some context, it will be easier to do some cost analysis benefits, because in some contexts, it's just more challenging to put a dollar value on specific outcomes, and in some others, it's easier depending on	

how the insurance system is built and the reimbursement system is built. If we look at the DIGA as an example, as one of the pioneers that are looking at this, right what the DIGA does, because it's extremely challenging to prove, like absolute value like clinical and economic they give them a chance to prove value in a year, collect your data, come back to us prove that you really deserve that price, and we're going to keep you on the market, and we have seen already in the last few years that a couple of those DIGA they were they were taken back from the from the database so that that's the DIGA status was taking back, meaning that we certainly need more than one here to be able to prove clinical end commercial value or cost efficiency, right. And this one year started after that being on the market so it doesn't take the whole development cycle in the background into account. They were already proved safety they went through the process by the time they hit the database. So this takes me back to the fourth five years that we certainly need at least that amount of time until you can prove a balanced value of clinical and economic value in a context but again, in some contexts, it's much more challenging to have a cost benefit analysis. Again, going back to your paper, we don't even agree about what costs to take into account when it comes to cost efficiency, right. Every study is taking different costs and some of them are not taking the entire costs into account, some of them take their direct costs, but not the indirect outcomes, or the more the softer sides of the outcomes. So we don't seem to even have an agreement yet on which elements do you take into account when doing a cost benefit analysis and that's why I'm saying in some contexts, it might be easier to prove economic value compared to others, depending on the clarity and how straightforward these are to measure and to take into account in some contexts in some low resource contexts. You don't even have EHRs you don't have records of things so how are you gonna measure that? Right, that's another challenge. I mean, practically, when we really look into what's happening on the ground, it is a pretty challenging area because sometimes there isn't even a record of how this looks like when we again, if even if we go to high resource environments like Germany, some of the adoption challenges that they're facing for DIGA, is some of those indirect costs. So when we look at how the adoption rates are suffering for the DIGA I think it's around 30%, when everyone's training was like it's gonna boom, right? And clinicians are often talking about things like implementation costs, like all the time that goes into managing those tools, like training and support costs. So these are all things that are not taking into account in today's DIGA, which is the pioneer of reimbursement. So the calculation is not taking all the cost elements into account, which is resulting in an adoption challenge. So again, you're really your model and your approach is excellent because it's putting the puzzle together and looking at all those things and how they relate to each other. Sorry if I went in all different sorts of direction, but it's a very multifaceted and very interconnected topic, correct? Yoann It's perfect. It's amazing! You mentioned about the implementation costs and definitely this is potentially under considered a or not considered consider at all… What are some of the key costs that you see when it comes to the implementation? You mentioned about the training, about the integrations of your solutions to the hospitals systems, etc. Are there any key implementation costs drivers but you have seen from your experience?	Context clarity on how to measure and define value in specific country and context Level of implementation costs Training and support costs Resources properly, ensuring resources are

Participant Sometimes it's also just not allocating resources for the management of those tools. So we've seen examples where the management takes the decision, they put the pilot in place, but then the poor nurse is doing the work, and she's not given any time allocation to do it. So she's basically sacrificing her lunch break, or she has to stay an hour extra after the shift to manage all the data that's coming through the tool. So, these things are also on a managerial level, like the resources that you put aside or the extra time that something like this takes or proper analysis of, okay, so is it bringing me efficiency on the other side, so I'm putting maybe an extra hour in managing the data and coming through the tool? Is it bringing better efficiency? On the other hand, so one of the key things that and that's in my view, a perception not reality, but it can be an adoption challenge is that most clinicians are afraid of the extra loads of work and the extra load of communication, the direct communication that comes through those tools because it gets easy access for the patients, right. And in most of the cases that proved not true after a pilot was done, because they said the patients that needed the most they had more complications, but the stable one needed less work. So if you could spend time with the people that need you, most overall, the workload was still more or less the same. It's just better results because they spent more time with the ones that needed the most. So sometimes it's the resource allocations, the understanding of the impact on the workflow. So sometimes you will need some changes in the workflow that need an extra support to the ones doing the job on the ground. One of the cases that I've read about and you might have come across it is the AI tool that Google implemented for diabetic retinopathy in India as well, so it was the same country and what happened that is that they compared the imaging when it's done by a specialist compared to the AI and I think they had 90% efficiency. So they applied it in no resource setups. And what happened is that they had of course, much more efficiency because the patient did not have to wait for a specialist or to drive a couple of hours to see a specialist and then wait up to 10 weeks until they get the report. They could find the thing on the spot. But then on the ground, there were some issues that there was a discomfort because the nurse had to wait like 10 minutes until the AI comes back with the results. So what does she do at that time? Do you give her some material to discuss with patients, for instance, or some of the information that she needs now to explain to the patients were not part of her initial workflow? So how do you adjust those things? Those are issues for adoption for at least smooth adoption, because it puts those guys in a very uncomfortable situation that might push them to drop the tool altogether. So that's also when what I mean when I say support and training so understanding how the workflow changes because it's not just an add on that you put and everything else is working as it used to be. There are sometimes differences in the roles that they have to play in many of the cases that empowers nurses much more, for instance, so do we give them enough support and training to play that new empower tool so that they would deliver the value that the tool is supposed to deliver? Otherwise, you're not going to meet the value not because the tool is not working but because the one running it did not get the support they need to run it properly. So that's what I mean with those indirect elements that you need to take into account. So clinical workflow is one of the things that I see overlooked, in too many cases, the understanding of what it means for the workflow Yoann You mentioned quite a few aspects on but on the readiness for implementation. You know, what I've seen in the literature is that the readiness for	set up properly, set for success. Ability to address physicians perceived concerns (extra loads of work, data, comms) Hospital/ healthcare provider managerial level of support More balanced and efficient workload, back to optimization Impact to the workflow and resources optimization, such as an extra support on the ground Level of support and training so understanding how the workflow changes because Consider the indirect elements Impact to the clinical workflow

implementations is going to play an important role that might make it or break it in terms of like supporting potentially the adoption and deployment of the DTx or not, but if you would, if you were to assess the readiness of for implementation of two healthcare systems, what are some of the sub factors that you will want to assess and consider? Participant So when you talk about context, do you mean context meaning, a country or an establishment? Yoann Let's see if we take just two hospitals in any market and you have a DTx and you want to assess the readiness for implementation of the two hospitals, hospitals a and hospital B. How will you go and assess such readiness for implementation what are the specific factors and sub factors that you will want to consider? Participant So from one side there is an infrastructure element or basically a very material aspect, which is the interoperability. So in a in a very on homogenous market, like in Europe, for example, every hospital sometimes has its own EHR system. So this puts it on the med tech side that they have to then adapt their technology to be sort of a plug and play in each of those different systems, which is not an easy thing to do. So from one side, that's not only that, like the readiness of the establishment or the hospital, but it's also the simply input, what sort of machinery and infrastructure do they have and use? What software do they have in house? There's also cultural and management side to it. So the buy in of course from the management and how much do they believe in the impact of those tools and whether they see digital health as the future or not? Sometime I get asked to assess pilot studies and the people funding it from the government even sometimes, they're just not believers of those technologies. They basically are waiting for the pilot to fail so that they said we tried it didn't work. Next! So management buy in and support is key because that management buy in will down into things like training into things like workflow adjustments, new roles and responsibilities like we've seen some of the hospitals now have a chief medical officer that's also working on technologies, right? So because when you leave it to IT, that's a completely different mindset, and that's one of the challenges that we have seen you want a medical doctor that's trained the into the technology, understands the technology and helps take that decision, what technologies to bring in and which not where to invest and we're not. Finding your internal champions, so identifying internal people that will actually help others train others. So quite often, we see the nurse champion on the ground that goes around and say hey, here's the new tool. If you need help using this, just let me know or seeing identifying which patients may benefit from that add-on tool and give it to them. I was working on a study with a Swiss hospital last year, and that's the biggest hospital in Switzerland, the University Hospital in Bern, and in their emergency department, they had a new VR tool for pain management, and they had those nurse champions so they identified two people that are young, dynamic, they love technology, and they told them go you entice everyone to you to use this right? And that was hugely important because older nurses for instance and here and I'm not trying to be you know judgmental from an age perspective, but naturally people who did not grow with technology, people who have been working for the last 40 years in a specific way, it's just harder to tell them today you're going to work differently. So those campaigns were going around and	Level of interoperability with current healthcare providers systems, ability to plug and play in each of those different systems Hospital management buy-in and support Having internal champions and ambassadors

you know, trying to entice people to tell them hey, now you have another patient to care for, what about putting that patient on the VR and giving them the 20 minute session, while you do something else, that's going to actually help you instead of them pushing the button every five minutes because they are in pain? That you're gonna distract them for 20 minutes, and that was as small as it may look like. It was instrumental in this culture of change in delivering the value because if people do not use it, it's not going to deliver value. So adoption is key here, understanding human behavior and the change process is very, very important. So organizations that are more willing to embrace change that are more willing to amend their workflow, their job responsibilities, to give training and support to their people so that they start adopting those new technologies is really key. I also see it with my husband, he's a physician. He's a neuro radiologist. So they use technology a lot in their work. They are one of the areas that are most impacted by AI, for example, and sometimes they have a multimillion software in the department and he's the only one using it. Basically, because they are super stretched. They did not have enough time to properly train people on the new technology or to even explain its benefits. If he is constantly frustrated, and he's like we have this extremely powerful software and I'm the only one that actually invested the time to see how it works and implement it in my protocols. So it's really and I know that it might seem cheesy that I'm talking about those human sides of things like, human behavior and change process, but I think it's not only about the software and interoperability, but it's also about management buying in the willingness to train people, workflows, job responsibilities, give people the time to adjust to that change. Because, as a matter of fact, clinicians and healthcare professionals in general they're super stretched, it's everywhere. So if you don't intentionally give them the capacity to adjust to the change and change their ways of working, it's going to be on them to do it. So you will only have the super innovators and early adopters that are willing actually to do this on their own time, like my poor husband who does it on weekends. But that's not your, your, like 80% of your physicians or employees. <u>Yoann</u> I agree. I mean, your husband is like, I don't know if it's 80%, your husband, maybe part of the 5% of the early adopters! On your point of the need of internal champions, but would it be fair to say you're correct to say that when we're thinking about the ability for digital therapeutics to deliver economic value, I think such a buying from physicians and having some of these some of these key champions, internal champions, might be one of the critical factor for a DTX to deliver economic value. Would it be fair to say that? <u>Participant</u> I would say an internal culture of innovation and change, including things like management buy in, workflow amendments, training and internal champions because another example came to my mind now quickly, just to also show the importance of that internal champion, so I what you're saying is correct. I just think that the internal champions are only one way to emphasize that culture of change and innovation, rather than a single example of things. But we worked on a pilot a few years back that included 10 clinics and hospitals in three countries, and one of the clinics was in Germany, and we were collecting patient feedback, and we found a miserable patient and very unhappy like creating everything one, on a scale of one to 10 and we weren't like there is something seriously wrong with it awkward enough to check what's going on. And we realized that the only nurse that was trained to use the tool, went on a	Ensure people supporting the tool implementation has the capacity and training to do so Having an internal culture of innovation and change, including things like management buy in, workflow amendments, training and internal champions

long holiday. Maybe she had burnout or some chronic illness. We don't know, she didn't hand over to anyone. So the patient was promised a really good tool to make them feel more safe, more monitored, that no one was monitoring and no one was responding. So here again, if you don't dig deeper and try to understand where is this lack of value coming from? You might mistakenly think the tool is not working. But it should it was this lack of internal championship and drive and ownership. And that was again, in my view, it goes back to the culture and the management. The management made the decision but they didn't pull through into how does this translate in a daily lives? Who's actually keeping this thing running? Do they have enough time? Do they have enough support, to take off their shoulders, one of the things they traditionally used to do so they can give more time to this thing? If they're not there? Is there someone else doing it? And I think you learn about those things, only when you're part of those pilots and then you realize, oh my god, this is actually a key element. Because if I only look at the survey results, it looks really bad. It looks like oh in that case, it didn't work. But the real reason was not at all the DTx it was the workforce in that location. Does that make sense? Yoann Once more I absolutely agree with what you said, and definitely it's this is a key key enabler in a way in the overall deployment of any solutions being mostly tech driven solutions, but any solution, so totally agree. On the we did cover quite a bit in terms of variety of different factors and thanks a lot for sharing your more personal experiences and stories are so that was really insightful. Anything that we have missed? Are there any additional considerations, dimensions factors that could impact the economic profile of the DTx that you will want to share? Participant Yeah, I think we covered pretty much everything that I could contribute with. I think the key things that you identified in your groundwork with the systematic review is already super clear on where the gaps are and where people focus in the current measurements, and I would hope that your very impactful work will help put some clarity around maybe new measures to consider how to measure them, how to take them into account how to reflect them, in the different contexts and also addressing the softer effects like change and innovation and mindset, even if people don't want to measure it, because in health economics, people are very, very focused on things we can objectively measure and quantify but human behavior is much more than that. So that's your work with we'll shed light on those softer factors of the of the equation. Yoann But, you know, I don't want to take too much of your time. Thanks a lot again for agreeing to be part of his research for sharing all this like amazing comments and insight today. Again. Thanks for your time and have a good day happened. Talk to you soon. Thank you so much. [end of the conversation]	Change required from a human behaviour, being the nurse, physician or patients? Ability to impact the overall patient experience

Appendix 2I. Focus group discussion materials

Hello and welcome to our discussion! Thank you for joining us to discuss DTx and the factors that influence their potential economic benefits. My name is Yoann Sapanel, and I am from the National University of Singapore. Part of the research study team, we also have Dr Smrithi, part of the National University of Singapore and Prof. Cloutier, from the University of Quebec in Montreal.

You've been invited based on your experience in developing, clinically validating, or implementing digital health technologies, particularly DTx. Today's discussion focuses on factors influencing the economic benefits of DTx.

Before we kick start, just to provide a bit more of context, the current technology development process involves a large number of individuals, including researchers, engineers, clinicians, and health technology assessment experts, to name a few. Numerous factors at each stage of this tech development process, may have an impact on how the technology delivers value, particularly economic value, when it reaches the hands of end users, often the patients.

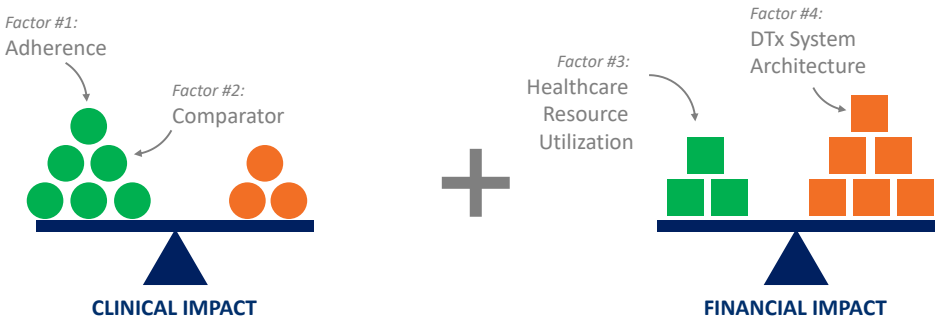
As a result, we would like to request your feedback today on the factors that may influence technology's ability to deliver economic value at each stage of its development, especially when it reaches the market. You may be wondering about the economic benefits for whom? Well, we will need to look at this from different perspectives. We can consider the economic benefits of a digital health solution for patients in an OOP market, or for a healthcare system. These economic benefits might also be necessary to secure potential funding or to demonstrate specific value to potential payers.

A Group Concept Mapping approach (1/2)

GOALS OF THE STUDY:

1. To comprehend the economic value drivers for DTx;
2. To learn more about how stakeholders involved in DTx development consider factors that might influence the DTx' ability to deliver economic value?
3. To comprehend how these stakeholders contribute to or create conditions that may drive the economic value of DTx.

PHASE 1: ECONOMIC VALUE DRIVERS IDENTIFICATION



Note: All perspectives are considered, of the patient, hospital/clinic, healthcare system or society.

2

This focus group is the initial phase of a three-phase research study (see slide). In the next phase, we will rate different economic drivers to evaluate their significance and importance. The third phase will also involve a focus group discussion to review and analyze the outcomes of today's conversation, as well as the results from the second phase.

Note: Go through the three-phase research stud, and the GCM approach.

A Group Concept Mapping approach (2/2)

PHASE 2: SORTING & RATING

DTx Inception & Development	DTx Clinical Validation	DTx Implementation
Is the [*factor X*] important? Is it considered? If yes, how?	Is the [*factor X*] important? Is it considered? If yes, how?	Is the [*factor X*] important? Is it considered? If yes, how?

PHASE 3: PARTICIPANT INTERPRETATION AND UTILIZATION OF MAPS

FIGURE 1
GCM project point map

FIGURE 2
Cluster map of thematic clusters identified

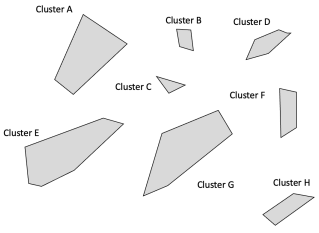
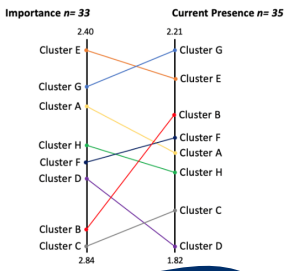
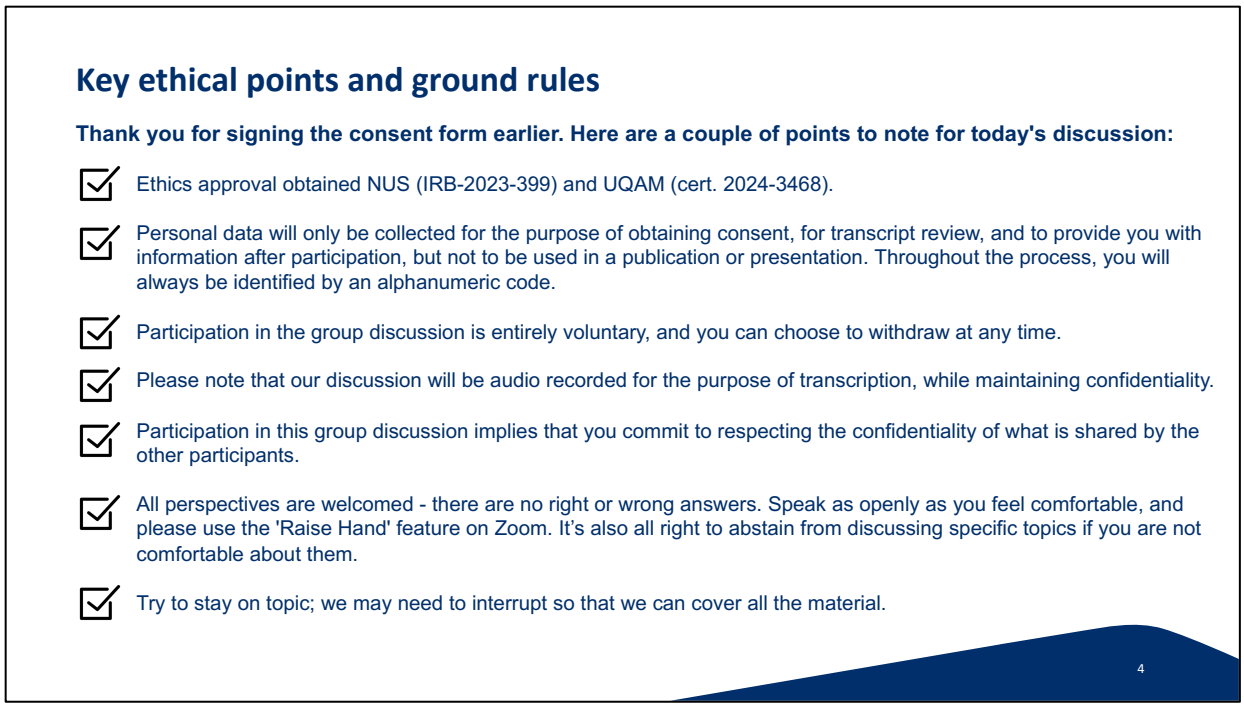


FIGURE 3
Cluster relative pattern match



3



Informed consent: Before starting with the interview, we would like to review with you the ethical dimension of the research. All the details regarding this were forwarded to you by email in the Information Sheet and Consent Form. We want to review the importance of the contents from the Information Sheet and Consent Form. We want to ensure that you understand the purpose of the research, the protection of your privacy and the confidentiality of the research records, that there are no possible discomforts and risks, that there is no remuneration or compensation for participating, that benefits are indirect for taking part in the research for the advancement of knowledge; that the interview will be audio recorded only; and that you can withdraw from the research at any point in time by informing the Principal investigator. Given that you are taking part in a group interview, if you are to withdraw your participation, it will not be possible to discard your data up to the moment you cease your participation to avoid invalidating the research, as it would disrupt the flow of the data content. However, the same privacy and confidentiality ethical dimensions will be maintained for the collected data you will have provided.

Please note that we are audio recording the session to ensure that we do not miss any of your comments. We will be on a first name basis today, and we won't use any names in our reports. You may be assured of complete confidentiality. Participation in this group discussion implies that you commit to respecting the confidentiality of what is shared by the other participants, not to identify by name people with whom you are in contact, nor to share information that would allow the group members to identify them.

There are no wrong answers but rather differing points of view. Please feel free to share your point of view even if it differs from what others have said. Keep in mind that we are equally interested in factors that might have a negative or positive impact on the economic benefits of DTx. The discussion will assist us in filling a research gap by describing all key factors driving DTx economic value across the DTx development life cycle.

If there are no further questions, let's get started!

Let's start the discussion:

What are the factors that might influence the digital therapeutics' ability to deliver economic value or benefits?

Appendix 2J. Focus group discussion transcript

Topic: GCM DTx Study
Interview date: Oct. 2nd 2023
Location: Online
Time: 11am
Interview type: in-depth interview over Zoom
Participant Profile: Clinical + Digital Health Expert with >20 years of experience in clinical/ advisory and business angel capacity.

Data	Codes
Participant #1 From a health economics or health technology, the first question is that is it a technology that is as a good the comparator, and for a DTx, it will be to be clinically as good as the standard of care. So like, an example might be computerized CBT. So the big advantage that computerized CBT has over a human therapist is that it's much cheaper, right? So like there's like a division between things which are cost saving, and then things which were actually better than the comparator. So they actually add some level of clinical performance, and then the question is, will the cost actually merits that additional level of performance, so maybe it's like a solution for, not sure if it's a therapeutic, but maybe it's a solution for improving compliance, so actually that people take their medicine or something like that, so in that case, there would actually be a clinical benefit from using the technology relative to the traditional approach.	Clinically as good as the SOC or comparator [referred as the clinical performance] Patients level of adherence to the therapy
Yoann Thanks a lot participant #1. Participant 2, you wanted also to share your perspective?	
Participant #2 I'll share a bit of a clinical perspective. Actually, while I had my virtual hand up, Alex said a couple of the things that I was hoping to say. One thought that I'll just add on is that I think early on in the development process of any of these therapeutics you can kind of predict which ones will be successful, just based on what type of clinical problem they're going to solve. I know TaT [a DTx solution] was one that was very popular in Scandinavia that fix a clinical issue that is solved very algorithmically, and so it's a perfect opportunity for a digital therapeutic to give patients a standardized questionnaire that you would give anyways in the clinic, and then prescribe them some kind of physiotherapy routine that you would be prescribing in the clinic. It's just a problem that was right for digital therapy, and a lot of clinical problems are not algorithmic in that sense. I think choosing the right problem to begin with is going to be a core predictor.	The existence and nature of the clinical problem to be addressed [as a core predictor]
Yoann Thank you. Yes!	
Participant #3 Nice to meet everybody. Hopefully, you can hear me okay. I'm based in Asia, so working in both in kind of high income countries, but also lower to middle income countries, and I have sort of dual conflicting roles in a way because I do sort of	

some of the policy councils for regulation and reimbursement of digital health but also investing into early stage technologies that are basically trying to break or circumvent such policies... But I was going to share with you just kind of a couple of things we've been working on that kind of feed into some of these variables, and I'll just hit the high points and explore them later but I think one thing is when it comes to the qualification and classification of digital health technologies like DTx, we found some deficiencies in the value assessment frameworks, and so we're of course looking at clinical, you know, economic value and to kind of traditional things, but we're also trying to incorporate things like consumer experience or user experience on the technology, data privacy, workflow, sort of optimization, or detraction, so what we're trying to basically say is, hey, governments, these technologies can possibly add additional value in these areas need to assess these differently from traditional medical technology. One thing I was going to say which is really I think still a challenge is things like telling the economic story in a broader kind of social context, I know you found this in your literature review as a kind of deficiency as well, but not just how governments allocate resources but also how they raise revenue for their system right and how these technologies contribute to revenue raising and also there's always a trick in like the short term storytelling versus like the long term impact, right? And so I would kind of probably summarize these things into what participant #1 had before which is like "cultural appropriateness" of the economic model, ad you see nowadays like value based contracting and stuff, they are trying to add this part to the equation to potential appropriateness of variables as well. So these are few things we've been working on that might be relevant. Participant #4 Nice to meet you, everyone. So my context is mainly from Germany, where you might know some years ago there was like a formal market access process established for DTx. So a lot of the feedback that's collected now comes from experience center, actually this process that guarantees reimbursement by the public health insurance, and so in terms of the economic parameters, which of course has been essential, most of the products developed is medical benefits. So there's a clinical benefit to patient of disease mortality, improvement of the disease state, but then also in terms of outcome quality, but then there's also explicitly encouragement to include improvements in process and structure. So things mentioned before like patient safety, adherence, health literacy, etc. It's not being excessively used so far, but it's been included in the model. And from what we're researching now, is the results of all of this, is that really, like highest benefit in the field, often comes back to the usability aspects, so acceptance by physicians, how does the product integrate, in the processes, and then also like acceptance for payers and patients, a big factors for the implementation. Participant #5 So yeah, I agree with what all my peers have said here, and especially about the need for clinical outcomes, so to have strong evidence that of the efficacy of the device, but I wanted to introduce a caveat, maybe not so much based on I mean, how badly base on my experience but also like, what I see around in the field, is that you can a very efficacious DTx, but if the person that has the ability to deny the payment for the therapy, thus then it doesn't matter how, how exactly as it is, and I think there are some cases of very, very important DTx companies that they found enough coverage or for reimbursement. It's quite I think it's, it's up pharmaceutical, it's not it's not so easy to get coverage for reimbursement for these digital modalities. So yeah, I would say the, that importance is also like, maybe a cultural, cultural change or the ability to yet to educate the people in charge, then the teacher mentors.	Country specific qualification and classification of DTx, and respective value assessment frameworks Compliance to data privacy standards Level of disruption in the workflow and protocols Short versus longer term impact assessment consumer experience or user experience the cultural appropriateness of the solution, and of the economic model level of medical benefits outcome quality, clinical, as well as improvements in process and structure patient safety adherence digital literacy health literacy usability aspects physician acceptance patient acceptance level of the solution integration to existing worklow and processes level of coverage or for reimbursement level of education of the various stakeholders

Participant #4 I'm happy to support that from my perspective, so we've had the traditional process, process in place to be negotiations, one year of trial, the vendor will set the price and then after that one year, it's a negotiation between the payer and the manufacturer, and many of these negotiations end up in arbitration, probably because of the value model is not strong enough to lead to a decision earlier, and the prices that result are often pretty homogenous... So the differentiation between the effects and the outcomes and how to value that in the current model is not strong enough. The dominant view is psychiatry or psychology, therapy substitution, but there's also a broad range of other indications. And I think that's good modelling and smart ideas for how to create and prove the value of these products would be very helpful…	effects and the outcomes DTx as a supplement or as a companion to an existing treatment
Yoann Thank you, participant #4. So we will discuss quite a bit on the on the clinical kind of efficacy, so to focus more the cost aspects, from your experience, what are maybe these few key cost considerations that might drive up or down the potential economic value of a DTx?	
Participant #1 Yeah, so I've been reflecting on the Singapore environment, one of the things that seems to me to be a challenge for developers here is the government is trying to develop a single platform, so there's health hub, and one of the things which I don't really understand about this industry, is that if you have all these different national or insurance system level platforms, you can see why people want to do this because having an ecosystem, which is fully integrated is very attractive from the customer point of view, but what does that mean for the developers, how do they create something which is going to interface with all of these different national level systems, so it's not really an answer, it's really a really another question. I don't know if it's at least tangentially relevant.	
Yoann Thank you. Sometimes it's about digital health solutions or DTx, we can try to differentiate later what might be relevant for digital health solutions versus digital therapeutics. So do not hesitate also to share to share your experience on digital health solutions and/ or DTx. Participant #3, you're about to go ahead.	
Participant #3 Yeah, I guess an observation and like a specific variable, but I think sometimes people are under the impression that every government is just out to kind of say, or be payers just out to, to bring costs down or to save costs, and not that that's not true, but I mean, I do think we're in kind of a nice period of you see, generally that health inflation is on the rise. You know, there's a fair amount of resource there, but I think the trick is, I still don't I see the direction of most areas going more for the population rather than for the niche. I mean, we've seen some governments just flat out refusing to pay for very niche interventions, right. So I do think that's a consideration when developing any intervention, normal digital health and digital therapeutics, which is, ultimately are you kind of in line with your broader vision of kind of how the money is being allocated with cost allocation perspective [the money flow].	Targeting a broader versus a niche population Alignment with the country priorities and current money flow/ resources allocation
Anything I was going to bring up a little bit later, like other variables are most important variables, but one major thing that I think is going to be coming in terms of assessing new interventions is that workforce or human impact. Today, it's kind of what you would call "soft economics". So things like productivity is not always a core part of the equation, because you know, someone is just more efficient with	Human impact, including Impact to current workforce including manpower allocation and productivity

their time, that may be more of like a soft game rather than a hard game per se, but I think the workforce issues become so big, at least my discussions with governments on new costing models. I think that they feel that sometimes people developing these technologies are not properly considering the whole workforce impact, right? Because even if you need to take someone's time off to the clinic to train them to use a new technology, there's a cost to that right, and I think sometimes that these costs are not currently being factored into models fully.. Yoann Just clarify, participant #3, on the soft economics, or the impact of a potential manpower, is your comment kind of rrelevant or both from the developing and the developed markets? Participant #3 Yeah, I wouldn't say both. I mean, the workforce impacts are very extreme in the developing markets because it is insufficient workforce, and the current one then to go to the developed markets, but that's in some ways, why the technology being adopted quicker in some of those places. But I think in terms of like maturity of the assessment framework, from a payer perspective, it's more than the developed markets but both types of governments I've talked to the this issue of the workforce bubbles up a lot, and I think it's something that technology developers would be good to better understand the economics to doing both the benefit but also the cost that they put onto the system. Yoann Yeah, thank participant #3 for clarifications. Anybody has would want to follow up on this on the overall cost drivers of digital health solutions? Participant #1 Yeah, so I can follow up on participant #3's point. So I mean, from an economic theory point of view, I guess the value of something is not necessarily the same as what you pay for it. And I think we're definitely in that situation, you know, with a lot of scarce human resources in the system, so to kind of touch on HTA methodology, we tend to cost staff as salary plus their add on cost, but I'm not sure that's really appropriate and in highly capacity constrained environment. I mean, the real, the real opportunity cost of someone's time is off the clinic sessions that are displaced when they become available, because there is no one to do the surgical operations, the colorectal cancer surgery, which they would do because there is nobody else to actually pick up that slack at the moment. So I think our HTA guidelines were designed for "time of plenty" and we're now in "time of scarcity" and we might want to design them now, we might want to think about them a bit differently. Yoann Thank you. Maybe, participant #6, I have a question for you. I know you have like a lot of experience in the implementations of digital health solutions, DTx, and have you seen some of the factors when you were, you know, in this entrepreneur shoes, that you have seen that would be more or less important when you need demonstrate some benefits to certain stakeholders from your experience? Participant #6 Yes, so from my experience, and something that I also would like to introduce to the discussion is, let's not forget about the patient perspective and how patients are actually interacting with the technology and do they want to interact with the technology. So I, I designed and worked on several different digital therapeutics or digital diagnostics, and what I found that one of them, which is a solution for	Level of education and training required of HCPs [part of onboarding] Level of scarce human resources in the system Cost of the manpower (salary and add on cost) opportunity cost of someone's time is off the clinic sessions that are displaced when they become available

cognitive decline post brain cancer, had 96% therapy adherence even though patient is not compensated per session. And in this case, there's quite a lot of sessions. It's three sessions per week for 10 weeks and remember that patients already have brain cancer which is very, very taxing on health. So it was very surprising for me that this kind of, it's definitely improving patient outcomes because we don't have a data that supports efficacy of the solution yet, it's just the clinical trial right? But there is this perceived improvement in patient outcome, and also, there's this kind of perceived purpose where patients on phone interviews, they want to help to develop something that will be useful for other patients with brain cancer, and I think it's very important to also focus on usability of the product and the actual needs of the product, because it will depend on the business model, of course, but if I think it's important to remember that this could also be driven not only by doctors and nursing practice that could be triggered by patients and their own need for products like this. Yoann Yeah, thanks a lot, participant #6. These patient centric considerations are extremely important. Anybody else will want to follow up on this? Smrithi (research study team) Actually have a follow up question to ask, as it's related to what participant #6 said, and this came up earlier as well about choosing the right problem is important and cultural appropriateness is important. So I was wondering if you had any reflections on how this is tied to the cost and economic value? Participant #2 I can get me started but my perspective, is there a lot of technologies that are developed in an attempt to solve problems that really are better solved by people fail before they reach market, and so there's no economic value to those. I think there's a lot more digital therapeutics that are developed that are ever adopted. And so when I meant earlier there's just I think there's a lot of strategy and upfront before going it's sort of the “measure twice, cut once” things spending a lot of time thinking about which problems this type of technology cater itself, before jumping on the development of something than trying to sort of haphazardly put it into a system where it's not really going to be well tailored for. Participant #4 Yeah, I would agree. It's the combination of the problem and also the audience. They did some research from DTx for patients with depression, and just because something makes sense clinically for them to do a certain exercise or to see certain information doesn't mean that you know, if it's hard for you to get up in the morning, it's not necessarily easy for you to open a technology interact with specific types of information, so we built something that works with the intended audience with the patient, and they're not supposed to deliver the clinical evidence based trial base but I think the user is very important and very different in these different versions of the products. Participant #1 I'll take up this challenge of how do you identify the right problem? I'd like to suggest three things to think about. So one is there a specialized scarce resource which was being used in providing the service and that's a signal that there is an opportunity to add economic value by automating some of the stuff that that that scarce resource does. Another signal might be if there is a lack of access, so that signals that people are finding difficult to read physical services for one reason or another, so the Scottish Government is implementing a digital sexual health pathway and that seems like a good thing to try, since sexual health is something	perceived improvement in patient outcome usability of the product business model of the solution (go to market and monetization model) level of patient centricity in the solution Not a single factor can explore, it’s might be a correlation/ combination of factors that might be required Level of specialized scarce resource supporting or optimizing time and productivity of such resource lack of or difficult access to a treatment

which people often struggle to access, both for reasons of convenience, but also for reasons of stigma. And then the third thing, which might be worth thinking about is where you know, there is a lot of coordination involved, and that seems like an area where digital health technologies can play a role and by sharing information in a coordinated and organized fashion between different specialties. Yeah, I think it's a great question, actually. So yeah, thanks for thanks for putting it out there.	degree of inefficiencies of current pathways and protocols, (where lots of coordination between HCPs might be required, with a better flow of patient and information)
Participant #3 I was gonna say as well, I think there's like a framework aspect and the story aspect to what you described. So I think on the framework side of things, that's why I mentioned before, you know, to take value based contracting, it's no longer just quality or a cost, right. And these models are very sophisticated these days and actually they have an appropriateness, there is a model that has an appropriateness variable, to me, that's something to look at for, for DTx. But I think also the storyline aspect is important to cultural appropriateness, and that can be at the very macro level. So for example, countries that are in a trade surplus mode tend to invest more quality than efficiency, when they're in trade deficit, they tend to be investment efficiencies, right? So you got to kind of understand this at the cultural level to frame the story, but even at a micro level bite, so you look at the use of let's say telemedicine in certain countries who still have a high contact culture, it's got to be like an online offline model to make some games online, right, so , that's where you take the framework but then you have to add the storyline that is very culturally appropriate.	level of sophistication in the value assessment framework cultural appropriateness of the solution
Smrithi (research study team) I was just saying very insightful responses. Thanks, everybody. Thanks very much.	
Yoann So maybe on following an on the patient aspect. You know, I want to get your thoughts and your perspective on how the profile of the patients you target, profiles and demographics of patients might also influence on the ability of a DTx to deliver economic value?	
Participant #6 In Singapore, we are lucky that elderly is actually quite familiar with technology. So even though I have done some studies with the elderly population, 50, 60, 70 and 80+, most of them actually handle by phone and know how to use mobile phone, play some games, candy crush, so they are familiar with that. But I can imagine it's different in other countries so differently, they each say they should have familiarity with technologies…	Tech literacy
Participant #4 I can add on one item that's maybe a bit indirect but we found that actually the treating physician is the biggest influencing factor in general for treatment choice and recommendations, including DTx. Your physician could be a good product ambassador, giving you some benefits, and patients are much more likely to actually engage and possibly stick with it. So the big step that's sometimes missing is educating and convincing and also training the physicians appropriately so they can guide and recommend like they were doing with drugs for example. So it's been a big factor. Participant #3 I've had some challenging experiences with digital literacy. And I think, you know, later maybe we'll talk a little bit about the subplot of patient monitoring versus	Level of influence of the treating physician to treatment choice and recommendations, including DTx Level of engagement of HCPs , and willingness in prescribing a DTx digital literacy.

intervention, because I see these technologies kind of going back and forth a little bit, but we were running a clinical trial of a patient monitoring sensor on the knee after total knee replacement, and the idea was for patients not to have to, you know, physically go into the care facilities that they can do their rehab, at home and send information to the doctor, but at first, when we were running the trials, the outcomes were showing really badly... But what we found is that some patients who just taking it off or didn't really use the app and just you know, and it was kind of across age ranges, and so, then we started to do, […] you have this like, three step before you provide an intervention to somebody to make sure that their digital literacy or their interaction with digital is sufficient enough that the outcomes can actually be achieved. And one of the things I've come across as kind of related to that is also just things like internet access. We take this for granted, but depending on the solution, again, the outcomes may not be achieved in certain infrastructural, profiles are not available to.	Patient adherence Internet access Level of infrastructural readiness (wifi, etc.)
Yoann Yeah, thank you participant #3. By the way, if you have later some additional points you will want to share you could always drop us an email or WhatsApp. I would want now to go one level deeper and focus on this initial stage, which is DTx inceptions and development, you're looking at your potential MVPs, it tends to be more like engineering kind of driven type of phase. I will want to get your thoughts at this stage, do you see any early factors that that could enable or hinder the ability of DTx to deliver economic value?	
Participant #2 I can start with a brief comment just to say that most of the really successful technologies I've seen, began with teams that had just a wide array of perspectives, kind of like this group here, and featured clinicians that understood clinical problems and developers that understood what was feasible to develop, and folks with expertise and implementation. I think it's necessary to have all those perspectives upfront. Similarly, same technologies that clinicians have tried to develop without input from folks that actually know how to do this, and there's never gotten off the ground…	Solutions being developed in silos, or in partnership with the broader community, with all expertise, etc. Addressing a genuine, real healthcare problem(s)
Participant #5 Yeah, I think it has been mentioned already. But yeah, in this phase, I think that it's critical to ensure that the DTx actually addresses genuine, real healthcare problems. And also I would add that some mistake that people might do is not engaged with their regulatory authorities early enough, I think to have a regulatory strategy from the beginning, and it can easily pave the way for you to market approval.	Level of engagement with the regulatory authorities Level of early adopters among the healthcare providers
Participant #6 I would like to point out the importance of early adopters and partnerships with healthcare providers, hospitals, organizations or any ecosystem that can help us to demonstrate the early market interest and help us validate the DTx.	Level of partnerships among healthcare providers, hospitals, organizations or the broader ecosystem
Participant #1 Also, doing your work on competitor analysis, I think, some of the technologies that I've seen developed or developed with great enthusiasm, but people have an idea but without really looking at, or to understand what's available in the marketplace already, and then how to develop this, and where they actually sit in that landscape?	
Participant #3	Classification of the therapeutics as a diagnostic versus interventional solution

I think what I would add from my side is a clear earlier decision on a diagnosis solution versus interventional solution, I still think it's really fuzzy there. And I mean, this comes from a little bit of an investor lens now but I think a few years ago, there was pressure to stop at diagnosis because that meant less or regulatory pathway, quicker to market, less capital you needed to be deployed. But I think once you've noticed over the last couple of years in some of the health tech kind of blow ups, it's actually there isn't a great business model. Right? There wasn't a core kind of fundamental sustainable business problem. So now you see a lot more pressure from investors for people to go further and say, don't just be diagnosis but also provide intervention and provide a solution, that solution became basically DTx. So, I think this decision point needs to be clear earlier on about that later, because that impact affects everything. It's kind of like if your car's broken in take it to the garage and they just tell you what's wrong with it. I'll tell you what to do about it. So I think there's a lot more pressure out to, to earlier on, define such intervention, and define the line. Yoann So I have maybe a follow up question some on what I guess most of you have mentioned so far, which is really about the need to ensure you're going to address a real need, a real problem basically being a clinical need or not, but I think this came out from every single conversations that we had so far for this study or for different study, but my question to you is how could you ensure that really there is a need but you could address with a digital health solutions 18 months down the road? And a need that is worth addressing? Participant #2 Yes, the short answer from my perspective is just befriend a clinician, find someone that you trust and engage with and is on my mind back as a clinical work, and if you see those problems every day when you go to work, you can't you can't miss them. So involving those people [clinicians] in your team, I think is a key step early on. Participant #6 I agree, and be friendly with other healthcare professionals as well. One of my most interesting projects actually stems from the nurses and their need to save time and to optimize the time, and develop a solution that will help them to be more present for patients that need them most. Participant #3 I think from my side a couple things so these days, needs based innovation is already quite well developed, right? There's a lot of such programs that exist, so I'm dubious of people that come up once that have not been through such a program, because more often than not, it's not just about listening to someone on the frontlines of has an idea but going through a structured process of validating that need space innovation, right? So I tend to focus on, let's say people that have ideas and take the time to go through such a program. But I think the other thing and it's just my own kind of perspective on life, I'm also kind of doubtful that someone that's got a DTx would unilaterally build that into a multinational company. I think it's wise early on to maybe find a corporate or like multinational partner because it's not just about the clinical need, but also how you can take something to market at scale, through the commercial, you know, navigate the different markets and stuff and I think that's where such partnerships even if it may seem a little competitive at first, but finding a way to work with someone is always the strategy I tried to.. Yoann	Level of clinicians involvement in designing the solution needs based innovation DTx level of validation of the needs to be addressed level of partnership with a corporate or like multinational partner

So, we covered the first phase of inceptions and development if we move on to the clinical validations right, which is most for DTx, do you see any factors at this stage specifically, that might influence again one way or the other on the DTX ability to deliver economic value during this clinical validations stage? Any factors that we have not discussed so far? Participant #6 Smrithi has all the more experience on that but she actually helps me with user engagement and kind of user study where we ask questions to the patient's telling us what do they think, how they improve, and then the therapeutic that is being tested. And I think if I've never done this before joining the stuff and I find this very, very beneficial to have those interviews or focus groups with patients and get their user feedback directly, not only on purpose or objectives, but also very small details like, what do you think about the interface? Will you add any button things like this? Yoann Yeah, definitely something which is critical, which is the early engagement of your potential end user, right? So definitely. Participant #4 When you prepare for reimbursement, It's also important how you design your study. I think there's not too many clear guidelines that I've seen, work, study science and you need how do you structure the populations that actually represents the clinical reality to a sufficient extent, I mean, given that we are usually targeting a less digitally literate population that you may have access to for testing so I think that's something to pay attention to, and then also to see what compare to that, what are you choosing and then comparing the standard of care and comparing with your just whitelisting and switching over and your trials that's been important to convince payers but I found and also the other aspect, that's been important is how you position the product in the clinic pathway, going from where we are today, with the physicians, and how would that be products that in and we have seen that it's a big, a big deal, whether it's somehow substituting a physician, or complementing to some extent, and then trialing and communicating appropriately. That's been another important factor that I've seen. Yoann Yes. You mentioned quite a few points of view on this, on this aspect, that's great. I heard before the need to be “efficient” when it comes to the design of your clinical trial, you know, having an efficient study design. Could DTx be efficient in the study design or it all depends on the context and therapeutic indications and so on. Is there any kind of recommendations, or ways to be efficient when it comes to the study designs? Participant #5 it's just common sense, just to clarify for some time since they're like these basic mistakes, right, so to have proper statistical power to choose the proper entry points, and then to choose the proper control arm, let's say comparator, and that's a problem because it's not always possible to find the right control arm. It's not as easy as a placebo in a drug, for example, by blinding is not always possible. But yeah, so the points I wanted to just address. Participant #3 I think it's related to a comment I want to make to just about the data aspect of stuff, but I think, personally speaking, there seems to be a little more hype than reality of I guess we would call it synthetic clinical trials just through pure data, like	Presence of user engagement study/ usability study Clinical trial/ study design Level of the representativeness of the trials participant to real population in clinics Type of comparator Positioning of the solutions in the clinical pathway, like substituting a physician, or complementing to some extent, and then trialling and communicating appropriately. proper statistical power, entry points and control arm. Presence of reconnaissance of synthetic clinical trials/ retrospective study or case study

if you see there's some movement now like cruelty free testing, right? At what point can you just run clinical trials based purely on synthetic data rather than trying to necessarily do full human trials like you've done in the past? And to me, that part still seems to be and then that could be where technology to be very efficient, right? For example, but something unfortunate more of a problem than a solution, something we've been studying a lot here, what I would call it the DTx paradox, and that is that you know, these solutions need to be proven to be adopted, but they need to be adopted to be proven, right? They just kind of sit in this chasm, and also the very iterative I like the software is going to prove as it's adopted, and currently the pathways are really not set up for this. I think RCTs have been quite challenging in this space, and there's been like sandboxes and stuff but it seems more like a kind of interim compromise than a full blown solution. So I think this kind of paradox, it's something that I think for DTx to survive, really, it's going to have to be figured out somehow or maybe somebody else has figured it out, but we struggle with that quite a bit. Yoann Thank you. Participant #1 Yeah, so I mean, I just like to throw into the mix. I mean, I think one of the things that is very important is compliance with you know, whatever the decision maker expects, so, you know, certainly in the pharma world, not probably our drug trials are not as efficient as they could be from a purely no statistical point of view. Certainly, the trial populations are not particularly representative of the real world, but the great success of the kind of pharmaceutical system is that people kind of know what's expected.. So they know what hoops you have to slightly cross or they know what hoops you have to jump through to get your product into the market. They know what the rules of the game are in that sense. And it does seem that for digital technologies, we're still at an earlier stage where there isn't really quite clear rulebook about what you should, what you should do and obviously that person, our level of risk, you know, for everyone who's staked their money or their livelihood, or […] results on these technologies. Yoann Moving on to the implementation, what have you ever seen is that in the literature, they have this readiness for implementations as a key factor that would impact again, either way, the adoption and, obviously, the ability to deliver economic value for DTx. So I wanted to get your thoughts on what does this readiness for implementation mean? What does it mean to you and how if tomorrow, you might need to assess the readiness for implementations of a healthcare provider A versus Healthcare Provider B? What would be some of these factors that you would want to consider? Participant #4 We already mentioned it, but digital literacy of the patients, target audience and clinician side. And then second factor will also be trust, because it is a new way of delivering therapy or receiving therapy. Yoann Trust, sorry, and trust to confirm participant #4, like trust from the end user perspective or physicians? Participant #4 Both. You know, healthcare providers and also the patient's you know, you know, as a patient receiving digital therapy instead of maybe something that's a face to	trial populations are not particularly representative of the real world Understanding of the DTx manufacturer on how to get reimbursement/ approval digital literacy of the patients, target audience and clinician side trust from the end user perspective and physicians trust from the physicians that I can prescribe a DTx

face intervention, and then also as a clinician to really trust the product and say, this is something that “I can prescribe”, you know, with a good confidence.	trust/ good confidence in the patients to use such digital solution
Participant #2 There is another element to this, is being physically ready to use the technology like I think many clinicians and nurses are, are also don't have the digital literacy that we might expect from some of our patient populations. And some technological rollouts come with an enormous learning curve and take months to be comfortable using. I've seen this with electronic medical record systems, at least in Canada, where most of our hospitals are operating on EMRs that are many decades old, and new and much more efficient technologies exist but there's such a barrier to entry right? We don't have to learn how to do it. They'd have to pay an enormous amount of money for like a rollout support team to come and hold their hands through learning this new system. And so I think the usability of a technology will dictate how long it takes the person, and how much use it takes to feel ready using it.	Upfront learning curves from the HCP adopters, and level of education and training required
Participant #6 I can agree with that. From my perspective, I cannot say that. It must work well on the back end and the front end and people can be discouraged very easily. And even though your product because even though the products, the need everything is there, but there's an issue in a login or something is lagging, people just stop using it. So that's number one and number two, well designed and test that interface for both clinicians and patient side.	
Participant #3 A couple things from my side. So I mentioned that kind of data paradox earlier but let's say I was able to overcome that, I still don't think a lot of systems are set up for iterative cycles of things like DTx. It kind of defies traditional logic of what's a proven drug and that's going to how you implement it for the next 20 years. Maybe some different indications, but you know, it's sort of a linear process versus you know, that software's that learn and get better over time and maybe even having total shift and realization and thinking and I just, you know, I think that part is still quite immature. The other thing I would say is, I often wonder if what if a payer truly believes in such a thing like DTx, would they be willing to go so far as to like basically nationalize adoption of it, meaning no it is more universal because when I say up in today's they may approve it. But then when it comes to purchasing, it’s a decentralized decision making down to the hospital or clinic level and so in the end, they kind of don't take authority for really scaling it up and then the technology company is forced to go hospital by hospital trying to convince them that it's something they should use, if the payers would really believe in it, they should, I think be willing to help scale it up to not just kind of push everything back down to the default level.	Ability to operate in agile manner, with iterative development cycles Level of support from goverment and regulators (direct procurement)
Yoann Participant #4- It's kind of a follow up questions maybe to you in a as you mentioned, being involved in the DIGA in Germany, and you know, he has been live now for 2019, I guess any on this readiness for implementations, we have a regulatory framework pathways where the uptake is maybe not up to the expectations, I guess, and especially from the DTx entrepreneurs, on this readiness for implementations, I don't know if there are some initial learnings and insights, at the country or provider level ?	
Participant #4 To add to what the participant said, I mean, in the German context healthcare in general, as apart from very high level regulation is quite regionalised, so it does	Centralised versus decentralised healthcare system and decision maker,

come back to basically the individual decision in the discussion between the patient and commissioners is something that we want to do, if the clinicians say yes, then they are allow to prescribe it and the patient will get [access to the DTx]. So that's all that comes down to convincing commissioners, like there is a gap for something in psychotherapy, we can see up to 20 weeks of waiting time to access face to face therapy, so there's a big opportunity in bridging that gap, for example, but it does come down to digital literacy, there are two levels of explanation possibly, and the patients, that a critical aspects from the payer perspective. What we see from payer's […] And so payers feel they don't have a say, but we have to reimburse. So they sometimes tend to develop their own DTx and recommend those to the patients. So there's some sort of competition that's also impeding access to some extent from what we see. Yoann Thank you, participant #4. So I would want to move on to the last question today, have we missed anything from this last one hour plus of conversations we had on some of the factors, or any additional considerations? Are there any anything, or any additional factors or dimensions that we should consider and what we have not discussed yet? Did we miss anything?	from government to local authority and healthcare providers.
Participant #2 I think we talked about trust. I'm not sure if we talked about privacy. And so with any therapeutic or any digital tool that interfaces at all with electronic medical record, keeping patient information confidential is sort of a deal breaker I think for these technologies..	Privacy aspects, concerns and adherence to standards.
Participant #1 Oh, I would like to put a word for rural populations. So the Scottish Government's telehealth implementation was very much for rural populations first, where you know there is a real need and there is a real clear economic argument you say, you save people time, both patients and healthcare workers, you reduce their travel costs, so that's for us in Scotland that was a that's a kind of useful entry point and some of the things are introduced for the rural populations first and then mainstream subsequently…	Profile of patients being targeted (including rural versus not, risk, comorbidities, etc.)
Participant #4 And I would make a second point to add me to look at more blend care options. So we looked for example, into physiotherapy where traditionally, you would get six weeks of quite intense face to face with your therapy twice a week, for example, and then it stops, so adherence is a big problem in that physical recovery. There are some experiments, like extending the phase and support intermediate steps by DTx, and basically if you get a better result, forces are combined, that's something that I think I would see some additional benefits to show our payers.	DTx as a standalone treatment or in a combination
Participant #6 No, it just shows the potential of personalized medicine that tailored intervention. I think we didn't mention that, but this is that one big thing that could help to push this DTx forward. Yes, this will be more targeted approach, reducing trial and real treatment strategies and also potentially lowering healthcare costs because we can do something that we couldn't do before right with the software, and AI. Yoann It's all about personalisation. Right. Thank you! Participant #3	The level of personalization in the interventions delivered to the patients

I think a lot of the variables I wanted to mentioned, have been raised and discussed over that. But I think kind of related to this question on your questions is about stakeholders, we talked about that a little bit, too, and I noticed from your literature review that a lot of these studies currently the economic models are kind of industry led and so I still think we're probably not considering enough voices... And I always love for example, when I see surveys about people's willingness to adopt digital health, and the survey was administered digitally, right. What about everybody else who could never even access that server to begin with? So I think a lot about you know, media companies or social media companies, I see a lot of conglomerate organizations and middle income countries that kind of move into health care to fill the gap, banking institutions, etc. I mean, there are so many touch points that people have in their lives that affect health, and they're going to in the future affect the way they transact with health and I just, I think that somehow this needs to also factor into the equation now, whether that be the strategy of the DTx or even the economic model of the decision making. So I would just advocate for that too. Dean (research study team) Hi. Good morning. Good afternoon. I don't know where everybody is. I don't know if this has been mentioned yet, but I think when it comes to DTx, and because of the non-pharmacologic nature of it, it does lead to the possibility of rethinking how clinical trials are designed for DTx, having spoken to a number of companies, the one of the questions they often have pertains to responders, and something we clearly see with pharmacologic is sometimes lower doses can catch more responders at the right time, not everybody needs a maximum tolerated dose, or in this case, maybe maximum tolerated intensity or difficulty of digital intervention, and so that being said, I think how we design trials, allowing each user to see more, if it isn't intensity, or difficulty modulated type of DTx, it would be almost like a basket of different difficulties per user versus a basket of different interventions per user. And so I think the trial design could be important and that has a ripple effect with regards to the economics of the trial itself. There's a possibility of not needing as many subjects I mean, it's got to be still has to be powered correctly, but kind of letting each subject see only certain fixed intensity, etc. It really limits the exposure of each person and you know, when it comes to the number of subjects needed, also, at the end of the day, the durations of intervention, which then ripples to adherence there's a lot of factors involved, but at the heart of it, trial designs could potentially be modified and changed. The US FDA commissioner was in Singapore two weeks ago and so we had a chance to discuss specifically the role of hyper personalization not only as a means of treatment, but as a means of designing trials more efficiently and maybe in a decentralized fashion. I think that's a that's an area where there's a lot of room to innovate. Final thing is, you know, the FDA issued guidance in January of this year about needing dose optimization in oncology. I think dose optimization, if you will, in DTX, is an area that should be explored and again, it's got implications in efficacy, response, economics, timeline to market adherence, all of the above. Thank you. Participant #4 Think maybe just one very different bottoming overall, at least from what I've seen, it's just also just a very big change process, irrespective of quantity and trust and privacy and functionality, it is a big change to most health care systems. I think that naturally, no matter what it is, creates that someone's distance that probably is to be expected. Yoann which is basically back to some of the points we discussed earlier, but the level of disruptions you might have to your current existing workflows and practice.	Design of the clinical trials (nber of participants, decentralized vs not, etc.) Ability of optimize an existing treatment (eg pharmacological treatment) Level of disruption or change in the system

So once again, I really would like to thank you for this conversation. [end of the recording]	

Appendix 2K. COREQ checklist

Item No	Guide Questions/Description	Comment
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/ facilitator	Which author/s conducted the interview or focus group?	YS conducted the semi-structured interviews, while both YS and LMC co-moderated the focus groups.
2. Credentials	What were the researcher's credentials?	YS holds an MSc in Entrepreneurship and Strategic Management, while LMC has a Ph.D. in Strategic Management and Applied Economics. LMC conducts research in the areas of IT management. He is an expert in GCM with advanced certifications and numerous publications using the approach. DH holds a Ph.D. in Biomedical Engineering.
3. Occupation	What was their occupation at the time of the study?	YS served as a Director at the Institute of Digital Medicine, National University of Singapore, while LMC was a Professor in the Department of Analytics, Operations, and Information Technologies, School of Management Sciences, at the University of Quebec at Montreal, Canada. DH was the Provost's Chair Professor, Director of the Institute for Digital Medicine (WisDM), Director of the N.1 Institute for Health, and Head of the Department of Biomedical Engineering at the National University of Singapore.
4. Gender	Was the researcher male or female?	Three male-identifying researchers.
5. Experience and training	What experience or training did the researcher have?	YS, LMC and DH have extensive experience in conducting qualitative health research. Additionally, LMC has both quantitative and qualitative training, teaches research methods in the areas of IT and is an expert in GCM with numerous publications using the approach.
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	YS and DH had varying relationships with the health community at large, while LMC had no relationships with participants prior to the study. All were perceived as unbiased enquirers rather than persons with a particular stake, stance or opinion about the topic.
7. Participant knowledge of the interviewer	What did the participants know about the researcher?	The interviewers introduced themselves to participants and describing the context, scope and purpose of the research, going through the different sections of the consent form. The contents followed the exact guidelines as certified by the ethics review boards for research with human beings of all institutions involved.
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator?	The participants were informed of the knowledge gap and corresponding research question as context for the interview, highlighting the interviewers' interest in addressing this gap without presenting specific assumptions or potential biases. The contents followed the exact guidelines as certified by the ethics review boards for research with human beings of all institutions involved.

Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study?	We employed GCM, a mixed-methods based approach that combines thematic analysis with multivariate statistical techniques to synthesize and visualize collective thinking on a topic.
Participant selection		
10. Sampling	How were participants selected?	Purposive sampling was used.
11. Method of approach	How were participants approached?	Email invitations were sent to individuals identified as having experience across the DTx lifecycle. The recruitment process followed the exact guidelines as certified by the ethics review boards for research with human beings of all institutions involved.
12. Sample size	How many participants were in the study?	For details on the number of participants at each project phase, please refer to the Table 13.
13. Non-participation Setting	How many people refused to participate or dropped out? Reasons?	While several individuals did not respond to the invitation and one person explicitly declined, all those who agreed to participate remained committed throughout the study. This followed the exact guidelines as certified by the ethics review boards for research with human being of all institutions involved regarding participants' informed consent and right to withdraw without justification.
14. Setting of data collection	Where was the data collected?	Data were collected either via Zoom for interviews and through groupwisdom™, a web-based platform for GCM data collection, analysis, and results visualization.
15. Presence of nonparticipants	Was anyone else present besides the participants and researchers?	None.
16. Description of sample	What are the important characteristics of the sample?	Fully presented in Table 13.
Data collection		
17. Interview guide	Were questions, prompts, and guides provided by the authors? Was it pilot tested?	A semi-structured interview guide with key questions and potential prompts was used (Appendix 2G). While the interviews generally followed a similar approach, the specific questions varied depending on the participant's experience in particular phases of the DTx lifecycle or the GCM project approach.
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	No.
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	All interviews were audio-recorded and later transcribed. This followed the exact guidelines as certified by the ethics review boards for research with human being of all institutions involved regarding data management procedures during the research, during the analysis, and post-reporting.
20. Field notes	Were field notes made during and/or after the interview or focus group?	Following each interview, the interviewers documented brief notes highlighting the interview's nature and key themes emphasized by the interviewee.
21. Duration	What was the duration of the interviews or focus group?	Interview times varied but were generally around 60mins.

22. Data saturation	Was data saturation discussed?	Not applicable.
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No.
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	Regarding qualitative data, the interviewer coded and described the data, regularly discussing the resulting codes with the three-member study steering committee (YS, LMC, and DH). Three cycles of coding were conducted, including pretests, to establish the final list of factors. Regarding the quantitative data (n=37).
25. Description of the coding tree	Did the authors provide a description of the coding tree?	Codes had tags and description within the software.
26. Derivation of themes	Were themes identified in advance or derived from the data?	Themes were derived from the data during Phase 2 (“Factors generation”), while they were identified in advance for Phase 5 (“Data interpretation”).
27. Software	What software, if applicable, was used to manage the data?	groupwisdom™ and web-based Microsoft Excel 365 spreadsheet.
28. Participant checking	Did participants provide feedback on the findings?	During Phase 5 (“Data interpretation”), participants provided feedback and contextual interpretation of the findings and participated to establish potential threats to results external validity.
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified?	The themes and findings were presented without illustrative participant quotations.
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Consistency between the data and the findings exists. The NMDS stress value is used to establish the inter reliability of the estimation. The interrater reliability test was conducted for the two scale ratings. Both test fall with the 95% c.i. based on meta-analytic GCM studies – as reported in the paper.
31. Clarity of major themes	Were major themes clearly presented in the findings?	Yes, major themes are clearly identified in the Discussion section of the paper.
32. Clarity of minor themes	Is there a description of diverse cases or a discussion of minor themes?	No.

Appendix 2L. Supplementary statistical analyses

This supplementary analysis examines stakeholder perceptions of clusters of factors influencing DTx economic value through comprehensive statistical testing. Four stakeholder groups (Healthcare Professionals, Researchers, Industry, and Public stakeholders, n=62) evaluated eight clusters of factors using two rating scales: (1) perceived importance for DTx economic value, and (2) extent of consideration in daily practice. The analysis employs multiple complementary statistical approaches to examine both between-group differences and within-group patterns, progressing from parametric to non-parametric methods to ensure robust findings despite sample size constraints.

1. Mean differences analysis

Mean differences was conducted to examine whether significant differences exist between stakeholder groups in their ratings of cluster importance and extent of consideration. This parametric test assesses whether observed variations between stakeholder groups are statistically meaningful.

Figure 29. Statistical comparison of DTx importance ratings across stakeholder groups: Mean differences analysis

			Public Stakeholders (n=7)	Healthcare Providers (n=10)	Researchers' Stakeholders (n=19)	Industry Stakeholders (n=26)
Public Stakeholders (n=7)	1	DTx Impact on Patient Outcomes				
	2	DTx Associated Costs				
	3	DTx Impact on Healthcare System				
	4	Technology Considerations				
	5	DTx Implementation				
	6	DTx Monetization Models				
	7	DTx Clinical Validation Methods				
	8	DTx Market Fit				
Healthcare Providers (n=10)	1	DTx Impact on Patient Outcomes	p-value > 0.05			
	2	DTx Associated Costs	p-value > 0.05			
	3	DTx Impact on Healthcare System	p-value > 0.05			
	4	Technology Considerations	p-value > 0.05			
	5	DTx Implementation	p-value > 0.05			
	6	DTx Monetization Models	p-value > 0.05			
	7	DTx Clinical Validation Methods	p-value > 0.05			
	8	DTx Market Fit	p-value > 0.05			
Researchers' Stakeholders (n=19)	1	DTx Impact on Patient Outcomes	p-value > 0.05	p-value > 0.05		
	2	DTx Associated Costs	p-value > 0.05	p-value > 0.05		
	3	DTx Impact on Healthcare System	p-value > 0.05	p-value > 0.05		
	4	Technology Considerations	p-value > 0.05	p-value > 0.05		
	5	DTx Implementation	p-value > 0.05	p-value > 0.05		
	6	DTx Monetization Models	p-value > 0.05	p-value > 0.05		
	7	DTx Clinical Validation Methods	p-value > 0.05	p-value > 0.05		
	8	DTx Market Fit	p-value > 0.05	p-value > 0.05		
Industry Stakeholders (n=26)	1	DTx Impact on Patient Outcomes	p-value > 0.05	p-value > 0.05	p-value > 0.05	
	2	DTx Associated Costs	p-value > 0.05	p-value > 0.05	p-value > 0.05	
	3	DTx Impact on Healthcare System	**p-value < 0.05**	**p-value < 0.05**	p-value > 0.05	
	4	Technology Considerations	p-value > 0.05	p-value > 0.05	p-value > 0.05	
	5	DTx Implementation	p-value > 0.05	p-value > 0.05	p-value > 0.05	
	6	DTx Monetization Models	p-value > 0.05	p-value > 0.05	p-value > 0.05	
	7	DTx Clinical Validation Methods	p-value > 0.05	p-value > 0.05	p-value > 0.05	
	8	DTx Market Fit	p-value > 0.05	p-value > 0.05	p-value > 0.05	

These results for importance ratings reveal general consensus among stakeholder groups, with most p-values exceeding 0.05, indicating no statistically significant differences between stakeholder groups. This apparent alignment suggests that, despite diverse professional backgrounds, stakeholders recognize similar factors as critical for DTx economic value. However, this statistical agreement outcome must be interpreted cautiously given the small sample sizes in two stakeholder categories (n=10 and n=7), which limit statistical power and the meaningful interpretation of group differences.

Figure 30. Statistical comparison of DTx extent of consideration ratings across stakeholder groups: Mean differences analysis

			Public Stakeholders (n=7)	Healthcare Providers (n=10)	Researchers' Stakeholders (n=19)	Industry Stakeholders (n=26)
Public Stakeholders (n=7)	1	DTx Impact on Patient Outcomes				
	2	DTx Associated Costs				
	3	DTx Impact on Healthcare System				
	4	Technology Considerations				
	5	DTx Implementation				
	6	DTx Monetization Models				
	7	DTx Clinical Validation Methods				
	8	DTx Market Fit				
Healthcare Providers (n=10)	1	DTx Impact on Patient Outcomes	p-value > 0.05			
	2	DTx Associated Costs	p-value > 0.05			
	3	DTx Impact on Healthcare System	p-value > 0.05			
	4	Technology Considerations	p-value > 0.05			
	5	DTx Implementation	p-value > 0.05			
	6	DTx Monetization Models	**p-value < 0.001**			
	7	DTx Clinical Validation Methods	p-value > 0.05			
	8	DTx Market Fit	p-value > 0.05			
Researchers' Stakeholders (n=19)	1	DTx Impact on Patient Outcomes	p-value > 0.05	p-value > 0.05		
	2	DTx Associated Costs	**p-value < 0.001**	**p-value < 0.001**		
	3	DTx Impact on Healthcare System	**p-value < 0.001**	**p-value < 0.005**		
	4	Technology Considerations	p-value > 0.05	p-value > 0.05		
	5	DTx Implementation	**p-value < 0.05**	**p-value < 0.01**		
	6	DTx Monetization Models	**p-value < 0.001**	**p-value < 0.01**		
	7	DTx Clinical Validation Methods	p-value > 0.05	**p-value < 0.05**		
	8	DTx Market Fit	p-value > 0.05	p-value > 0.05		
Industry Stakeholders (n=26)	1	DTx Impact on Patient Outcomes	p-value > 0.05	p-value > 0.05	p-value > 0.05	
	2	DTx Associated Costs	**p-value < 0.05**	**p-value < 0.001**	**p-value < 0.001**	
	3	DTx Impact on Healthcare System	**p-value < 0.001**	p-value > 0.05	p-value > 0.05	
	4	Technology Considerations	p-value > 0.05	p-value > 0.05	p-value > 0.05	
	5	DTx Implementation	p-value > 0.05	**p-value < 0.05**	p-value > 0.05	
	6	DTx Monetization Models	p-value > 0.05	p-value > 0.05	**p-value < 0.002**	
	7	DTx Clinical Validation Methods	p-value > 0.05	p-value > 0.05	p-value > 0.05	
	8	DTx Market Fit	p-value > 0.05	p-value > 0.05	p-value > 0.05	

The extent of consideration analysis shows mixed results with p-values ranging from <0.001 to >0.05, indicating both significant differences and agreement depending on the specific cluster examined. While some factors like *DTx Impact on Patient Outcomes*, *Technology Considerations*, *DTx Clinical Validation Methods*, and *DTx Market Fit* show general agreement (p>0.05), other clusters reveal significant disparities in how different stakeholder groups incorporate these factors into their daily decision-making processes. This heterogeneity suggests that while stakeholders may agree on what is important, their practical engagement with these factors varies considerably. However, the small and sample sizes compromise the reliability of results, reducing statistical power to detect differences. These limitations necessitate validation through more robust non-parametric methods.

2. Pattern match analysis by stakeholder groups

Given the limitations of parametric testing with small sample sizes, the non-parametric Kruskal-Wallis test on ranks was employed as a more appropriate analytical approach. This test is particularly suited for small sample sizes and data that may not meet normal distribution assumptions (Kruskal & Wish, 1978), examining whether median rankings differ significantly between stakeholder groups without relying on means and variances, making it a more appropriate analysis for the GCM study design.

The results provide statistical validation for conducting detailed comparisons across all stakeholder subgroups for both rating scales, with $p<0.01$ for importance ratings (Figure 31) and $p<0.05$ for extent of consideration ratings (Figure 32), both indicating significant differences between stakeholder groups across the clusters of factors.

The test's robustness to small sample sizes and not assuming any distribution property make it particularly valuable for our study design, demonstrating the independence of each stakeholder group and paving the way for the subsequent stakeholder group comparisons undertaken.

With statistical significance established, pattern matching analysis provides a detailed visual comparison of mean rating scores across and within stakeholder groups, enabling detection of specific convergence and divergence patterns while revealing how different stakeholder groups prioritize and engage with the eight clusters of factors.

Figure 31. Mean importance ratings of the clusters of factors perceived to influence the economic value of DTx: Multiple pattern matches arrayed by stakeholder groups (n=62)

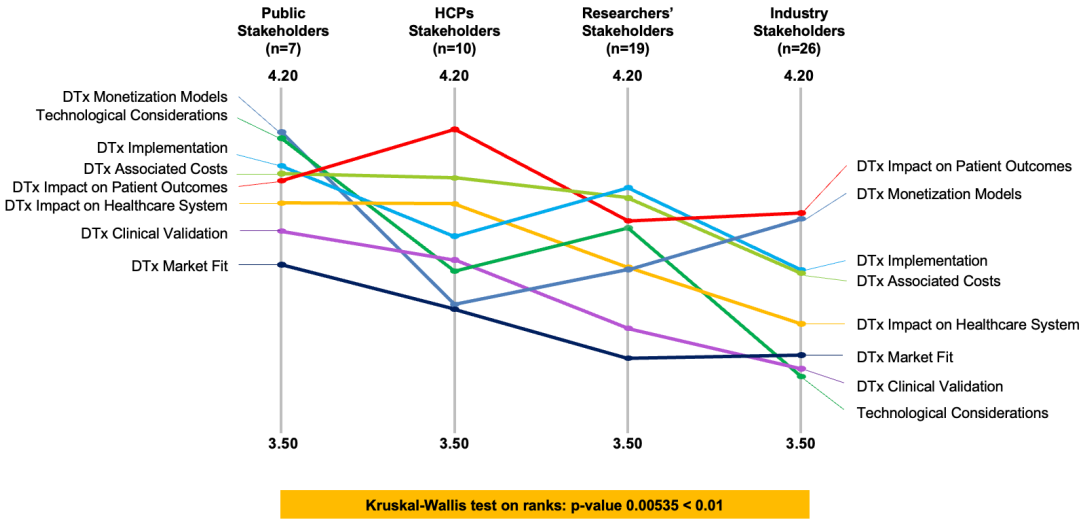
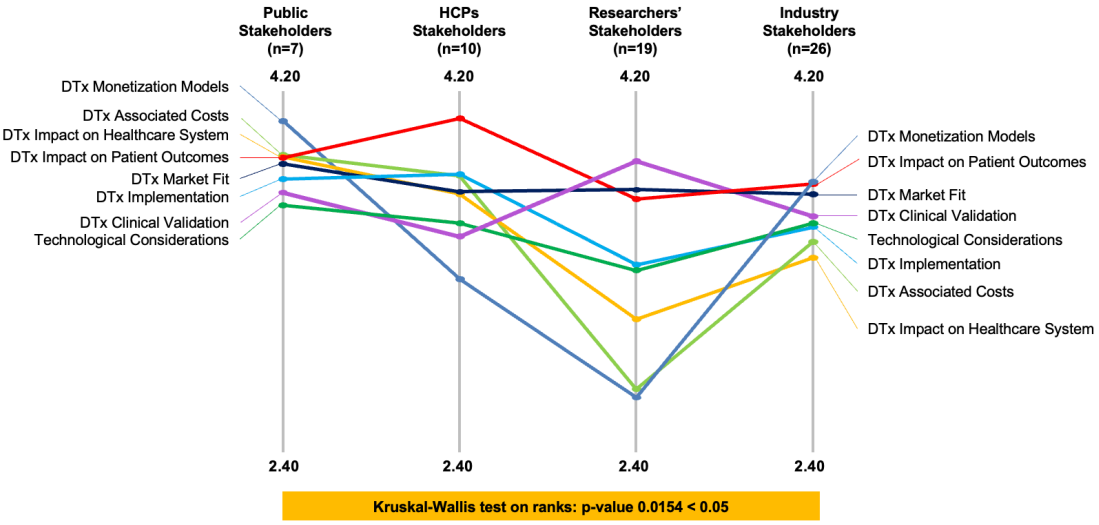


Figure 32. Mean extent of consideration ratings of the clusters of factors perceived to influence the economic value of DTx: Multiple pattern matches arrayed by stakeholder groups (n=62)



The multiple pattern matches analysis reveals striking convergence and divergence patterns across stakeholder groups. *DTx Market Fit* consistently emerges as the "least important" cluster across all groups, suggesting potential undervaluation of market dynamics in economic value considerations. Conversely, the *DTx Monetization Models* cluster demonstrates the most pronounced stakeholder divide: while Public and Industry stakeholders prioritize

this cluster highly, Healthcare Professionals and Researchers assign it minimal consideration, reflecting potentially fundamental differences in professional priorities and organizational contexts that warrant further investigation.

3. Pattern match analysis for each stakeholder groups

Complementing the between-group comparisons established through Kruskal-Wallis testing, the Wilcoxon matched pairs analysis serves as a non-parametric approach for examining ratings within each stakeholder group. This analysis enables identification of systematic gaps between the importance and the extent of consideration ratings, revealing whether stakeholder groups consistently rate factors as more important than they actually consider in daily practice (Wilcoxon, 1992).

The Wilcoxon analysis reveals statistically significant differences ($p<0.05$) between the importance and the extent of consideration ratings within each stakeholder group (Figures 33-36). This consistent pattern across all groups indicates a universal importance-practice gap—stakeholders systematically rate factors as more important than they consider in daily practice. This finding, as detailed in the main thesis, provides crucial insight into the disconnect between theoretical recognition of factor importance and practical implementation across all stakeholder categories.

The transition from cross-group to within-group analysis reveals distinct stakeholder profiles and specific gap patterns, offering granular insights into each group's unique characteristics.

Figure 33. Public stakeholders rating scales pattern match (n=7)

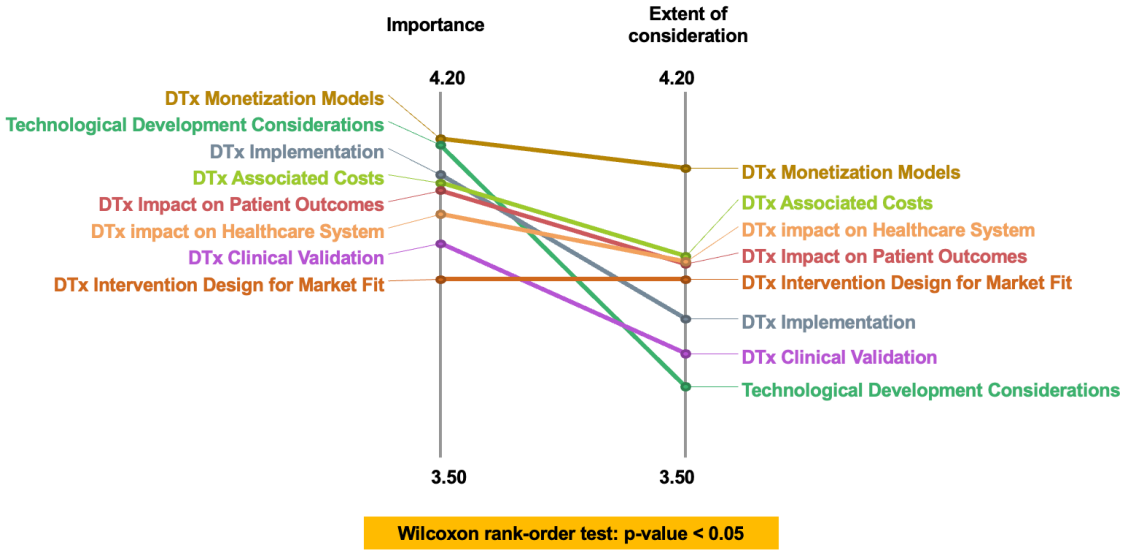
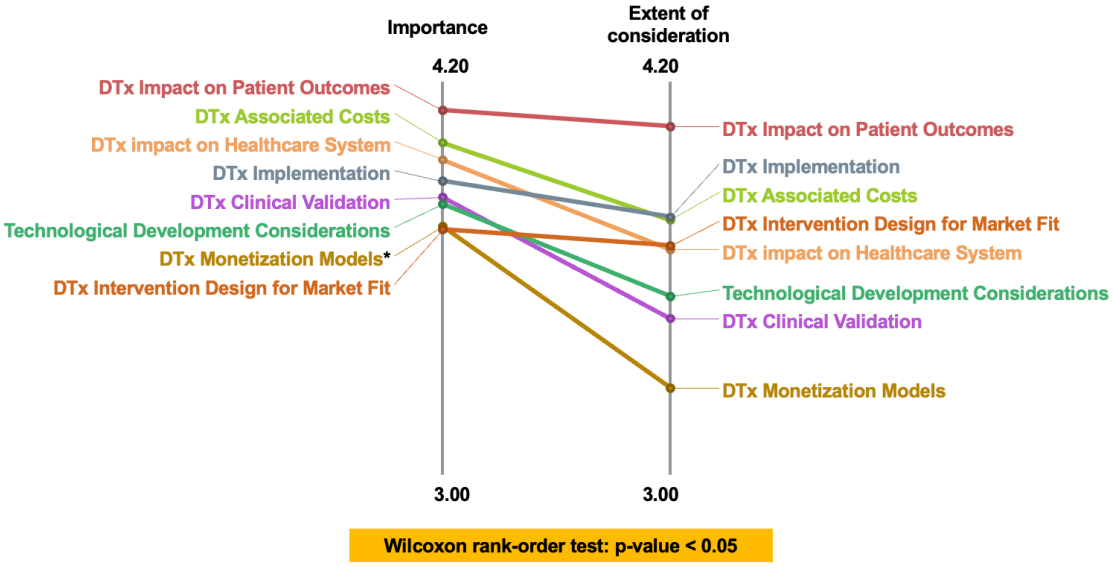
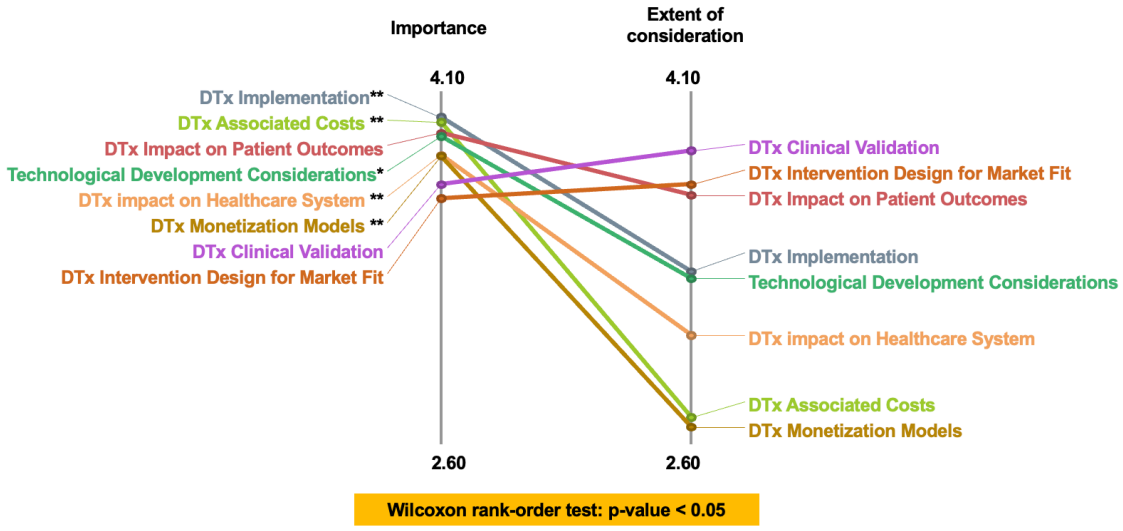


Figure 34. Healthcare practionners rating scales pattern match (n=10)



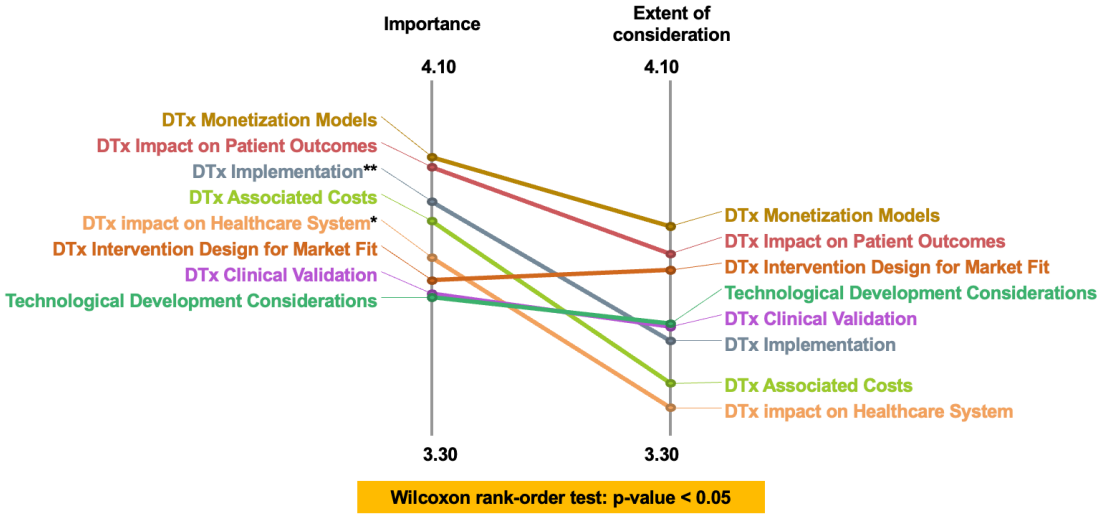
A single asterisk (*) indicates a p-value < 0.05.

Figure 35. Researchers' stakeholders rating scales pattern match (n=19)



A single asterisk (*) indicates a p-value < 0.05, and double asterisks (**) indicate a p-value < 0.001.

Figure 36. Industry stakeholders rating scales pattern match (n=26)



A single asterisk (*) indicates a p-value < 0.05, and double asterisks (**) indicate a p-value < 0.01.

The pattern matching results for each stakeholder group reveal numerous correlations between the importance and the extent of consideration for certain clusters, which could potentially differ with larger sample sizes, yet provide valuable insights into stakeholder-specific characteristics. These pattern matching analyses prove particularly helpful for visualizing commonalities and differences, or "gaps" in ratings—defined as significant differences in mean

ratings between the two scales—thereby informing current research conclusions and future exploration directions.

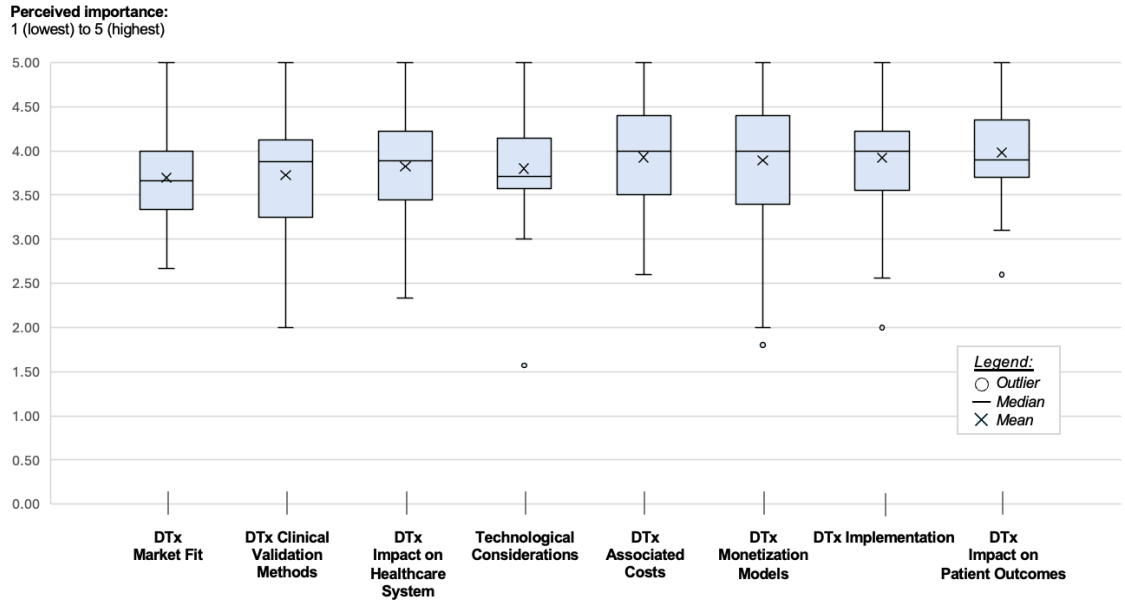
Each stakeholder group—proven earlier as distinct and independent groups—demonstrates distinct correlation patterns between the two rating scales, each showing unique profiles in how their importance ratings relate to their extent of consideration ratings across the eight clusters of factors. For example, Researchers (n=19) show selective gaps, particularly in monetization and market-related factors, reflecting a potential academic focus on scientific validation over commercial considerations.

These visual patterns provide actionable intelligence for further exploration and for potentially developing targeted stakeholder engagement strategies.

4. Distributional analysis and response variability

If GCM studies focus more on consensus-building and aggregate patterns rather than individual response variability (Trochim, 1989), a box plot analysis is included in Figure 37 to complement previous statistical and visual analyses. This analysis provides a comprehensive assessment of distributional characteristics, outlier patterns, and response variability across all participants, revealing central tendencies and identifying unusual patterns that could merit further investigation.

Figure 37. Perceived importance of the clusters of factors to influence DTx economic value among stakeholder groups: Box plot analysis (n=62)



The importance ratings demonstrate remarkable consistency across stakeholder groups, with all eight clusters maintaining median ratings above 3.7, indicating that DTx economic value is conceptualized as inherently multifaceted rather than dependent on a single dominant factor. The final four clusters show the highest median importance ratings (>3.90), with *DTx Implementation* and *DTx Impact on Patient Outcomes* exhibiting the most concentrated distributions, suggesting strong consensus on these factors as critical economic value determinants.

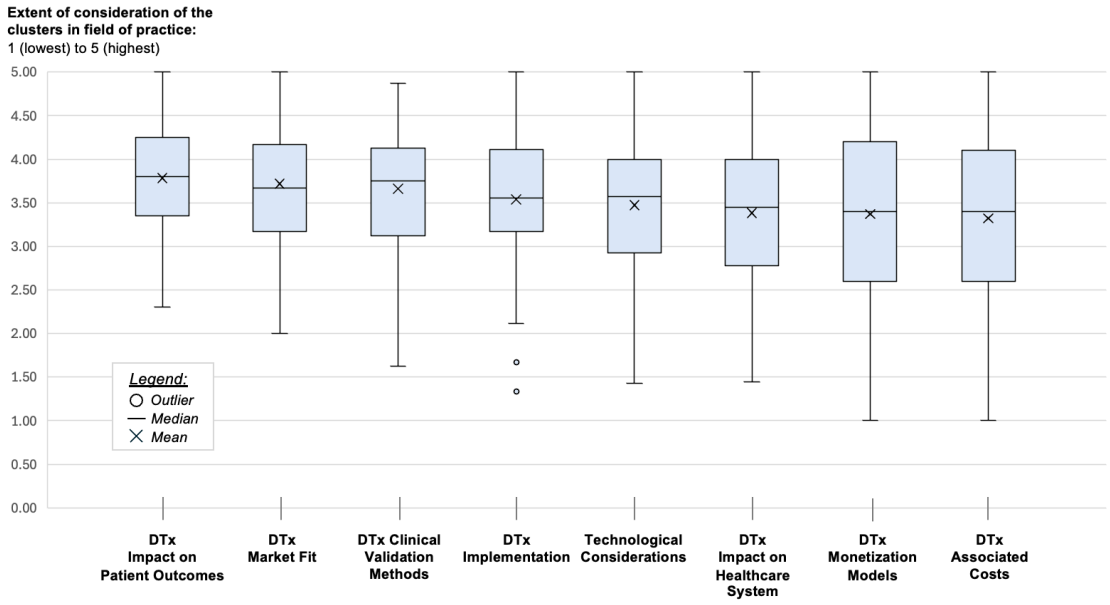
However, wider distributions in certain clusters, particularly *DTx Monetization Models*, indicate reduced agreement and likely reflect divergent stakeholder experiences with commercial DTx models or varying perspectives on monetization strategies within the evolving digital health ecosystem.

Despite the overall agreement, a few outliers emerged in four clusters, representing participants who rated these clusters significantly lower (1.5-3.0 range) and who likely represent distinct stakeholder archetypes with varying priorities. For instance, researchers may attribute lower importance to monetization considerations compared to industry stakeholders, while technology

developers might prioritize different validation approaches than clinical practitioners. These outlying perspectives represent potentially important contrarian viewpoints or legitimate alternative priorities that merit further exploration to understand the full spectrum of stakeholder positions.

Finally, the distributional analysis reveals that means and medians demonstrate remarkable similarities across all factor clusters—a finding that strengthens the reliability of the central tendency measures. This convergence suggests that responses follow approximately normal distributions rather than exhibiting heavy skewness, indicating that the identified outliers do not substantially distort the overall distributional patterns. This statistical stability enhances confidence in the robustness of the findings.

Figure 38. Extent of consideration of the clusters of factors perceived to influence DTx economic value among stakeholder groups: Box plot analysis (n=62)



Beyond the primary findings presented in the main thesis, the substantial variation in individual practice patterns (i.e., variation in the extent of consideration ratings), as illustrated in Figure 38, warrants further examination. The extensive whiskers observed across all clusters of factors demonstrate considerable heterogeneity in how stakeholders consider and incorporate DTx

economic considerations into their daily professional activities. While some stakeholders exhibit deep engagement with these factors (represented by upper outliers), others demonstrate minimal consideration (evidenced by lower whiskers extending toward the 1-2 range). This disparity suggests two plausible explanations: first, uneven awareness and understanding across the stakeholder community regarding how specific factors influence DTx economic value; or second, deliberate strategic decisions by stakeholders to prioritize certain factors over others based on their organizational context, role responsibilities, or resource constraints. The magnitude of this variation indicates that significant divergence exists among the stakeholder groups involved in DTx development and validation, warranting further investigation to understand the underlying drivers and implications for decision-making practices.

5. Summary and statistical validation

The comprehensive statistical analysis further validates and strengthens the study's findings through multiple complementary approaches. While stakeholders demonstrate general agreement on factor importance, significant variations emerge in practical consideration and application. The non-parametric tests confirm the robustness of these findings despite sample size constraints, and the visual analyses reveal both convergence points for collaboration and divergence areas requiring targeted stakeholder engagement strategies.

PAPER 3 APPENDICES

Appendix 3A. Preprint published in Research Square, a preprint platform

Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Generative Mechanisms Influencing Economic Decision Making in Digital Therapeutics Development

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Abstract

Despite their potential, digital therapeutics (DTx), software as a medical device, face adoption and use challenges partly due to insufficient economic evidence. This study investigates how researchers - including research engineers, health systems researchers, clinician-researchers, and practitioner-researchers - approach economic decision-making during DTx development through semi-structured interviews with 17 diverse research professionals. Using critical realism, decision theory and system dynamics modeling, three interrelated generative mechanisms were identified: (1) *Professional Norms* that prioritize clinical validation while marginalizing economic considerations; (2) *Researcher Experience* showing how limited economic literacy creates cognitive biases; and (3) *Adoption Uncertainties* demonstrating how implementation concerns influence development decisions. These mechanisms explain why economic considerations remain peripheral even with their recognized importance. Our findings reveal complex interactions between institutional structures, intrapersonal factors, and implementation uncertainties that systematically deprioritize economic considerations, providing valuable intervention points for strengthening DTx development processes toward comprehensive value assessment.

Introduction

DTx represent a transformative shift in healthcare delivery, offering software-driven, evidence-based therapeutic interventions that prevent, manage, and treat a diverse spectrum of medical conditions[1]. These digital solutions, ranging from mobile applications to virtual reality environments, are designed to improve patient outcomes through evidence-based therapeutic interventions. The promise of DTx lies in their ability to provide accessible, scalable, and personalized interventions. For instance, mobile applications can deliver cognitive behavioral therapy for mental health conditions, while virtual reality environments may assist in pain management or rehabilitation[2,3]. This emerging class of medicine can potentially reach underserved populations, provide continuous support between clinical visits, and generate real-time data for healthcare providers to optimize treatment plans.

In the context of global population aging and the concomitant rise in chronic and mental health conditions, DTx offer the opportunity to improve patient outcomes while potentially mitigating the escalating costs associated with traditional healthcare delivery. However, notwithstanding their potential, the literature is unanimous: the adoption of these therapeutics remains low across countries and healthcare systems, with limited integration of DTx into access and care pathways[4–8].

The path from concept to market implementation is marked by unique levels of complexity, which differentiate DTx from conventional pharmaceutical drugs and medical devices. These complexities stem from the rapid pace of technological evolution and the intersection of software development with clinical validation requirements. Additional challenges include the “regulatory gap” in approval and reimbursement processes across countries and the numerous decision-making processes involving stakeholders from multiple disciplines[8–10].

With healthcare systems under pressure to “do more with less”, robust clinical and economic evidence is critical for DTx to be considered for regulatory and reimbursement decisions[11–13,6,10]. Recent studies also underscore that economic factors related to a DTx intervention - such as costs, funding, and resources - have been identified as both barriers and facilitators to adoption and use[14]. However, relatively little is known about the capacity of DTx to provide economic value in care[15–17].

Recent research has extensively examined decision-making in healthcare innovation[18,19], yet significant knowledge gaps persist regarding stakeholders' approaches to economic decisions in DTx development[1]. Although the literature offers valuable insights into clinical decision-making processes[11,20] and technical development frameworks[10,21], the intersection of economic considerations with these domains remains understudied.

A recent study exploring stakeholder roles in driving DTx economic impact revealed a significant pattern: researchers consistently placed higher emphasis on technical validation while giving less consideration to economic and implementation factors compared to other stakeholders[22]. This disparity raises important questions about the underlying causes of researchers' apparent deprioritization of these considerations.

While researchers play a crucial role in establishing the scientific foundation and clinical efficacy of DTx solutions[7], their limited consideration of economic factors could potentially impact downstream commercial viability and healthcare system integration. Despite economic evidence being critical for adoption, there remains limited understanding of how stakeholders approach economic decisions in DTx development, particularly how researchers' early-stage decision-making impacts downstream value creation.

Thus, the following research question is raised: What are the underlying mechanisms and contextual conditions that shape researchers' decision-making processes regarding economic factors perceived to influence a DTx economic value in its technological development and clinical validation, and how do these manifest in practices?

This study employs Critical Realism (CR) as its philosophical foundation, examining both observable researchers' decision-making practices and their underlying mechanisms through the lens of Decision Theory (DT) - specifically Expected Utility Theory (EUT) and Behavioral Decision Theory (BDT) - and Systems Thinking (ST). The integrated theoretical framework guiding this study and informing the methodological approach is shared in Supplementary Note 1.

Through a qualitative analysis of in-depth interviews with 17 researchers, the paper seeks to reveal why they consistently give less consideration to economic factors compared to other DTx stakeholders, and how these decisions operate within complex systems-based relationships. This understanding could ultimately lead to more effective DTx development processes that better integrate economic

considerations, potentially improving the adoption and use rates of these promising healthcare interventions.

Results

Content analysis at the first step, *"Coding and Identification of Demi-Regularities,"* revealed three core themes: (1) the centrality of clinical evidence in the DTx development processes, (2) the crucial role of implementation factors in development decisions, and (3) the consistent absence of economic value considerations in early development stages (Supplementary Note 2 and Supplementary Table 2).

The subsequent abductive analysis (step 2) revealed key puzzling facts in DTx researchers' decision-making processes, suggesting a complex interplay between institutional logics, individual expertise boundaries, and conceptual frameworks (Supplementary Note 2).

Three primary generative mechanisms were then retroduced (step 3) to explain how researchers' approach to DTx development and their consideration of economic factors: (1) the *Professional Norms*, (2) the *Researcher Experience* and (3) the *Adoption Uncertainties*.

Each mechanism is examined individually below through causal loop diagrams (CLDs), identifying respective variables (the measurable factors that can change within each mechanism) and their primary balancing (B) or reinforcing (R) loops[2]. Theoretical propositions are developed for each mechanism to explain how causal[3] relationships influence researchers' decision frameworks. Building on each mechanism's CLD (Figs. 1 to 3), an integrated model combining the three mechanisms into a comprehensive system is presented in Fig. 3.

The Professional Norms mechanism

The first mechanism, *Professional Norms*, refers how embedded healthcare norms and practices fundamentally influence the development trajectories of DTx. This mechanism operates through a reinforcing loop (R1) alongside an exogenous variable—the *comprehensiveness of funding requirements*. These *Professional Norms* create self-perpetuating patterns that systematically prioritize clinical validation while obscuring other forms of complementary evidence or value dimensions.

This mechanism functions through an interconnected set of causal relationships that collectively prioritize clinical evidence while marginalizing economic considerations (Fig. 1). This pattern, while unsurprising within healthcare contexts, significantly constrains the development process and highlights the persistent tension between rational decision-making frameworks and behavioral influences that drive researcher choices.

Reinforcing loop 1 (R1): Clinical value loop

In R1, the *degree of organizational translational research focus* emerges as a primary influence, bolded in Fig. 1, to express the centrality of this node of the causal model. The findings reveal an important

aspect that influences researcher decision frameworks: the translational nature of the research institution, as hypothesized during step 2 of abduction (Supplementary Note 2).

Researchers in our sample worked across institutes. Their roles cover varying orientations, from basic scientific and technological development to clinically focused or translational research bridging academia and healthcare practice. These institutional visions exist along a continuum from basic science to translational approaches oriented toward commercialization. Such positions influence both institutional and individual research agendas, creating predetermined key focus areas and performance metrics for researchers. This effect is exemplified in how Ezra (P3) described the relationship between his lab's vision and their output: "*The aim of our lab is to do something that could potentially impact society. We consider multiple aspects, such as implementation or translation. We're not just doing research for the sake of publishing, nor are we focused solely on basic science. We want to do something impactful that could potentially be translated into real-life benefits for the general public.*"

Team composition and multidisciplinary expertise within research organizations, directly impacted by the translational nature of these organizations and shapes researchers' mindsets and priorities. Engineer-researcher Eva's (P2) experience working alongside behavioral scientists illustrates this dynamic: "*Researchers like me, we are too focused on numbers, like how effective is the solution, and our expertise domain. When I joined [Bioengineering Research Institute Name], I was surprised about the behavioral component. I didn't appreciate it at first, but now I see its importance. It opened my mind and perspective, especially for improving DTx usability and engagement*." This excerpt demonstrates how diversifying team composition can potentially disrupt R1 by introducing alternative perspectives, although the data suggest such disruptions rarely extend to economic considerations.

Simultaneously in R1, the imperative to satisfy regulatory requirements—which emphasize DTx safety and efficacy demonstrations for market approval—reinforces research organizations' singular focus on clinical validation. This creates a self-reinforcing cycle that perpetuates the almost exclusive prioritization of clinical validation in institutional evaluation frameworks, despite growing literature recognition of economic evidence importance. While clinical validation represents a necessary milestone, it constitutes a short-term endpoint relative to the ultimate goal of successful DTx implementation in clinical practice.

Two additional observations merit attention. First, while EUT would predict comprehensive integration of regulatory requirements throughout development, the findings reveal these considerations often emerge much later. As Cheah (P13) noted: *"A lot of times, the solution solves a problem, but it doesn't end up somewhere because considerations of regulatory and reimbursement, with the actual greater landscape, are not in our minds."* The *satisfaction of the regulatory requirements* tends to be considered more as a chronological endpoint of clinical validation, rather than serving as guidance throughout the DTx development process.

Second, participants noted a "regulatory gap" for DTx, which may explain the limited consideration given to regulatory aspects by researchers early in the DTx process. For these reasons, the relationship

between the *satisfaction of the regulatory requirements* and the *level of economic consideration* is depicted as a dashed line in Fig. 1.

The positioning of research organizations on this translational spectrum is also largely influenced by the available funding sources, such as research grants, subsidies, donations or investor capital. This influence is particularly significant regarding the comprehensiveness of their requirements (i.e., how extensive the elements required in a grant proposal are, whether they include the clinical, technological and economic impact of a potential DTx). As Emma (P1) noted: "*Some grants now require us to think about commercialization pathways, which forces us to consider the economics earlier on*." Similarly, Camirah (P15) observed: "*More and more, I find that these grant application forms require you to justify the economics of your innovation... So to justify that, we always have to tell them how much economic benefit our solution would provide, which is hard to find*." While some funding bodies require cost impact assessments for DTx solutions, participants described this as an emerging rather than established practice.

These funding sources through their requirements can either enable or constrain action, influencing researchers' consideration of various aspects in DTx development. In the causal model, the *comprehensiveness of funding requirements* represents a potential intervention point that could disrupt the R1 loop by introducing economic considerations into performance metrics, though this effect appears limited in current practice.

System implications and propositions

R1 and the impact of current requirements of funding mechanisms create persistent patterns that institutionalize clinical outcome prioritization while marginalizing complementary value dimensions necessary for sustainable implementation (Fig. 1). Hence, it is posited:

- Current organizational settings, funding and regulatory requirements collectively establish a rigid evaluative framework that systematically and exclusively prioritizes clinical evidence, effectively precluding the integration of alternative value dimensions, particularly economic considerations, throughout the DTx development process.
- The temporal delay between *satisfying the regulatory requirements* and the *level of economic considerations* creates a structural barrier that persists even when funding bodies begin to incorporate implementation-related factors into their awarding processes.
- Organizational settings, toward more translational aspects, that diversify team composition beyond clinical expertise will demonstrate greater integration of economic considerations throughout the DTx development lifecycle.
- Interventions targeting the weak causal links[4] between both the regulatory and funding environments to the *level of economic considerations* offer potential leverage points for system change.

The *Professional Norms* mechanism functions primarily as a "situational mechanism"[24]. It describes how macro-level contextual conditions and institutional power dynamics, which reflect embedded healthcare norms, influence DTx development approaches, predominantly driven by clinical considerations. The power of this mechanism lies in its ability to shape the decision space available to researchers before individual factors come into play, effectively defining the range of considerations perceived as legitimate or necessary. The subsequent mechanism reveals how intrapersonal factors and cognitive constraints further shape the way researchers make decisions in this predefined space.

The Researcher Experience mechanism

The second mechanism (Fig. 2) demonstrates how researchers' professional background, including their training, experience and expertise, alongside cognitive patterns, influences their DTx development decisions, particularly regarding economic considerations.

In Fig. 2, the researcher's *level of professional specialization* serves as a fundamental determinant that shapes how narrowly focused their roles become (positive relationship in R3), influences their *economic literacy level* (negative relationship in R2), and contributes to the formation of cognitive biases (positive relationship in B1). This variable, bolded in Fig. 2, indicates the centrality of this node, being in each of the three loops that constitute this mechanism.

Reinforcing loops R2 and R3: Literacy and Role boundary loops

The study revealed indeed that researchers' training and educational backgrounds - whether in engineering, clinical, or social sciences - created distinct mental models for approaching DTx development. Rather than optimizing utility or outcomes across all value dimensions, researchers demonstrated strong domain-specific thinking patterns. Eisa (P4) candidly acknowledged that it might create a tunnel vision: "*because from my engineering background, I will not see things from a health economics point of view*." This domain-specific focus was reinforced by Ezra (P3): "*maybe it's just me, like most of the classes I took, they were more like tech or science heavy. I don't think they ever mention anything regarding a translational type of work*." While Cheah (P13) noted some exposure to economic concepts during his specialization training, this proved to be an exception rather than the norm.

These statements illustrate how the R2 and R3 loops begin with the *level of professional specialization* and creates path dependencies that shape decision frameworks. Professional training creates expertise in narrow fields, often accompanied by pressures to publish in specialized journals and/or secure domain-specific funding. This leads researchers to prioritize familiar domains (clinical or technical), thereby reinforcing the tendency to specialize further in those same domains. This creates a reinforcing loop where specialized expertise further narrows focus, decreasing the likelihood of acquiring broader economic competencies.

Within the R2 loop, the observed limited *level of economic literacy* among researchers, created or reinforced by the *level of professional specialization*, represents a key intermediate variable that creates

persistent knowledge gaps in DTx development. It establishes a self-reinforcing cycle where researchers gravitate toward familiar domains and methodologies, whether clinical or technological. As noted earlier, while EUT suggests that researchers aim to complement their expertise by incorporating economic considerations, observations instead reveal satisficing behavior when faced with unfamiliar economic aspects. This behavior further strengthens the tendency to stay within familiar areas and exhibits a negative relationship with the *level of cognitive biases*: the higher the researcher's *level of economic literacy*, the less likely they are to engage in satisficing behavior and the fewer cognitive biases they exhibit in this domain (Supplumentary Note 1).

Within the R3 loop, the *level of professional specialization* strongly influences the *narrowness of the researcher's role* as discussed above, which is further shaped by the *degree of organizational translational research focus* and the *comprehensiveness of funding requirements*.

As noted earlier, research institutions evaluate research-related performance metrics and incentives around publications and clinical validation. These metrics serve as visible manifestations of underlying *Professional Norms*, and effectively constrain researchers' roles and foci. They systematically exclude consideration of translational aspects or alternative value forms, such as economic utility, and they marginalize the implementation-oriented knowledge generation that could facilitate broader DTx adoption. Such metrics, while creating what EUT would consider a rational framework for maximizing utility within institutional constraints, potentially introduce what behavioral economists term "reward substitution"[25,26]. This phenomenon occurs when proximate goals substitute for ultimate goals. In this context, researchers focus on publications and clinical validation (proximate goals) rather than successful broad DTx implementation for improved clinical outcomes beyond limited trial participants (ultimate goals).

Consequently, two tensions emerge. First, academic publication and patenting can conflict due to their opposing requirements regarding public disclosure. Public disclosure can directly impact a researcher's ability to patent an invention because most patent systems require "novelty" - meaning the invention must not have been disclosed publicly before filing the patent application. Second, a potential and interesting tension exists where rational responses to institutional incentives may produce suboptimal outcomes from a broader utility perspective. As engineer-researcher Emma (P1) explained: "*As a researcher, my KPIs are that I need to develop something, I need to publish something... the time that I have to implement it is not in my KPIs*." This statement illustrates how the R3 loop operates in practice, with performance metrics directly shaping researcher priorities in ways that exclude economic considerations.

Balancing loop B1: Bias loop

The B1 loop in the causal model demonstrates how the *level of cognitive biases*, reinforced by researchers' specialized expertise and a gap in economic literacy, systematically influences development decisions. Surya (P10) attributed these biases also to the consequences of professional training (*déformation professionnelle* in BDT terms), which offered limited to no exposure to economic principles,

which further reinforces these biases. Sasha (P6) offered a more nuanced perspective: "*This is how it works* [referring to the DTx development process], *what you do, and your choices are partially driven by your past experiences*." This statement captures how the B1 loop operates in practice, with past experiences shaping current perceptions and decisions. From the interviews, these biases manifested in various forms in DTx development decision-making, ranging from optimism bias regarding technical solutions, confirmation bias in clinical efficacy assessments, and status quo bias favoring existing healthcare delivery models: "*Engineers often have unrealistic expectations about adoption rates because they underestimate institutional resistance to new technologies*" as Surya (P10) observed. Also, Sasha (P6) mentioned: "*I know from my professional experience...that potential end-users, such as patients,* [in a feedback session] *don't tell the truth, might not care, or pay attention. The data will be seriously tainted if you just ask them straightforward questions*." This statement—based on professional experience—reveals the preconceived notion that participants are unreliable, a cognitive bias. Such beliefs may "seriously taint" (to use Sasha's own terminology) the interpretation of future patient interactions, potentially leading to confirmation bias in data interpretation.

While these cognitive patterns are expected and appear throughout the DTx development process, they seem to systematically obscure economic considerations. They represent domain-specific expertise that shapes how researchers evaluate evidence and approach decision-making throughout the DTx lifecycle. They are identified in Fig. 2 as negative influences on the *level of economic considerations*. The power of the balancing loop B1 lies in its largely unconscious operation, with researchers often unaware of how cognitive biases shape their perception of what constitutes relevant considerations. Emma (P1) illustrated this phenomenon: "*Engineers think this is the problem and they work on a solution for it and then after they finish the solution when they're trying to implement it, they realize that that's actually not the problem; there's something else*."

System implications and propositions

The interaction between loops R2, R3 and B1 and their set of interdependent variables creates a particularly robust system resistant to change, one that maintains the observed gap in economic consideration throughout the DTx lifecycle. As Fig. 2 demonstrates, when domain-specific training combines with cognitive biases, the effect is not merely additive but multiplicative, creating what SD identifies as a "success to the successful" archetype[27,28]. This dynamic generates momentum through reinforcing loops, establishing patterns where initial specialization becomes increasingly strengthened over time. This self-reinforcing mechanism can be moderated through the balancing loop B1, with carefully designed interventions that target these causal relationships.

These interdependent variables create a robust *Researcher Experience* mechanism influencing the timing and depth of economic considerations in DTx development. While the *Professional Norms* mechanism operates at the institutional level to constrain the decision space, this second mechanism operates at the individual level to shape how researchers navigate within that space. While researchers demonstrate rational decision-making within their domain expertise, they exhibit satisficing

behavior when encountering unfamiliar economic considerations. The implications of this mechanism for DTx development are important, hence it is posited:

- The more specialized a researcher's training in clinical or technical domains, the greater the likelihood they will exhibit satisficing behavior when confronted with economic considerations in DTx development.
- Researchers' cognitive biases, particularly domain-specific thinking patterns, will systematically influence their perception of what constitutes relevant evidence in DTx development, with economic evidence being reported as being systematically obscured.

The *Researcher Experience* mechanism represents an "action formation mechanism"[24]. It explains how researchers' characteristics generate specific actions and decisions in DTx development. Unlike the *Professional Norms* mechanism, which shapes the broader decision context, this mechanism explains how individual researchers process information and make decisions within that context. The analysis demonstrates how these individual-level factors lead researchers to prioritize familiar domains, creating systematic patterns in DTx development approaches.

The investigation revealed a third critical mechanism related to the uncertainties of DTx adoption within healthcare systems. This *Adoption Uncertainties* mechanism addresses how researchers navigate the complex landscape of implementation challenges and stakeholder engagement throughout the DTx lifecycle, revealing a different dimension of barriers to economic consideration in DTx development. It operates in conjunction with the previous two, as illustrated by the cross-mechanism relationships in Fig. 3, where elements from each mechanism ultimately influence economic considerations through various direct and indirect pathways.

The Adoption Uncertainties mechanism

Implementation uncertainties surrounding DTx adoption within healthcare systems emerge indeed as a third critical mechanism shaping researchers' development decisions. This mechanism (Fig. 3) demonstrates how adoption challenges influence DTx development trajectories through an interconnected set of balancing (B2a/b) and reinforcing (R4) loops. Similar to the *Researcher Experience* mechanism, it emerges from the interplay between balancing and reinforcing forces, creating a complex system of development influences.

Balancing loops B2a and B2b: Implementation-Driven Development and Stakeholder-Driven Development loops

The *awareness of implementation considerations* serves as a central imperative throughout the DTx development process, functioning as the primary driver in both the B2a/b and R4 loops in the causal model. In the interviews, researchers consistently emphasized workflow integration, resource requirements, and organizational readiness. Practitioner-researchers confirmed implementation considerations as critical determinants of DTx success, reflecting both rational planning and practical

responses to uncertainty in complex healthcare environments: "*Focus [during implementation] should be on widespread adoption rather than profit maximization*" as mentioned Cheah (P13).

The findings reveal that greater researcher awareness of implementation adoption challenges positively associates with an increased *perceived importance of unmet needs validation*, ensuring future DTx interventions address specific unmet needs and reduce instances of having a "*solution looking for a problem*."

Participants reported conducting consultation focus groups with patients and physicians, but revealed these sessions often narrowly target clinical unmet needs rather than broader implementation challenges: "*We should also consider complex approval processes, challenges with pilot projects and sustainable funding, or yet the resistance to change from healthcare professionals..."* (Priscillah, P16). Although literature frames this step as "problem-specification" for identifying real-world needs[10], the participants' narrower interpretation represents another manifestation of bounded rationality (Supplementary Note 1), where clinical validation takes precedence over comprehensive value assessment. This focus on clinical unmet needs, while important, often fails to incorporate broader economic dimensions necessary for successful implementation.

As the *perceived importance of unmet needs validation* grows, it reshapes research priorities and considerations beyond simple technological requirements, ultimately slowing the *DTx technological development pace* (negative feedback dynamic). Researchers respond by breaking the DTx development process into more manageable sequential DTx processes as a step-by-step approach. They spend more time ensuring their technology can address the unmet need – despite growing recognition of the need for more integrated approaches.

This sequential approach temporarily reduces uncertainty by emphasizing short-term, step-by-step linear progression rather than iterative development. However, this creates potential long-term integration challenges. While some researchers like Santana (P11) advocated for a "DTx implementation-aware development", where adoption considerations actively shape early decisions, most researchers reported having a more linear and sequential approach, which contributes to the persistent gap between clinical validation and economic consideration. This is visualized as a dashed green line in Fig. 3, where the *level of DTx process sequentiality* tends to delay *the level of economic considerations* to later stages, beyond the "responsibilities" of the interviewed researchers, to use their own words. This sequential approach further delays implementation considerations (negative relationship). It creates a balancing effect in the system, counteracting the reinforcing dynamic of loop R4, and contributes to the system's stability.

Reinforcing loop 4 (R4): Collaboration loop

In R4, the importance placed on addressing clinical needs creates a positive feedback dynamic, driving the *level of stakeholder engagement*, with a more multidisciplinary and interdisciplinary approach, acknowledged as crucial by the participants for successful DTx development. The interviews identified a complex network of stakeholders potentially engaged throughout the DTx lifecycle, including engineers,

data scientists, behavioral scientists, economists, healthcare providers, clinicians, hospital administrators, regulatory bodies, and commercial stakeholders.

These collaborations enhance the *awareness of implementation considerations*, which ultimately reinforce the *perceived importance of unmet needs validation* (positive relationship, completing the R4 loop). However, rather than following EUT's prediction of comprehensive stakeholder integration, the interviews show that stakeholder engagement patterns typically follow a more sequential approach. This results in what participants characterize as *delayed stakeholder engagement*, which is reinforced by the negative influence of the *level of DTx process sequentiality*. This challenge is illustrated by Camirah's (P15) reflection: "*I initially did not involve hospital administrators in my solution development, which created later challenges in the implementation process.*" When the R4 loop functions sub-optimally due to limited stakeholder engagement —as in Camirah's (P15) example—it may fail to address the full complexity of implementation, including economic considerations.

System implications and propositions

The dynamic tension between loops B2a/b and R4 in Fig. 3 creates what is called in SD a "fixes that fail" archetype[27,28]. Short-term solutions, such as sequential development to address a clinical unmet need, create longer-term consequences like fragmentation and delayed stakeholder engagement. While ensuring a DTx addresses clinical needs is important, this approach produces an ongoing tension between immediate development priorities and long-term implementation success. Researchers increasingly recognize the need for early stakeholder collaboration to address adoption uncertainties. However, translating this recognition into systematic practice remains a key challenge in DTx development. Hence, it is posited:

- The greater the perceived implementation uncertainty surrounding a DTx, the higher the likelihood researchers will seek a more multidisciplinary approach, integrating various stakeholder feedback throughout the DTx development process.
- DTx development projects with formalized processes for early stakeholder feedback across diverse stakeholder groups will demonstrate higher levels of economic consideration throughout the development process.
- The temporal disconnect between the *level of DTx process sequentiality* and the *level of economic considerations* creates structural barriers that persist even when researchers recognize the importance of implementation factors.

This mechanism represents a "transformational mechanism"[24]. It shows how researchers' responses to implementation uncertainties and their decisions about stakeholder engagement collectively transform into broader patterns in DTx development practices, ultimately aggregating into systematic patterns of sequential development processes and delayed stakeholder engagement.

While the first two mechanisms primarily explain why economic considerations are marginalized in DTx development, the *Adoption Uncertaintites* mechanism helps explain why implementation concerns (which often have economic dimensions), even when recognized, tend to be addressed in ways that are clinical as one priority while further fragmenting the development process rather than promoting integrated approaches.

Cross-mechanism relationships and secondary loops

Beyond the primary feedback loops that characterize each of the mechanisms, the analysis reveals six secondary loops (B3a/b/c, B4 and B5a/b). These are detailed in Supplementary Table 3 and integrated into the CLD in Supplementary Fig. 1. The loops function as crucial integrative elements between these mechanisms. While exerting less direct influence than primary loops, these cross-mechanism relationships operate through “contingent causality,” where outcomes vary based on interactions with prior effects from other mechanisms[29]. They demonstrate how effects propagate throughout the system, creating an interconnected web of causality that ultimately shapes economic considerations in DTx development. By identifying these secondary loops, the analysis transcends mere pattern recognition to reveal the underlying generative mechanisms at work, highlighting both the complexity of researchers' decision frameworks and potential intervention points where development practices might be modified to better integrate economic considerations.

Discussion

This study advances understanding of researchers' economic decision-making in DTx development through the lens of CR, revealing complex interactions between institutional structures, researchers’ intrapersonal factors, and implementation uncertainties. By identifying three interrelated generative mechanisms—*Professional Norms, Researcher Experience,* and *Adoption Uncertainties*—the research provides a comprehensive explanatory framework for the systematic deprioritization of economic considerations observed in DTx development, despite their acknowledged importance for successful implementation. By integrating insights from both EUT and BDT, the findings demonstrate how researchers navigate complex decision environments. They seek to optimize outcomes within their domain of expertise, while exhibiting satisficing behavior when they encounter economic considerations outside their professional training.

The findings both validate and expand upon existing literature on healthcare innovation decision-making, especially about decision frameworks tendency in early development phases to prioritize technical feasibility and clinical applicability, with economic considerations often introduced later in the development cycle[30]. Several studies analyzed decision-making in healthcare and emphasized a tendency toward focusing on short-term results and using a single-performance measure for problems in the decision-making process[31]. This observation echoes current research findings regarding researchers who prioritize short-term endpoints, such as clinical validation. The literature highlights how well-intentioned interventions and inherent trade-offs might generate ripple effects throughout the

system, extending far beyond the isolated and more short-term consequences that stakeholders might initially anticipate[32].

The predominance of clinical considerations in this study aligns with previous research on DTx technology development[7,22], while the identification of specific mechanisms through which economic considerations become systematically deprioritized advances the understanding of researcher decision-making processes. The findings on the influence of professional training on decision frameworks corroborate earlier research about educational background's role in innovation development[33–35]. Additionally, the analysis of adoption uncertainties provides novel insights into how implementation concerns shape early DTx development decisions. The significance found regarding adoption considerations is consistent with existing literature documenting implementation challenges in digital health interventions[5,6,36].

These findings suggest several actionable approaches for different stakeholders, offering intervention points to enhance economic consideration throughout DTx development and creating a foundation for more integrated approaches to value assessment in digital health innovation.

Translational research organizations should adopt structured development frameworks incorporating economic assessments at multiple stages, systematically diversify team composition to include economic expertise from project inception, and revise evaluation metrics to include implementation feasibility indicators. Individual researchers would benefit from structured decision-making frameworks that explicitly consider economic factors, simplified economic assessment tools, targeted training in health economic principles, and early implementation planning with stakeholder engagement. For policymakers and funding agencies, developing standardized economic evaluation guidelines specific to DTx creates incentives for early economic consideration through funding mechanisms. This approach would support for implementation research and promote more integrated approaches to value assessment in digital health innovation.

Several limitations should be considered when interpreting these findings. Methodologically, while the sample included researchers from diverse backgrounds and settings, it predominantly comprised participants from academic and public healthcare contexts, potentially limiting transferability to more commercially oriented DTx development environments. The sample, while international, had greater representation from specific regions, which may have missed contextual factors unique to other healthcare systems and regulatory environments. Additionally, the recruitment approach may have introduced selection bias, attracting participants with a greater interest in economic considerations, although the findings of limited economic integration suggest this was not a genuine concern.

The retrospective nature of interviews introduces the possibility of recall bias, where participants may have reconstructed past decision processes in ways that differ from actual events. While attempts were made to mitigate this through specific probing questions about concrete examples, future studies using real-time observation of decision processes would complement these findings.

From a theoretical perspective, CR emphasizes that generative mechanisms are “context-sensitive” and operate contingently[37,38]. This implies that the mechanisms identified in this study may produce different outcomes in varied organizational, regulatory, or funding contexts.

The CLDs, while developed through rigorous triangulation procedures, represent a simplified model of complex decision processes. The relative strength of different causal relationships and feedback loops likely varies across contexts in ways not fully captured by an exploratory qualitative approach.

Despite these limitations, the rigorous methodological approach, theoretical grounding, and consistent findings across diverse participants suggest that the identified mechanisms represent robust explanatory frameworks for understanding economic consideration in DTx development.

This study opens several promising avenues for future investigation. Methodologically, longitudinal research tracking DTx innovations from conception through implementation would illuminate how economic considerations evolve throughout the lifecycle and identify critical junctures where economic factors become more salient. Developing quantitative instruments to measure the strength of the three identified mechanisms across different contexts would determine which one has the greatest influence, while intervention studies targeting specific aspects could test which approaches most effectively enhance economic consideration integration. Theoretically, further research should investigate boundary conditions across different healthcare contexts and organizational settings, while applied research could evaluate educational interventions to enhance economic literacy among researchers, assess integrated development frameworks that incorporate economic considerations throughout the DTx lifecycle, and investigate how different policy approaches influence economic decision-making.

Methods

A qualitative, exploratory methodological framework was designed to examine how researchers understand and consider factors deemed to influence DTx economic value, as well as to uncover underlying generative mechanisms for such consideration and their operationalization at the DTx development phase.

Participant selection and recruitment

The decision-making processes of 17 researchers were investigated, including five (5) research engineers, six (6) health systems and social science researchers, four (4) clinician-researchers, and two (2) practitioner-researchers (Supplementary Table 4). A nonprobabilistic purposeful sampling procedure was used to identify and select participants based on their relevant experience within specific contexts[39], to facilitate comparative analysis, and to meet the following inclusion criteria: (1) a minimum of five years of experience in DTx development or clinical validation, (2) current involvement in the technological development or clinical validation of a DTx, (3) fluency in English or French. Initial recruitment occurred through the research team's professional network, with participants encouraged to refer qualified colleagues through snowball sampling.

The study was approved by the Ethics Boards of the National University of Singapore (certificate number: NUS-IRB-2023-399) and the University of Quebec at Montreal (certificate number: UQAM-CIEREH-2024-6028). Written informed consent was obtained from participants to engage either in-person or in web-based interviews. No compensation or incentive was provided. All interviews were audio-recorded and transcribed in their entirety. Interview data were securely stored on protected servers with access restricted to the research team. To ensure participant privacy and confidentiality, data were labeled with participant codes, and a separate secure list of code-to-name matchups was maintained. The study was conducted according to the Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines[40] (Supplementary Table 5).

Data collection

Semi-structured interviews between April and September 2024 were conducted, either in-person or via video conferencing, lasting 30-60 minutes. This interview format balanced an exploration of existing literature on researchers' decision-making processes while allowing the emergence of novel insights. The interview guide (Supplementary Table 6) covered topics including: (1) the participants' roles as DTx researchers, (2) their priorities and key considerations throughout the DTx lifecycle, and (3) their day-to-day prioritization and decision-making processes.

The interview questions evolved iteratively both within and between interviews throughout the data collection process. Early interviews revealed the importance of implementation considerations, leading to additional questions about how researchers anticipated and addressed implementation challenges. Similarly, emerging themes around professional training prompted new questions about how researchers' educational backgrounds influenced their approach to economic considerations.

Detailed field notes were taken during and immediately after each interview to capture non-verbal cues and emerging insights. Data collection continued until theoretical saturation, when additional interviews yielded no substantial new themes or insights and resulted in "*little or no change to the codebook*"[41,42].

Data analysis

The data analysis followed a structured three-step analytical framework grounded in CR principles, as developed by Fletcher[23]. This approach progressed through coding and identification of demi-regularities, abduction, and retroduction—with each phase building upon the previous one. Supplementary Table 2 outlines these key analytical steps, which uncovered the underlying mechanisms driving decision-making in DTx development.

Step 1: Coding and identification of demi-regularities

A "*deductive yet flexible*"[23] coding process was implemented that synthesized theoretical foundations and existing literature, while also capturing CR's stratified ontology to develop the initial coding

framework. This approach began with the creation of a theoretically informed codebook derived from multiple complementary sources.

First, key concepts from DT were extracted, specifically BDT and EUT, to develop foundational codes (Supplementary Note 1). These included “Bias > Availability heuristic” (capturing researchers' tendency to overestimate the likelihood of events based on recall ease) and “Probability > Probability calculations” (documenting objective and subjective probability assessments in DTx development decision-making). Health Technology Assessment (HTA) principles from EUT were further incorporated, generating codes, such as “Economic Considerations > Economic evaluation methods” to document approaches for assessing DTx cost-effectiveness, including cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis.

Second, the theoretical framework was enriched by integrating findings from recent DTx development literature[4,6,8,10,17,22,36,43]. For example, “Economic Considerations > Funding sources” captured available financial resources and funding options that van Kessel et al. described as “vital” during and post-research DTx phases[43]. Similarly, “Economic Considerations > Implementation related” documented researchers' awareness of practical deployment considerations, such as clinical workflow integration and provider training needs, which Cirkel et al. identified as primary barriers to DTx adoption[4].

To ensure philosophical alignment with the research approach, codes derived from CR tenets were integrated. These included “Knowledge Integration > Patient feedback integration” to document attempts to incorporate patient perspectives into the DTx development process, and “DTx Development > Patterns” to identify recurring approaches in development processes and decision-making.

Most codes appeared across multiple sources: theoretical literature, empirical research, and CR principles. For instance, “Bias > Overconfidence,” addressing the tendency to overestimate one's abilities and prediction accuracy, appears both in CR as a cognitive constraint and in BDT as a fundamental decision-making bias.

The initial codebook comprised 58 theoretically derived codes (Supplementary Table 7). This framework was applied to transcripts using ATLAS.ti software (ATLAS.ti Scientific Software Development GmbH), with a sample coded transcript shown in Fig. 4.

In alignment with CR principles, while the deductive approach provided theoretical foundations, an inductive process was incorporated to ensure an authentic representation of participants' perspectives[44]. To systematically analyze the data, Saldaña's cycles of coding methodology were applied throughout the coding process (Supplementary Note 3)[45].

Codes were integrated into a coherent analytical narrative that connected empirical observations with theoretical constructs, thereby facilitating the identification of tendencies in empirical data - what CR practitioners term “demi-regularities”, searching for recurring patterns in participants’ experiences and perspectives within the developed codes[23].

Through subsequent cycles of axial coding, enhanced by ATLAS.ti software's visualization tools—including word clouds and treemaps where code size dynamically reflects application frequency—commonly coded elements and their relationships were systematically explored and mapped. This analytical approach enabled the establishment of connections between second-order categories, progressively distilling the data into eight third-order subcategories (Supplementary Fig. 2). These were ultimately consolidated into three overarching core themes discussed in the Results section: (1) the centrality of clinical evidence, (2) the importance of implementation considerations, and (3) the notable absence of economic value consideration.

Step 2: Abduction

Following CR principles, the analysis proceeded through complementary abductive (step 2) and retroductive processes (step 3)[23]. Abductive reasoning is a process of forming explanatory hypotheses for less understood phenomena[46]. Dunne and Dougherty defined abduction or 'retroduction' as a form of "*reasoning that generates and evaluates hypotheses in order to make sense of puzzling facts*"[47]. Sætre and Van de Ven highlighted that abduction "*begins with observing and confirming an anomaly, and generating and evaluating hunches that may explain the anomaly, for subsequent deductive constructing and inductive testing*"[48]. Critically, abductive reasoning does not produce definitive answers but suggests plausible explanations that warrant further investigation.

Sætre and Van de Ven's four-step approach was adopted for the abductive reasoning process, which they note, "*may overlap, iterate, and unfold in stochastic ways over time*"[48]. The first step involves observing anomalies or puzzling facts in the empirical data that might not align with initial assumptions or existing models and thus remain unexplained. The second step confirms that such anomalies exist and are grounded in evidence, defining what is known or unknown about them. The third step involves formulating hypotheses or generating hunches that may provide plausible explanations for the anomalies. The final step consists of evaluating these hunches and alternative explanations.

Through this process, the iterative movement between empirical data and theoretical literature identified potential puzzling facts and initial patterns in researchers' decision-making processes. The Results section reconceptualizes and redescribes these puzzling facts and provides plausible explanations for these observations.

Step 3: Retroduction

Through retroduction, the final stage of CR analysis, the causal mechanisms and conditions underlying the observed patterns in researchers' decision-making were investigated[49,50]. These mechanisms, defined by Bhaskar as the "*causal structures that trigger events or outcomes*", represent the layer of the "actual"[51]. This investigation revealed deeper causal powers and structures producing observable phenomena, moving beyond surface-level correlations or patterns. The analysis specifically examined

interrelated mechanisms that either stimulate or constrain the consideration of economic factors in DTx development.

Following Danermark et al.'s framework[52], three fundamental questions were explored: How were these patterns in researchers' decision-making possible? What properties were essential to their existence? And what causal mechanisms drove them? This investigation involved iterative analysis of data from steps 1 and 2.

From the coded data, three primary generative mechanisms were retroduced that best explain the observed patterns in researchers' decision-making practices: (1) the *Professional Norms*, (2) the *Researcher Experience,* and (3) the *Adoption Uncertainties*. These mechanisms are discussed in the Results section, with illustrative quotes in Supplementary Table 8.

Drawing on the methodological approaches of Lawani[53], Stohr et al.[29], and Nguyen et al.[32], SD was applied to enhance understanding, visualize, and synthesize to articulate how these mechanisms and their components manifest and influence each other through causal relationships via a CLD. SD modeling has been used extensively in healthcare to better understand complex behaviors and interconnected challenges in healthcare technology development[31,54–56].

To conceptualize these mechanisms and elucidate their interdependencies through a CLD, an iterative three-step process was implemented to: (1) identify influencing variables, (2) map relationships and assign polarity, and (3) validate and refine the model. Throughout each phase, three distinct categories of unit triangulation were incorporated[57], comprising multiple sources of data, iterative triangulation with existing literature and investigator triangulation, as detailed in Supplementary Note 4.

These triangulation categories were employed to serve CR aims in developing deeper explanatory accounts while acknowledging knowledge limitations, ultimately capturing the complexity involved in the system of interrelated variables shaping researchers' decision-making and their considerations of economic aspects. This process facilitated the refinement and validation of identified generative mechanisms while visually mapping the cause-effect relationships underlying DTx decision-making processes[29]. Ultimately, this triangulation approach aimed to achieve a higher degree of internal and external validity, strengthening confidence in the findings[57].

Declarations

Data Availability

All data generated or analyzed during this study are available from the corresponding author on a reasonable request.

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Author Contributions

Y.S. and L.M.C. conceptualized the study, with Y.S. conducting all interviews and data analysis before drafting the manuscript. Y.S., L.M.C., A.M., S.L., G.S., and D.H. contributed to refining all sections and critically editing the manuscript. All authors contributed to and have approved the final manuscript.

Competing Interests

YS and DH are the coinventors of Singaporean Provisional Patent Application No. 10202400360W, “Method for Optimizing a Health Plan” (unrelated to current work). DH is coinventor of previously filed pending patents on artificial intelligence–based therapy development (unrelated to current work). LMC, AM, SL and GS have no conflict of interest.

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Footnotes

1. Throughout this article, the term “DTx development” is used to encompass both the technological development process and subsequent clinical validation through interventional trials.

2. Primary loops are feedback loops that operate entirely within a single mechanism. These loops contain strong causal relationships between closely related variables and represent the essential dynamics within a distinct part of the system. Primary loops typically demonstrate immediate and direct impacts on key system variables. Secondary loops, by contrast, connect across different mechanisms within the system, creating bridges between primary loops. These loops often contain at least one weak causal link and exert less direct influence than primary loops. Secondary loops reveal how effects propagate throughout the entire system, showing cross-mechanism interactions that create more complex emergent behaviors than would be visible from primary loops alone.
3. The term “causal” as used in this qualitative study does not imply statistical causation as established through experimental design or quantitative methods. Rather, it refers to theorized causal mechanisms and relationships that emerge from participants' lived experiences and narratives. This understanding of causality aligns with critical realist approaches that seek to identify underlying generative mechanisms while acknowledging the contextual, complex, and often non-linear nature of social phenomena[23].
4. Weak versus strong causal links, or the “importance” of a relationship, is evaluated by both the frequency and intensity of identified connections. Causal links were categorized as “weak” when mentioned by only a minority of stakeholders (i.e., 1–2 researchers) or described by respondents using qualifying language, such as having “somewhat” of an influence or being “emerging,” “nascent,” or “weak” in nature. Conversely, strong causal links met two critical criteria: broader stakeholder recognition (acknowledged by at least 3 researchers) and substantial supporting evidence (frequently emphasized in interview transcripts as having a direct, significant impact on core system behavior).

Figures

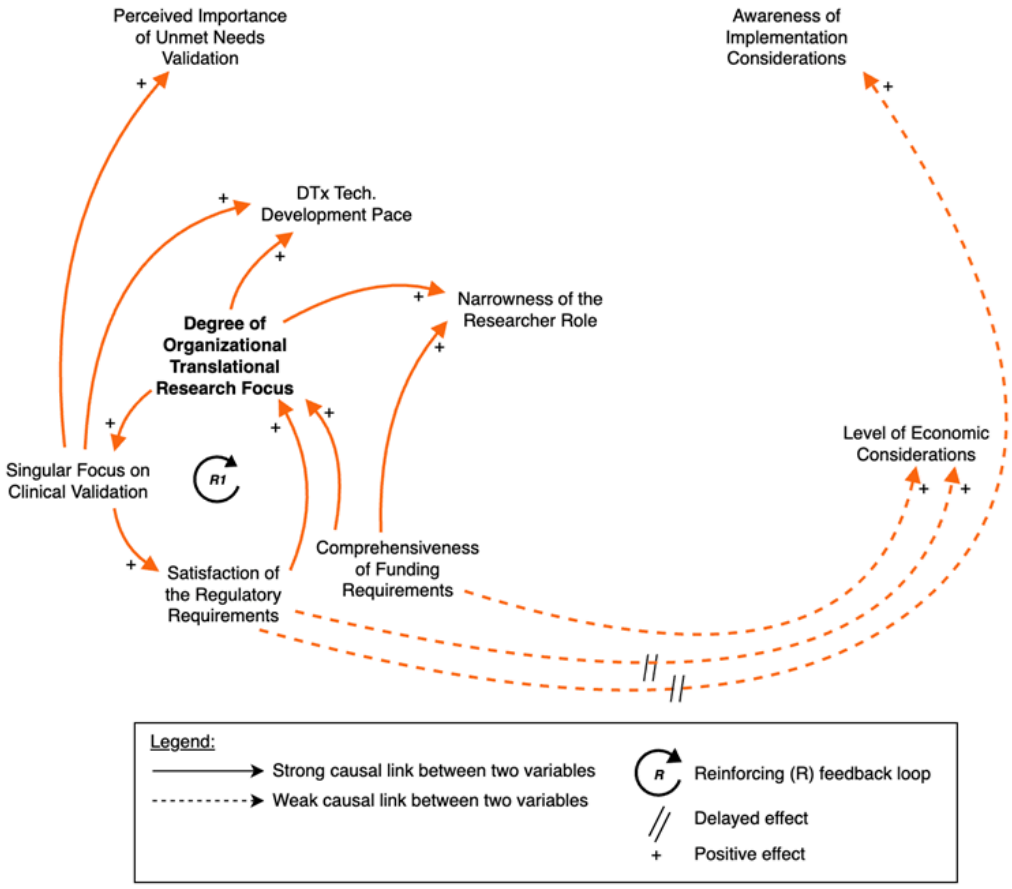


Figure 1

The *Professional Norms* mechanism and its manifestations shaping economic considerations in DTx development. This figure introduces the *Professional Norms* mechanism that illustrates how healthcare norms, institutional settings, and regulatory requirements, which are reinforced by funding requirements, create a reinforcing loop (R1: Clinical Value Loop) that prioritizes clinical validation while marginalizing economic considerations in DTx development (emerging connection indicated in dashed line).

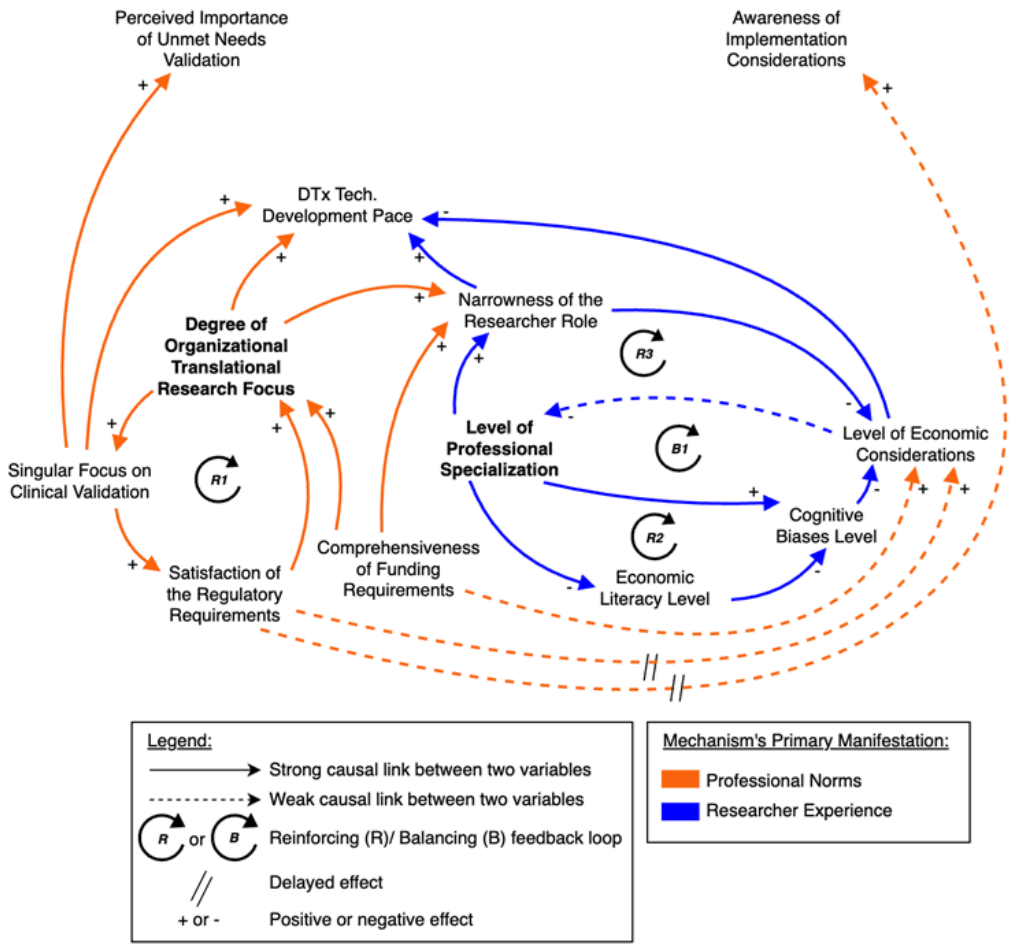


Figure 2

The *Researcher Experience* mechanism and its manifestations shaping economic considerations in DTx development. This figure introduces the *Researchers Experience* mechanism that demonstrates how researchers' professional background, training, and cognitive biases create two reinforcing loops (R2: Literacy Loop and R3: Role Boundary Loop) and one balancing loop (B1: Bias Loop) that systematically channel focus toward familiar domains and away from economic considerations.

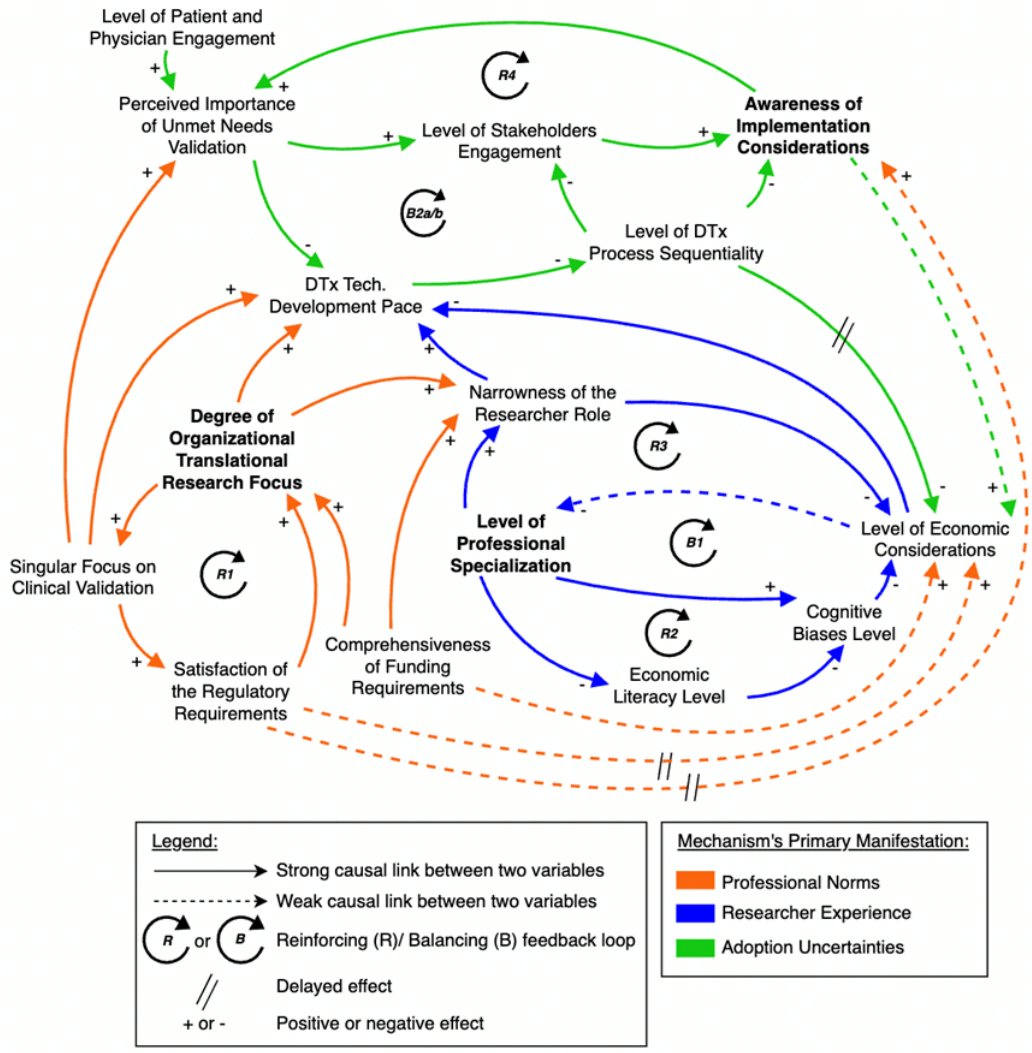


Figure 3

Generative mechanisms and their manifestations shaping economic considerations in DTx development. This figure introduces the *Adoption Uncertainties* mechanism that illustrates how implementation challenges create dynamic interactions between two balancing loops (B2a: Implementation-Driven Development and B2b: Stakeholder-Driven Development) and one reinforcing loop (R4: Collaboration). This mechanism reveals how researchers' awareness of adoption challenges drives increased focus on clinical needs, while stakeholder engagement simultaneously influences

development approaches. Additionally, the figure presents an integrated model that combines all three generative mechanisms with their respective primary loops, demonstrating how institutional forces, researcher intrapersonal factors, and implementation uncertainties collectively influence economic considerations throughout the DTx development lifecycle.

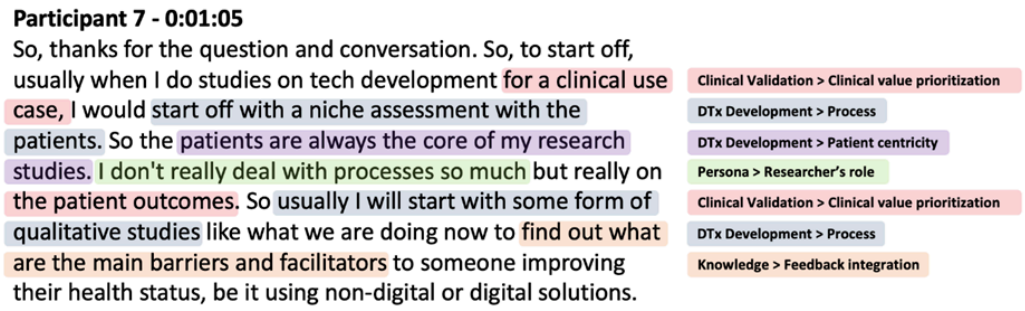


Figure 4

Sample coded transcript. This figure provides a sample coded transcript showing qualitative data analysis with color-coded thematic categories applied to a participant interview.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SapanelSupplementaryInformation20250601.pdf

Appendix 3B. Final codebook

Number	Code Category	Code	Frequency	Short description	Primary Sources
1	Bias >	Anchoring	7	Anchoring to initial estimates, that is, researchers' tendency to rely potentially too heavily on the first piece of information they encounter when making decisions.	DT > BDT based CR > Cognitive constraints
2	Bias >	Availability heuristic	2	Related to the tendency to overestimate the likelihood of events based on how easily they come to mind.	DT > BDT based CR > Cognitive constraints
3	Bias >	Confirmation bias	7	Researchers' tendency to search for, interpret, and recall information in a way that confirms existing beliefs.	DT > BDT based CR > Cognitive constraints
4	Bias >	Cultural	1	Influence of cultural background and values on research decisions and interpretations.	Code emerged from Chevannah's (P14) transcript analysis
5	Bias >	Loss aversion	-	Related to the tendency to prefer avoiding losses over acquiring equivalent gains.	CT > BDT based CR > Cognitive constraints
6	Bias >	Other	7	Miscellaneous cognitive biases affecting research decisions that do not fit into other specific categories.	Code emerged from Eisa's (P4) transcript analysis
7	Bias >	Overconfidence	14	Related to the tendency to overestimate one's own abilities, knowledge, and accuracy of predictions.	DT > BDT based CR > Cognitive constraints
8	Bias >	Professional training	21	Impact of professional education and experience on DTx development processes and related decisions.	Code emerged from Eva's (P2) transcript analysis
9	Clinical validation >	Clinical value prioritization	150	Focus on generating evidence of DTx safety, efficacy, and health benefits.	Literature Review CR > Actual Domain
10	Clinical validation >	Clinical trial results	37	Documented outcomes demonstrating DTx safety and efficacy from trials.	Literature Review CR > Empirical Domain
11	Clinical validation >	Participant selection	5	Criteria for choosing appropriate study participants for clinical validation.	Literature Review CR > Actual Domain
12	Clinical validation >	Study design decisions	20	Methodological choices for validation, including outcome measure selection.	Literature Review DT > EUT based CR > Actual Domain
13	Context >	Healthcare system characteristics	10	Structural aspects of healthcare systems affecting DTx implementation.	Code emerged from Cheah's (P13) transcript analysis
14	Context >	Market fit	42	DTx's ability to address significant clinical needs in the target market.	Literature Review
15	Context >	Regulatory influence and considerations	67	Impact of potential (or the absence of) guidelines, standards, and requirements on DTx development.	Literature Review CR > Real Domain
16	Context >	Reimbursement considerations	42	Planning for payment and coverage mechanisms.	Literature Review DT > BDT based
17	Context >	Resource-related considerations	102	Constraints in funding, time, expertise, and other development resources (e.g., missing information or expertise needed for	Literature Review DT > BDT based

				development Knowledge gaps). Defined as constraints on Agency, under CR.	CR > Cognitive constraints
18	Context >	Decision-making >	28	Environmental and situational factors influencing decision processes.	Code emerged from Ezra's (P3) transcript analysis
19	DTx development >	Access	7	Considerations related to ensuring equitable access to the DTx solution across user populations.	Code emerged from Chevannah's (P14) transcript analysis
20	DTx development >	Diversity of stakeholders	104	Involvement of varied stakeholders in the DTx development process.	Code emerged from Emma's (P1) transcript analysis
21	DTx development >	Patient centricity	45	Focus on incorporating patient needs, preferences, and experiences throughout the DTx development process, ensuring the solution addresses real patient challenges and promotes engagement.	Code emerged from Emma's (P1) transcript analysis
22	DTx development >	Patterns	4	Recurring approaches in development processes and decision-making.	CR > Empirical Domain
23	DTx development >	Process	142	Stages of technological innovation and development.	Code emerged from Emma's (P1) transcript analysis
24	Eco. consideration >	Long-term costs	10	The long-term impact of DTx onto society.	Code emerged from Christoph's (P12) transcript analysis
25	Eco. consideration >	Business model	70	Strategy for DTx monetization and market deployment.	Literature Review
26	Eco. consideration >	Clinical validation costs	6	Expenses for trials, recruitment, data collection, and analysis.	Literature Review
27	Eco. consideration >	Development costs	14	Expenses for initial creation and iterative improvements of the DTx.	Literature Review DT > EUT based
28	Eco. consideration >	Direct medical and non-medical costs	54	Including costs of pharmaceutical treatment, of the DTx, health resource utilization, intervention-specific training, and participants' time spent on the DTx.	Literature Review DT > EUT based
29	Eco. consideration >	Eco. prioritization	94	Emphasis on economic considerations in development.	Code emerged from Eva's (P2) transcript analysis
30	Eco. consideration >	Economic value awareness	145	Researchers' understanding of the concept of economic value (e.g., strategies implemented to ensure economic viability of the DTx)	Literature Review
31	Eco. consideration >	Economic evaluation methods	66	Approaches for assessing DTx cost-effectiveness and value, such as cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), or cost-utility analysis (CUA).	Literature Review DT > EUT based > HTA
32	Eco. consideration >	Funding sources	15	Available financial resources for DTx development.	Literature Review CR > Real Domain
33	Eco. consideration >	Implementation related	114	Awareness of practical deployment considerations, such as clinical workflow integration, provider training needs, or support requirements.	Literature Review DT > EUT based
34	Eco. consideration >	Indirect medical and non-medical costs	37	Including costs related to the productivity impact and DTx maintenance.	Literature Review DT > EUT based

35	Eco. consideration >	Influencing factors	16	Including participants' baseline characteristics, reimbursement rate, treatment adherence, attrition rate, degree of clinical inertia and sustained DTx clinical effectiveness.	Literature Review
36	Emotional factors >	Confidence	6	Self-assurance in development decisions and approaches.	Code emerged from Surya's (P10) transcript analysis
37	Emotional factors >	Fear and anxiety	5	Concerns, worries, or anxieties influencing decision-making processes.	DT > BDT based
38	Emotional factors >	Optimism and hope	7	Expressions of positive expectations or confidence influencing choices and strategic decisions.	DT > BDT based
39	Emotional factors >	Passion and commitment	24	Indications of personal investment, dedication, or emotional attachment which drive decision-making and persistence.	DT > BDT based
40	Emotional factors >	Pressure and stress	11	Mentions of time constraints, workload, or external demands affecting decision-making behavior.	DT > BDT based
41	Knowledge >	Best practices	22	Proven effective methods, techniques, and approaches in DTx development and implementation.	Code emerged from Eva's (P2) transcript analysis
42	Knowledge >	Expert consultation processes	26	Methods for incorporating subject matter expertise.	Literature Review
43	Knowledge >	Feedback integration	73	Incorporation of stakeholder perspectives and input, such as patients and HCPs.	Literature Review CR > Empirical Domain
44	Knowledge >	Market intelligence utilization	13	Use of market data in decision-making.	Literature Review
45	Knowledge >	Talent development	4	Strategies and processes for building and maintaining necessary expertise and skills within the development team, including training and knowledge transfer.	Code emerged from Cheah's (P13) transcript analysis
46	Organizational context >	Institutional research priorities and mandates	73	Formal organizational goals directing research focus.	Literature Review
47	Organizational context >	Organizational culture toward commercialization	48	Institutional attitudes and practices toward research commercialization.	Literature Review
48	Organizational context >	Strategic alignment	3	Alignment between DTx goals and broader organizational objectives (e.g., level of leadership support).	Literature Review
49	Outcome evaluation >	Market potential evaluation	19	Assessment of commercial opportunities, market size and potential, and therefore of the DTx potential value.	Literature Review DT > EUT based
50	Outcome evaluation >	Regulatory outcomes	5	Considerations related to obtaining regulatory approval in order to commercialize a DTx in specific markets.	DT > EUT based CR > Empirical Domain
51	Persona >	Adoption related	91	Considerations (and concerns) related to DTx uptake by target users.	Code emerged from Surya's (P10) transcript analysis

52	Persona >	Clinicians' mindset	45	Unique perspectives and decision-making approaches that distinguish clinicians-researchers in their work.	Code emerged from Eva's (P2) transcript analysis
53	Persona >	Engineer's mindset	34	Unique perspectives and decision-making approaches that distinguish engineers-researchers in their work.	Code emerged from Eva's (P2) transcript analysis
54	Persona >	Researcher's mindset	34	Insights and perspectives that characterize researchers' general approach and thought processes.	Code emerged from Eva's (P2) transcript analysis
55	Persona >	Researchers' priorities	108	Day-to-day priorities of researchers, and therefore key considerations in decision-making processes.	Code emerged from Emma (P1) transcript analysis
56	Persona >	Researchers' role	95	Interviewee's involvement and contributions across different stages of DTx development and technical lifecycle. It also captures the personal experiences of the researchers with DTx development.	Code emerged from Emma (P1) transcript analysis CR > Empirical Domain
57	Probability >	Probability calculations	10	Objective and subjective probability calculations.	Literature Review DT > EUT based
58	Probability >	Uncertainty	13	Acknowledgment of potential uncertainty.	Literature Review DT > EUT based
59	Social influence >	Competitive pressure	8	Impact of market competition on decisions.	DT > BDT based
60	Social influence >	Norms	30	Established practices, standards, and unwritten rules that shape behavior within the DTx ecosystem.	DT > BDT based
61	Social influence >	Peer pressure	3	Direct and indirect influence exerted by professional peers and industry colleagues on decision-making.	DT > BDT based
62	Social influence >	Status and reputation concerns	2	Decision-making influenced by considerations of professional standing and organizational reputation.	DT > BDT based
63	Stakeholder relationships >	Communications	17	Related to the communications between the different stakeholder groups.	Code emerged from Shiva's (P9) transcript analysis
64	Stakeholder relationships >	Cross-disciplinary collaboration structures	72	Formal and informal arrangements for working across different fields of expertise, encompassing collaborative networks that facilitate knowledge exchange.	Literature Review CR > Actual Domain
65	Stakeholder relationships >	Group and power dynamics	12	Distribution and exercise of authority in decision-making (e.g., stakeholder alignment issues). It includes the "network effects", i.e., the impact of existing relationships and connections on researchers' decision-making and development choices.	Literature Review CR > Actual Domain
66	Stakeholder relationships >	Industry-academia relationships	21	Connections and interactions between academic researchers and industry partners.	Literature Review CR > Actual Domain
67	Stakeholder relationships >	PPP dynamics	6	Public-private partnership interactions and relationships.	Literature Review CR > Actual Domain
68	Tech. development >	Features prioritization	10	Decisions about which features or capabilities to develop first.	Literature Review
69	Tech. development >	Interoperability considerations	16	Ability to integrate with other systems and platforms.	Literature Review

70	Tech. development >	Security and privacy features	8	Measures for protecting data and ensuring privacy.	Literature Review
71	Tech. development >	Tech. architecture	5	Choices and decisions about technological structure and components.	Literature Review
72	Tech. development >	Tech. limitations	3	Constraints imposed by technology or infrastructure.	Literature Review CR > Real Domain
73	Tech. development >	Tech. prioritization	67	Focus on technological capability development. It could also be considered as a “pro-innovation bias”.	Code emerged from Emma’s (P1) transcript analysis
74	Tech. development >	User interface	12	Choices affecting how users interact with the DTx (e.g., decisions related to the end-user experience).	Literature Review
75	Utility >	Resource	2	Resource allocation-related decisions and considerations.	DT > EUT based CR > Actual Domain
76	Utility >	Risk	10	Notion of risk and uncertainty evaluation.	DT > EUT based
77	Utility >	Scalability	31	Scalability potential of the future DTx intervention.	DT > EUT based
78	Utility >	Time	1	Time-value considerations (e.g., specific deadlines).	DT > EUT based

Appendix 3C. COREQ checklist

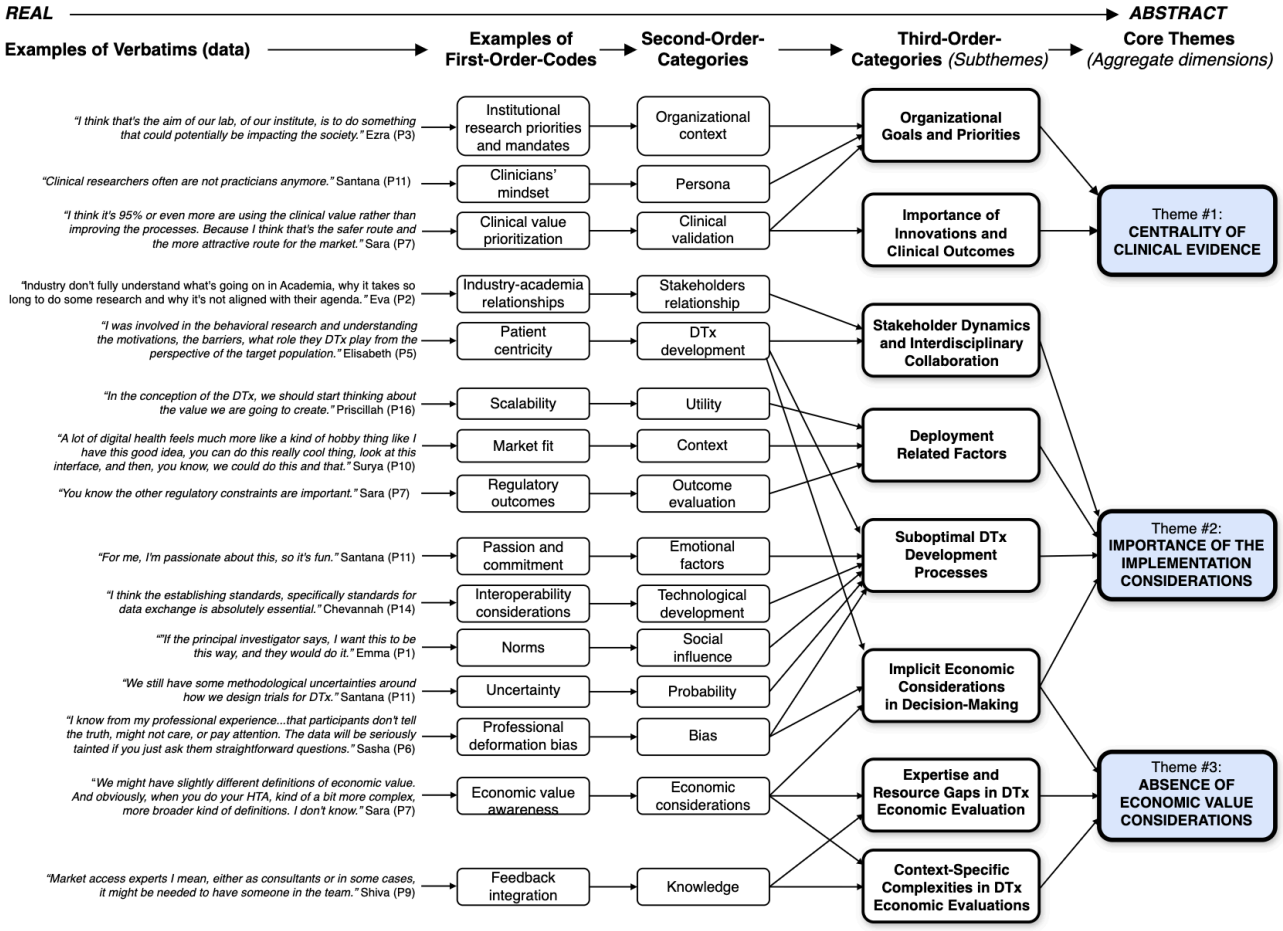
Item No	Guide Questions/Description	Comment
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/ facilitator	Which author/s conducted the interviews?	Y.S. conducted the semi-structured interviews.
2. Credentials	What were the researcher's credentials?	Y.S. holds an M.Sc. in Entrepreneurship and Strategic Management and is a doctoral student researching economic value drivers for DTx. L.M.C. has a Ph.D. in Strategic Management and Applied Economics and conducts research in Information Technology management. A.M. holds a Ph.D. in Management Science, specializing in decision analysis and operations research, with expertise in healthcare decision-making and health economics. D.H. holds a Ph.D. in Biomedical Engineering, G.S. a Ph.D. in Economics, and S.H.L. in Communication and Information.
3. Occupation	What was their occupation at the time of the study?	Y.S. served as a Director at the Institute of Digital Medicine (WisDM), National University of Singapore, while L.M.C. was a Professor in the Department of Analytics, Operations, and Information Technologies, School of Management Sciences, at the University of Quebec at Montreal, Canada. D.H. was the Provost's Chair Professor, Director of the Institute for Digital Medicine (WisDM), Director of the N.1 Institute for Health, and Head of the Department of Biomedical Engineering at the National University of Singapore. A.M. holds joint appointments at the National University of Singapore, Duke-NUS and the University of Strathclyde. G.S. and S.H.L. are both research fellows at the Institute of Digital Medicine (WisDM), National University of Singapore.
4. Gender	Was the researcher male or female?	One woman-identifying researcher and five male-identifying researchers.
5. Experience and training	What experience or training did the researchers have?	Y.S., L.M.C., G.S., S.H.L., A.M., and D.H. have extensive experience in conducting qualitative health research. Additionally, Y.S., L.M.C., and D.H. have recently published relevant papers to the research question. L.M.C. teaches research methods in the areas of information technology. A.M. researches developing methods for supporting complex decisions in healthcare resource allocation and policy. He has made significant contributions to the field of health technology assessment and healthcare prioritization. G.S. specializes in decision-making and behavior changes in health and public policy.
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	Y.S. and D.H. had varying relationships with the health community at large, while L.M.C. had no relationships with participants prior to the study. All were perceived as unbiased researchers rather than persons with a particular stake, stance or opinion about the topic.
7. Participant knowledge of the interviewer	What did the participants know about the researcher?	The interviewers introduced themselves to participants and describing the context, scope and purpose of the research, going through the different sections of the consent form. The contents followed the exact guidelines as certified by ethics review boards for research with human beings of all institutions involved.

Item No	Guide Questions/Description	Comment
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator?	The participants were informed of the knowledge gap and corresponding research question as context for the interview, highlighting the interviewers' interest in addressing this gap without presenting specific assumptions or potential biases. The contents followed the exact guidelines as certified by ethics review boards for research with human beings of all institutions involved.
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study?	The study adopts a CR epistemological stance. Theoretical frameworks such as DT and ST were introduced to examine and interpret how researchers navigate the complex choices involved in DTx development.
Participant selection		
10. Sampling	How were participants selected?	Purposive sampling was used. Initial recruitment occurred through the research team's professional network, with participants encouraged to refer qualified colleagues through snowball sampling.
11. Method of approach	How were participants approached?	Email invitations were sent to individuals who could potentially meet the following inclusion criteria: (1) a minimum of five years of experience in DTx development or clinical validation, (2) current involvement in the technological development or clinical validation of a DTx, (3) fluency in English or French. The recruitment process followed the exact guidelines as certified by ethics review boards for research with human beings of all institutions involved.
12. Sample size	How many participants were in the study?	17 Participants. For details of the study participants' demographic data, please refer to Table 17.
13. Non-participation Setting	How many people refused to participate or dropped out? Reasons?	While several individuals did not respond to the invitation, nobody explicitly declined the invitation. All those who agreed to participate remained committed throughout the study. This followed the exact guidelines as certified by ethics review boards for research with human beings of all institutions involved regarding participants' informed consent and right to withdraw without justification.
14. Setting of data collection	Where was the data collected?	Data were collected through either Zoom or face-to-face interviews and analyzed using ATLAS.ti software (ATLAS.ti Scientific Software Development GmbH).
15. Presence of nonparticipants	Was anyone else present besides the participants and researchers?	None.
16. Description of sample	What are the important characteristics of the sample?	Fully presented in Table 17.
Data collection		
17. Interview guide	Were questions, prompts, and guides provided by the authors? Was it pilot tested?	A semi-structured interview guide with key questions was designed to explore topics including: 1) participants' roles as DTx researchers, 2) their priorities and key considerations throughout the DTx lifecycle, and 3) day-

Item No	Guide Questions/Description	Comment
		to-day prioritization and decision-making processes. Please refer to Table 3 for details of the topics discussed.
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	No.
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	All interviews were audio-recorded and later transcribed. This followed the exact guidelines as certified by ethics review boards for research with human beings of all institutions involved in data management procedures during the research, during the analysis, and post-reporting.
20. Field notes	Were field notes made during and/or after the interview or focus group?	Following each interview, the interviewer documented brief notes highlighting the interview's nature and key themes emphasized by the interviewee.
21. Duration	What was the duration of the interviews or focus group?	Interview duration varied but typically ranged from 45 to 60 minutes.
22. Data saturation	Was data saturation discussed?	Yes.
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No.
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	The interviewer coded and described the data, regularly discussing the resulting codes with the research study team. The analysis combined deductive and inductive coding, followed by abductive and retroductive processes, to identify generative mechanisms underlying observed decision-making patterns.
25. Description of the coding tree	Did the authors provide a description of the coding tree?	Yes. Please refer to Appendix 3D for the verbatim to codes, subthemes, and themes developed through Fletcher's “deductive yet flexible” coding (2021) with Saldaña's coding cycles (2021).
26. Derivation of themes	Were themes identified in advance or derived from the data?	Derived from the data.
27. Software	What software, if applicable, was used to manage the data?	ATLAS.ti software (ATLAS.ti Scientific Software Development GmbH).
28. Participant checking	Did participants provide feedback on the findings?	Discussions were scheduled with three DTx experts at different time intervals who met the study inclusion criteria but were outside the original sample to interpret, validate, and refine emerging versions of the CLD.
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified?	Yes.

Item No	Guide Questions/Description	Comment
30. Data and consistent findings	Was there consistency between the data presented and the findings?	SD modeling was applied to visualize causal relationships through triangulated data sources, ultimately aiming to achieve a higher degree of internal and external validity, strengthening confidence in the findings.
31. Clarity of major themes	Were major themes clearly presented in the findings?	Yes, major themes are clearly identified in the paper, as well as the generative mechanisms underlying observed researchers' decision-making patterns.
32. Clarity of minor themes	Is there a description of diverse cases or a discussion of minor themes?	No.

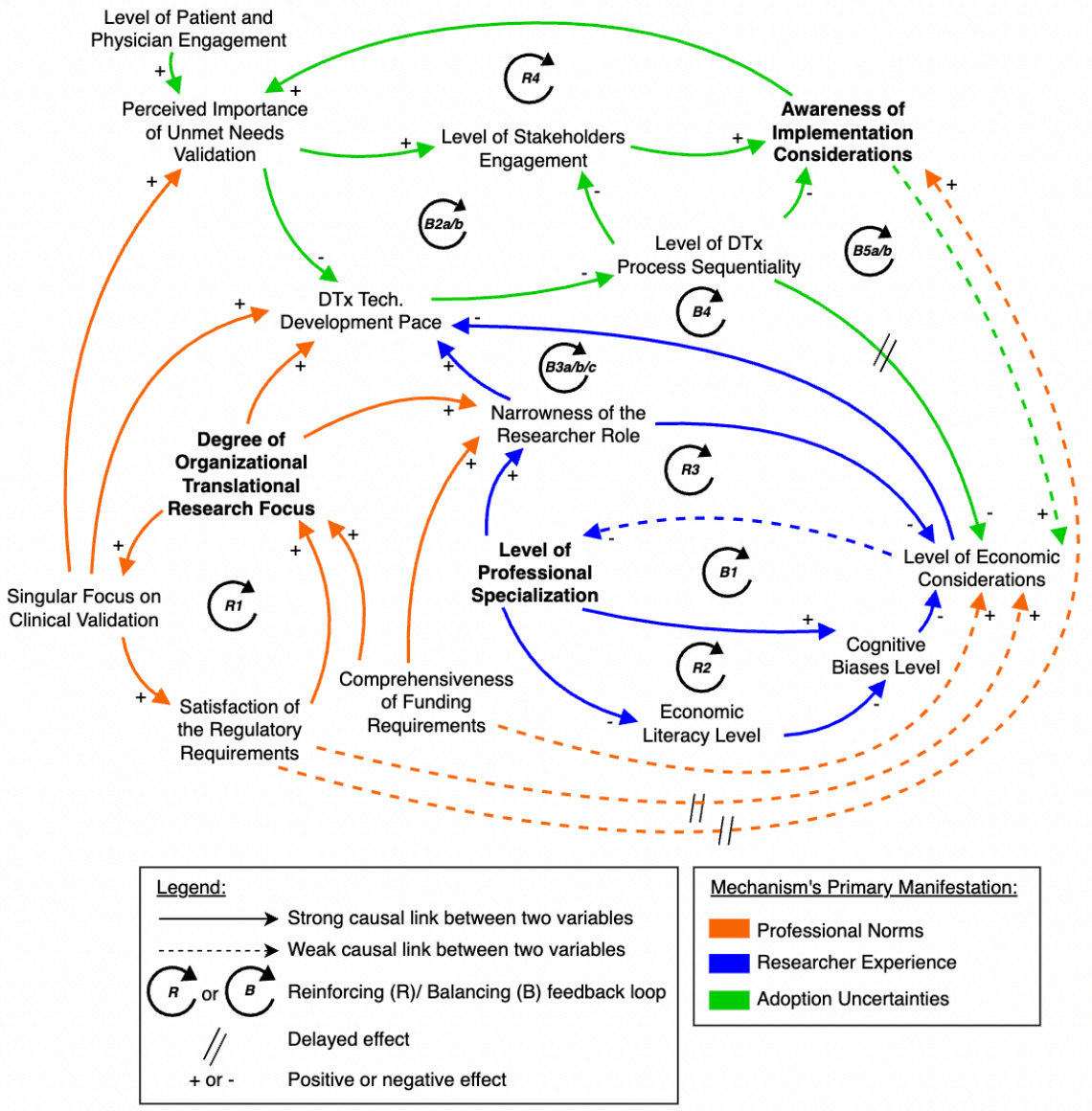
Appendix 3D. Verbatim to codes, subthemes, and themes



Appendix 3E. Illustrative quotes for the three primary mechanisms

Mechanisms	Representative Quotes	Context	Interpretation
Professional Norms	"*As a researcher, my KPIs are focused on publications and clinical validation... economic considerations aren't part of our metrics*" (Emma, P1) "*The priorities would be focused on technical performance and the clinical value this solution can have*." (Elisabeth, P5) "*We were too focused on the clinical service delivery team [and did not engage some of the stakeholders'. So we developed that and then went through a couple of trials. One was a pre-test, post-test study first, now a randomized controlled trial to see whether it really works. At this point, we still have not done cost-benefit analysis. So it may be a money-losing intervention, we don't know, but we may be throwing money into the ocean. So this is one downside*." (Camirah, P15)	Discussion of research priorities	Demonstrates how institutional structure and dynamics shape decision-making focus
Researcher Experience	"*From my engineering background, I naturally focus on technical performance... economic aspects weren't part of my training*" (Ezra, P3) "*I don't really consider myself an expert in this area at all. I have some knowledge, partly during training, there are specific components of our examinations that cover things like cost effectiveness*" (Cheah, P13) "*It's safer to follow guidelines. That's what we're trained to do throughout our training*." (Surya, P10)	Reflection on professional training	Shows the influence of educational background on decision frameworks
DTx Adoption Uncertainties	"*Implementation is always the biggest unknown... you can have perfect clinical results but fail completely in real-world adoption*" (Christoph, P12) "T*he kind of the end goal is really about the adoptions, basically, the deployment and the adoptions of these technologies*." (Priyah, P17) "B*esides economics, it's the implementation part, like how do we assess or evaluate the fidelity or the adoption of this kind of program, how do we do stakeholder engagement, how to analyze their responses, how to overcome barriers and facilitators when you look at the big picture*" (Camirah, P15)	Discussion of development challenges	Illustrates how adoption uncertainty shapes DTx development-related decisions

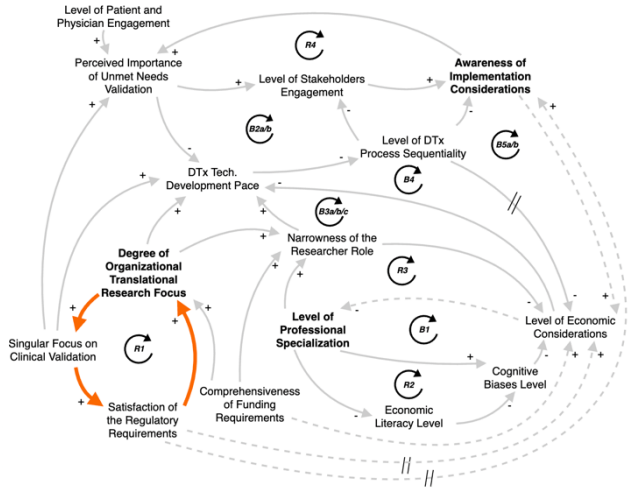
Appendix 3F. Integrated causal loop diagram: Primary within-mechanism and secondary cross-mechanism loops in DTx Development



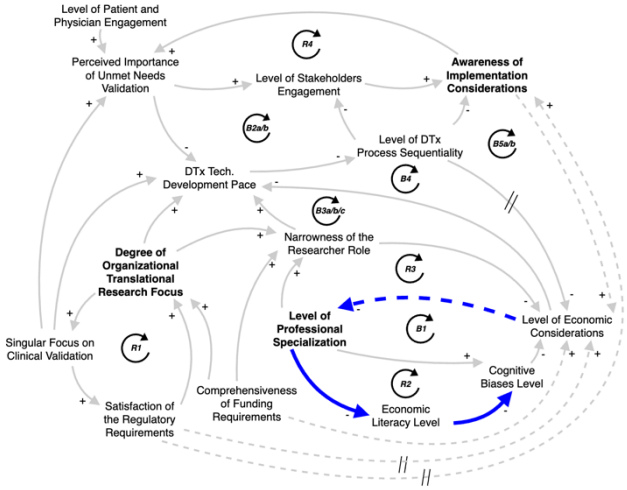
Appendix 3G. Overview of individual primary and secondary balancing and reinforcing loops in the causal loop diagram

Primary within-mechanism loops

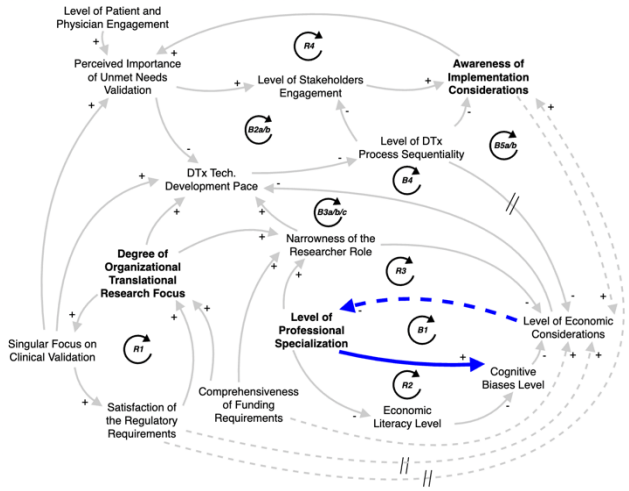
R1. Clinical Value Loop



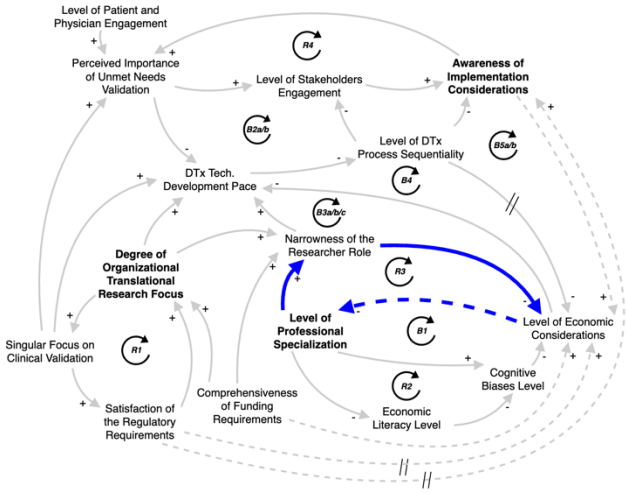
R2. Literacy Loop



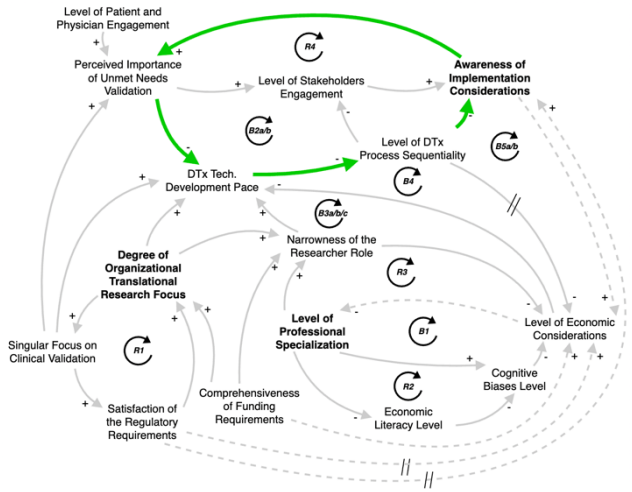
B1. Bias Loop



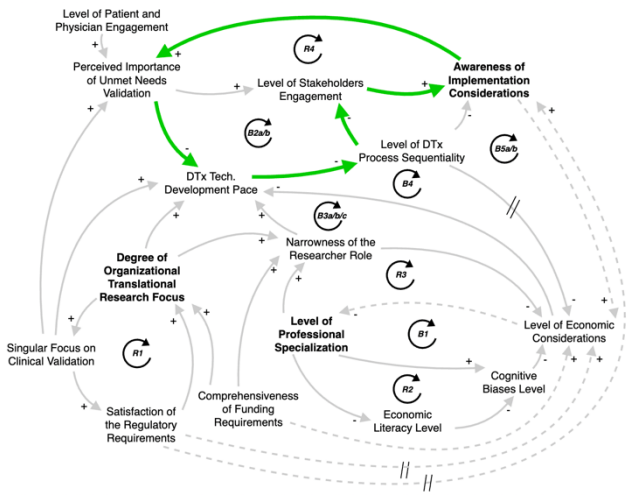
R3. Role Boundary Loop



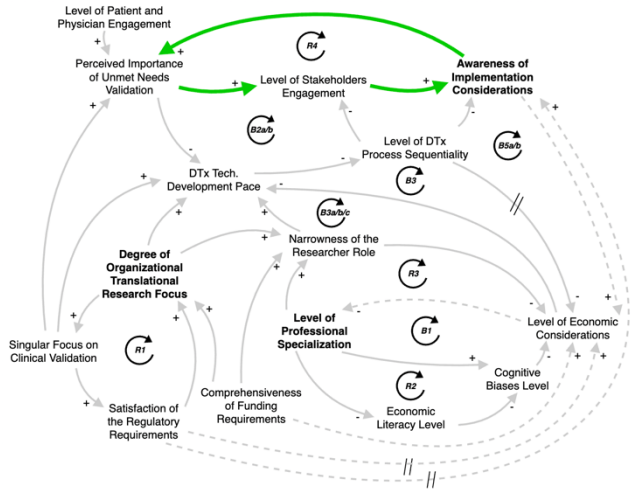
B2a. Implementation-Driven Development Loop



B2b. Stakeholder-Driven Development Loop

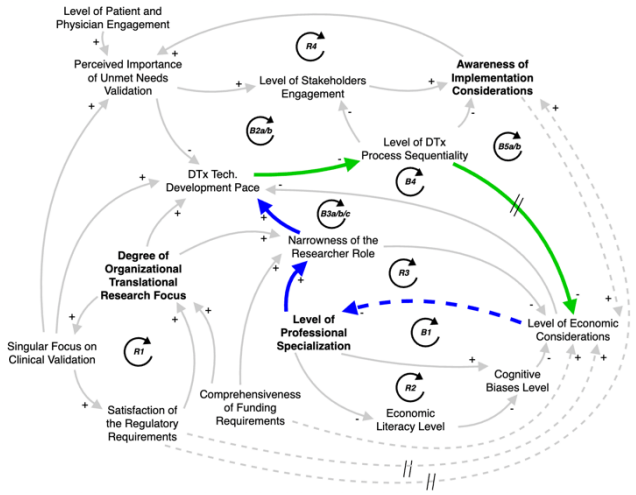


R4. Collaboration Loop

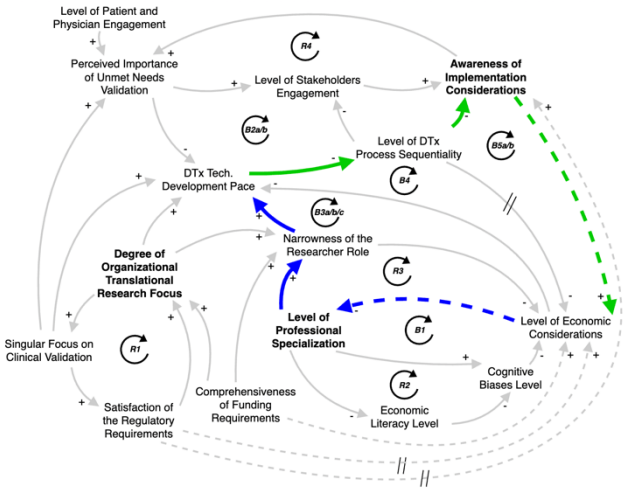


Secondary cross-mechanism loops

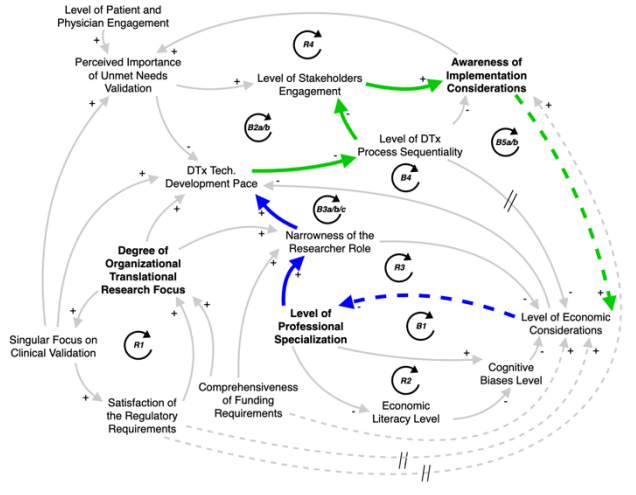
B3a. Specialization-Technology Loop



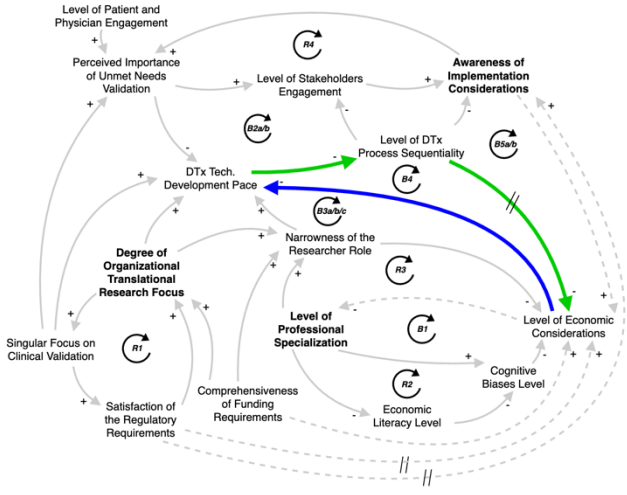
B3b. Implementation-to- Specialization Loop



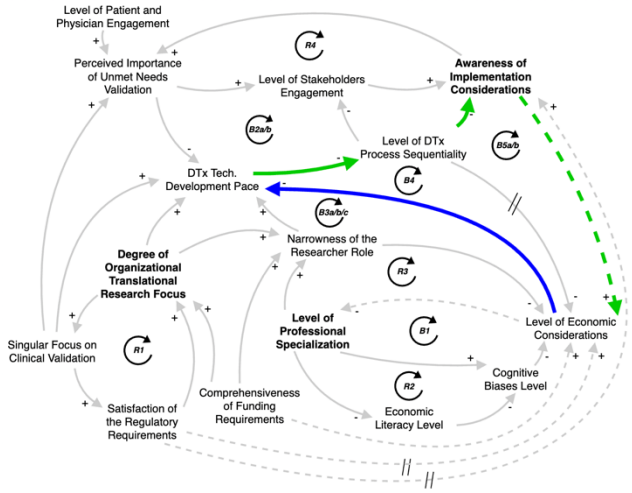
B3c. Stakeholder-Guided Implementation-to-Specialization Loop



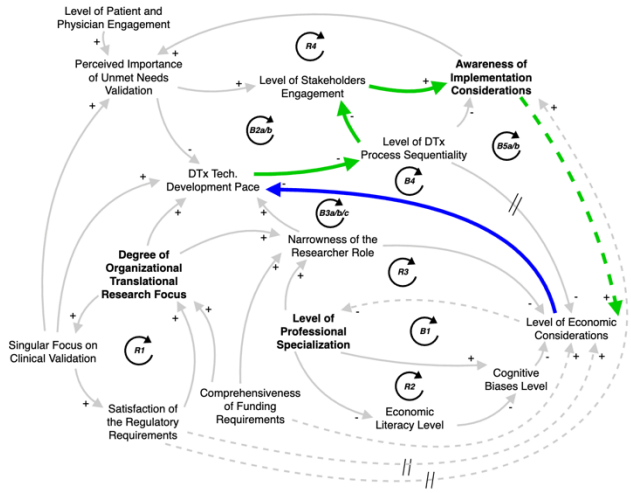
B4. Development Efficiency Loop



B5a. Implementation-Economic Development Loop



B5b. Stakeholder-Informed Implementation-Economic Loop



Appendix 3H. Interview transcripts

Interview Transcript with Emma (P1)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:00:00 So maybe I will start with asking you, if you don't mind to describe your role, and how are you involved in a DTx-ish, you know, it could be like a DTX or digital health solution, but what's your role in, how would you describe your role basically and how you're involved or engaged with the DTX kind of lifecycle process?

Emma - 0:00:40 Okay, my role is a researcher, so I work on clinical decision support system development, and also, we kind of see how it's implemented in the clinical setting. So I am highly involved in development and the clinical trials of the solution.
Yoann - 0:00:59 Would you want, or could you share one or two solutions in terms of like applications or therapeutic areas that you've been?

Emma - 0:01:07 So, the first solution I've been majorly working on is Curate AI. It's a clinical decision support system that helps in doing, you know, recommending doses for clinicians. So it's kind of like a personalized treatment, personalized therapies and so on. So my major trials that I work with is in oncology, hypertension and we've also done some retro analysis of data for personalized medicine, for liver transplantation and so on.

Yoann - 0:01:43 I see. And so, you said you mentioned that you were involved in the development as well as the clinical validations. If we try to break down these kinds of high-level steps into sub-steps, when you look at the development, what, from your experience, what are some of the critical or the key phases or the key steps of the development, slash, what could be some of the key steps from a validation standpoint?

Emma - 02:06 Okay, so in terms of development, the first step is ideation. Ideation and trying to understand which research problem that you want to solve, and whether this problem is big enough or critical enough that you pursue it, spending time, resources, and so on. So the first step is ideation. And second step, we understand the research problem, trying to see whether do we have external parties who are, because as a researcher, we are also trying to implement this, right? So, we're also trying to understand whether our tech is a good fit to that research statement. So, we're trying to understand that. We analyze that statement, we analyze that entire segment, and are we having enough, are there enough resources out there for us to understand this better and do we have an expert who we could also engage? So, this is kind of understanding. So first the citation, then it's like looking deeper into the research question and then from then we move on and we try to do a very minimal retrospective analysis of any data that we could get before we proceed to direct implementation or for a clinical trial, we do retroanalysis with the technology that we have and see what do we learn from the retro-analysis. Is it a good fit to even pursue a clinical trial or not? Or whether this technology works, are we finding good enough solutions?

Yoann - 0:03:33 I see. And on this stage of tech development, what would be your top priority, your first top priority or the first two priorities? What would drive your day to day kind of decisions basically from a development standpoint?

Emma - 0:03:52 For development standpoint, because this tech is in, there are fundamentals of this tech that we have that is a primary base, but there are also secondary segments where it's movable and modifiable. So, first thing is to see whether the fundamental segment fits for the

problem statement, and the second thing, are we able to modify this enough to fit into the secondary statement as well. So, there are two segments to it. Some is like fixed, some are like, you know, movable.

Yoann - 0:04:26 I see. So, it's really about the fit as kind of a top priority in a way, or fit and alignment with the kind of needs of the patients slash customers, right? Whoever is going to be the end user. And when it comes to the clinical validations, so we tend to look at clinical validations as clinical trial, but could you help us elaborate a bit more on some of the steps, assuming there are a few steps when it comes to the clinical validations that you went through or that you have experienced?

Emma - 0:04:56 Yeah, the first thing is to design the study. When we design the study, what we're trying to understand is how many participants do we need to validate this system at a very logistical sense, because one of the studies that we did is very logistical and feasibility. So, before you went to see whether this solution is good enough, the first thing is to see whether this solution can be implemented. So that was the logistical side of it. Whether there's a workflow that can be put into this ecosystem when the solution is being set. Whether is it a smooth workflow, is it gonna be like a, you know, when we say disruptive technology, is it going to disrupt a lot of workflows? But what we need is a technology that aligns with the workflow and it's not going to add extra load to the system itself. So, the logistical feasibility would be that. That would be a very big priority to make sure it aligns and it goes through the workflow and not disrupts the workflow and does not add any other workload to any of the participants along the line. And the second one in terms of implementation that we look at is the resources that we have. Are people engaged enough? Do we have enough financial resources to support? And how much do we need good enough to validate the system, validate the technology?

Yoann - 0:06:19 Okay, so on this last part, on the resources, is it fair to say that what you just mentioned is like just to ensure that you have the manpower that will help and be able to support the implementations of your technologies?

Emma - 0:06:39 One is manpower, because, and also, their passion to support, I would say.

Yoann - 0:06:45 Okay, so the buying.

Emma - 0:06:46 Yes, because we have another study that we're doing, the hypertension study. So, what we're actually currently facing is, in the beginning, a month or two, we had so many patients being recruited, and when it was December holidays and so on, and then it's been so monotonous that we do not have, we don't see recruitments. It's not because patients are not coming in, it's not because we have a very strict criteria to put in the study. It's maybe because the clinicians themselves forgot about the study, because there are so many other studies going on. So, I think one thing that I really learned from that study is to have regular checkups with the clinicians or have a debrief to the clinicians to reintroduce the study so it's still fresh in their memories during the entire phase.

Yoann - 0:07:31 And so, we're discussing about clinical validations but you mentioned quite a lot of aspects that are more kind of towards the implementations, like all the logistical feasibility, you mentioned about the workflow and so on. Is this what you would expect in any kind of, let's say, DTX research institute? Or is this specific to Wisdom and of One? Because you have experience in quite a few different kinds of organizational environments. So what's kind of unique to here? What, in terms of like, I don't know if it's a best practice or not, but what's kind of different maybe, I should say, here, what you have seen?

Emma - 0:08:05 I feel it's quite different when it comes to WisDM, N-of-1, because we are very implementation driven. Because as engineer, as a researcher, I'm also, usually we only care about the solution. But the implementation side is someone else who's doing it. So typical

mindset of a researcher or an engineer would be I focus on my technology, which I think this is the problem and I work towards the problem. And I focus on developing the best AI technology or the best digital health solution. But the reality is how fit is the solution, but not a lot of engineers. When you have an engineer mindset or researcher mindset, you don't think so far ahead because you're not exposed to the problems that come beyond. You're so focused on the tech itself.

Yoann - 0:08:58 And how do you explain that? Because it seems that from what you just said, that ideally, engineers slash researchers might be, should maybe be more exposed in some of this kind of don't want kind of challenges they are going to, they are like the solutions they are going to face. So how do you explain this oversight maybe?

Emma - 0:09:18 From what I've seen, from my personal experience, majority of them do not see themselves as entrepreneurs or do not see themselves like solutions to be translated. They see themselves as I'm a co-engineer and I want to work on this tech. Like I'm good at coding so I just want to code, or I'm good at you know finding innovative solutions, I just want to find it. Then what happens to it? Do you want to pursue with the technology? Do you want to make a startup out of this? Or do you want this to be commercialized or implemented, like you know do implementation? They might not really have the skill set or the urge to push it. Maybe they want to be a CEO someday, but then I don't think they have enough resources that supports them. They're not the subject matter expert to do this kind of things.

Yoann - 0:10:12 So it's not only a question of like having the right mandate, right? Because sometimes, you know, what I've seen in some publications is that, okay, my mandate is to do, or kind of from a KPI standpoint, is to do A and B, but not C. So I will not care about C. So is it more like a mindset, skill set kind of challenge, I would say, or issue? Or it's a mandate issue? It's a bit of both?

Emma - 0:10:38 I think it's a bit of both because as a researcher, my KPIs are I need to develop something, I need to publish something. So when it comes to these two things, the time that I have to implement it is not even in my area of KPIs. So it's really out of personal interest or it's probably thought driven from my supervisor or investigator that this would be pushed down. If my supervisor is not interested in having a startup or if my supervisor is not interested, if my supervisor is just like, I just want to publish papers and I just want to climb the academic ladder, then this is not even relevant. Until less, there are universities out there that are also ranked based on the number of startups or the number of technologies that come out of them. So now slowly they're getting into the KPIs as well. So I've seen the ecosystem change so much in the past, you know, like eight years in Singapore in terms of commercialization, in terms of startups and the funding and the support.

Yoann: So what are some of the KPIs that might help? Like you mentioned about commercialization, like as a KPI, like you know, spin-off or is this kind of KPI that you think might help kind of change a bit?

Emma: I feel it's really about passion. It's really that you want to do it. Because if your business is going to be like, you have to do it, I don't think everyone is in for it. I don't think it's something one, like five different KPIs and everyone is going to get it done. Even if there are 10 passionate individuals who want to get a startup done in the medtech field with digital health, and I don't think not all of them are going to succeed, right? Even though they have the passion. There's so much more about a lot of other factors than just passion. And if they just want to do a startup, I think they'll probably be doing an MBA and finding innovative solutions that way and not be an engineer to do that.

Yoann - 0:12:45 Specifically, yeah. Makes sense. And so we briefly discussed about the economic impact of DTX. What does it mean to you? How would you define, if someone would

say, OK, we need to look at or assess the economic impact of DTX, what's your definitions? How would you define the economic impact of DTX?

Emma - 0:13:09 So as a researcher, if I'm looking at this, it would be like, am I developing a low-cost solution, which is a good to have. So from a researcher point of view, it's definitely a good to have, unless that is my driving factor for developing that particular technology. If not, if I'm gonna develop a technology that is very good, economic factor is not something that I would really keep in mind, because that's really not my thing, or that's not in my list of things to be worried about. My worry would be whether the technology is working or how good the results are going to be and how efficient it's going to be.

Yoann - 0:13:48 So who defines, if it's from the get-go, I guess, like a low-cost solution versus kind of a premium or top kind of... Who defines such mandate in a way?

Emma: I think it's the next phase. The parties who are having the decision makers, I guess, because in terms of, if this is a low cost or a high-cost solution, what's in the market, and what kind of customer base that we're doing. Because there's one example that I have is, I worked on a project that works on a skull robot. And that skull robot, I'm developing my lab, and it could easily cost like a million if I'm gonna commercialize it. Because that's the market fit, that's the market rate and so on. But there is also another solution that I've worked on, it's like a blood collection device, and it costs just 20 cents because it's just a membrane. So there are two different segments, but what decides the price is the utility of the solution and also the customer base, I would say.

Yoann - 0:15:08 And so assuming you might be involved in a kind of low-cost solutions development, what would be some of the kind of considerations or factors or cost factors that you might be a bit more careful, you know, through the development of the clinical validations, like from your experience, what are some of the top considerations in this area?

Emma - 0:15:31 So the first thing would be ease of access. If I want, if I'm trying to look at a digital health solution that should be low cost, I should be able to see that most people have access to it. So the threshold is not so high that they get there. So if it's just an app, they already have a smartphone. If the nation, the country is already digitized to a certain extent, it's easy for me to implement the solution and bring it to them at a very low cost. Then compared to a segment where digitalization is very much lower and for me to get it implemented, that would drive my cost high. So I think it's really depending on the ease of access.

Yoann - 0:16:19 The ease of access. So you are a researcher but with kind of an implementation hat, right? I mean, from your experience or so. When do you think, like maybe traditional researchers or engineering researchers without such kind of commercial or implementation hat, when do you think that they should consider some of these like cost considerations or cost element factors toward this tech development, the clinical trial validations, and the implementations. When is it to be considered and when they should be considered?

Emma - 0:16:57 Honestly, I don't think they consider it.

Yoann - 0:16:59 They are not, okay.

Emma - 0:17:00 They are not. Most of the time, they are not, because according to them, it's like, my job scope is to do research. If it's not, they are lifetime goal to do this. If just, because traditionally, researchers do from lab to lab, they're not specific to a particular lab, they don't stay there for decades. So when that happens, the technology that they're working on is changing. Though the core fundamental expertise that they have holds, My biggest pressing point that I have in academia is that, as a researcher, is that there's so many amazing technologies developed for three to four years and they just dropped then and there and then researchers

move on but the technology stays on in the labs and no one touches it, no one ever touches them because the next person coming in, they look at the technology, they only take it up from whatever they understand of it. Because the person who started the technology has a very different idea in mind. When it goes from different person to person, it keeps changing, it keeps evolving. It's good sometimes that it evolves, but then the core idea or the main reason why this technology was built is sometimes the passion, the purpose gets dissolved over time.

Yoann - 0:18:25 That makes sense. And in this role, or maybe the previous one, have you had any conversations with some sort of stakeholders, like administrators, clinicians, patients, anyone, where these kind of cost considerations were mentioned, or that some of the stakeholders had some sort of influence on the team to kind of anticipate some of this, or this like never came up in any of the conversations you had, or none of the stakeholders had any influence or mentions there?

Emma - 0:19:01 None of them. We never spoke about how much this technology could cost or should cost, because as a researcher, I'm really focused on seeing how this technology is implemented and what is the value that this technology brings more than how much it should be priced or how much people would be ready to pay for it. First of all, because I'm not an expert in the cost segment, so I would not even have an idea. For example, QA.AI, it could be $10, it could be $100,000 bought by a hospital. It could be $10 paid by the clinician for every use. It could be diverse and I have no idea how to judge that.

Yoann - 0:19:49 Do you know who, or do you know, or do you have access to some of the like individuals with expertise like health economics kind of expertise internally that you could tap on and have access and have conversations to help you as a researcher. Do you know who might be these kind of individuals within the, I was about to say NUS or within your professional network? I do not know anyone who is doing this. And you never had conversations?

Emma - 0:20:20 Maybe my previous role as a researcher, because I was trying to do a startup, then I had, I've been talking to commercial champions and venture managers and investors, so on, to understand this kind of area. But just as a researcher and an engineer in the lab setting doing R&D, this is not something that I come upon, or this is not something I even have access to, because that was because of my personal interest that I went out to pursue something like that.

Yoann - 0:20:50 And your previous lab or organization, was it private? Or was it within NUS? So what's the difference in terms of the two environments from your previous experience versus this one? Is just like the focus of the teams where one is more towards the implementation versus one is more towards the R&D?

Emma - 0:21:13 Yes. Yes, my previous lab, I would very openly say I was the only one who was trying to drive commercialization. I was the only one who was really, I want to get a startup out of this product or this project because I don't want to see my technology sitting down in the lab and dying down in the lab. So, at the same time, N1 has a very different mindset. They develop technologies to be implemented, not just for research purposes, but also to be implementable technologies. So, it's like a very, very wide difference.

Yoann But even in your previous lab, it was more like the reasons why you were so involved in the tech and how some of the technologies might be implemented is more kind of self-driven because of your passions than anything else, right?

Emma - 0:22:03 Yes. And most of my peers were also kind of just into like, I want to do my research, I want to get my paper published, and I want to move. I want to do my research, and that's it.

Yoann - 0:22:15 Are you aware of any framework that might help researchers throughout these product life cycles, kind of consider or kind of assess or evaluate some of the costs? Are you aware of any frameworks or any kind of best practices?

Emma - 0:22:35 In terms of cost, not really.

Yoann - 0:22:38 Okay. What are some of the kind of challenges do you think researchers might have tomorrow? Let's say if I go to a team of researchers and say, okay, you must consider the cost elements of these technologies and so on. What are some of the challenges that this team might have to try to consider these cost elements? Any challenges that you might expect? You know, all the cost effectiveness of the solutions and how researchers might want to do that.

Emma -
One thing that I actually faced was when I was trying to do the startups, I really had to put down my engineering hat and put on a business hat to think of the solution individually, as a solution, as a product. Because when you're an engineering hat, that's why CTO and CEO can never be the same person. Because they have different brains and they think very differently. Because they just never together. It's very hard and rare that I see both of them being the same person. But you have to, they just really think differently. Because when it comes to cost, the technology person is not involved or is their least priority because they're so driven to develop the best technology or the right technology. But when you talk about business, it's about the right numbers. It's two different things.

Yoann
And so if we take a kind of a, let's say a traditional lab, how do we pivot slightly the lab towards more looking at the implementations of some of the technologies. Do we, how do we do that? Do we kind of change the KPIs, the mandate of the lab? Do we get a KTK in this lab to bring a different DNA? How will you take a traditional lab and kind of ask them to focus a bit more on the implementation side?

Emma So sometimes it really comes top down. I'm not sure is it because it's an Asian context that this is happening, because I started seeing professors getting into this bandwagon, like the startups and everything, because I'm not sure is it because they're really interested, that's what they want to do, or is it a KPI, or they think it's cool to have or something. Because when it's top-down, researchers are actually working towards it. Because I've seen other labs where the prof is really into startups and everything. So naturally, the mindset of the researchers are like, my PhD student is like, I want to develop a tech so I can also have a startup with my prof. You know, I can have my own thing to do. So it's a mindset shift that's coming from top down.

Yoann - 0:25:38 I see. OK, we covered quite a lot of questions, so thanks a lot. Is there anything else that we have not discussed that you would want to share? I'm just looking at the title again. OK, I share with you a research question. So it's basically how are the factors affecting the economic impact of the DTX are basically, so the top three that we know is, you know, the usage on the healthcare resources, and you mentioned that as one of your key factors, looking at the attrition rate, you know, adherence, compliance of the patients to the solutions, which would impact obviously the potential ability to deliver clinical outcome, and also the cost of the DTX, which could be the cost like all the infrastructure, the maintenance, and grading and so on. So these are the top three. And so how are some of these costs considered early on by researchers, by the different stakeholders that are involved. Like you know you mentioned about a clinical trial and clinicians have really specific kind of mandate and scope. It's just about let's say the safety and efficacy is great, but it will not answer any of these questions, basically.

Emma - 0:26:55 Yes. One thing maybe I want to add about the attrition rate, because in our current trials at N1, we are really focused or we are really trying to understand how much patients adhere or clinicians and users adhere to these solutions. And I mean, I can share something with

one of the qualitative analysis, quality study that I was doing with the hypertension patients. What's happening is we asked them, so it's a new routine that we introduced to them to take their blood pressure at morning and evening twice a day. And they are supposed to keep it into the system and they are in the trial for 30 days. So they have been carrying on this habit for 30 days and at the end of 30 days I interview them and when I talk to them they say that they still continue to do it even though they're off the trial because they say I have more access, I feel more in control of my health because I know what's my blood pressure and even if I don't need to input even though the trial is done I still take it every day. Because they would want to know. Because they want to know because they feel they're more in control. Today it's high then maybe I try to you know like calm myself down I try to do something about myself and tomorrow it's low and it's a normal rate so I feel happy about it. So I that's what's something surprising to me because that's something I saw that majority of them were telling me the same thing because they continue to adhere to the habit because it was a habit for 30 days I think it has become a habit for them to do this every day from then on.

Yoann - 0:28:28 I see. And how do you translate... So what you just mentioned is like, so this is kind of like trying to understand some of the drivers underlying the attrition, right? How do we basically support adherence, compliance of the patients? How do you translate this into kind of more like a tech requirements. So how do you feedback, let's say the engineers back at the lab and say, okay,

Emma - 0:28:55 these are like the input from your end user and let's ensure that we meet their requirements or whatever will be required for them to add it to the solutions into the tech development. What's the feedback loop? One thing I saw from the end user, which is a very common man, right? General people who are trying to see, they want to know what's happening with them. They want to know, as a patient, they want to know how their health is. Is it better today? Is it not? It's like a, probably it's like a game, right? I score 100 today and then I'm scoring 90 today, then maybe I want to improve myself to score 100 again. So they try to be better at their health because they know what's happening with their body. They know what's happening. So they have access to that. So which is like, it's a number that they can like physically see. It's tangible for them. So I have more control over what I see and I have more control over my health. If at all, if someone's going to have high cholesterol and we happen to, you know, check their cholesterol every single day, they'll probably be more in control of their cholesterol levels, because that's what I kind of reflected from these interviews.

Yoann - 0:30:07 It seems that in your role, and obviously coming from an OR wisdom, I come with a bit of bias or so, but it seems that in your role, you kind of interact and engage with patients, the hand user, quite a bit. I know we have a behavioral team also helping some of these usability studies. Is this what's happening in some of the lab, most of the lab, or none of the lab, having the engineers? Because again, you come with the implementation kind of hard and responsibilities and your passions. But is this something that how often an engineer slash researcher will interact with patients and try to understand how do I meet, as a researcher's requirements of a hand user, from a tech features requirement standpoint?

Emma - 0:30:56 Hardly, hardly, hardly anybody, because all the labs, I mean so far the environment labs that I've come across, that I've interacted with people, it's always the researcher doing everything, if at all they're interested to do it. Because what I've seen a lot of problems is engineers think this is the problem and they work a solution for it and then after they finish the solution when they're trying to implement it and they realize that that's actually not the problem there's something else. So this goes it's never an agile approach. It's always like I think this should be the problem because that's a mindset that I've tried to drive across to my peers and colleagues in my previous labs as well like try to talk to the user and see what is an actual problem and when I came to N1 that was the most surprising factor for me that really drove me into staying here is because that qualitative research, the behavioral side of it is already being implemented and I cannot emphasize how important it is to understand what is the actual solution

that's needed then what because there was a study done by the behavioral team for EPICO and I cannot advocate more on the results because I was also pregnant after the study was completed and when they shared the study results and I'm like this is so true I agree with every single results of the study because one of the interesting points that I felt it was a personality because

I never had the perspective before was, I have my gynae and my gynae tells me do this and do that and I'm so scared because it's my first pregnancy or even if it's like the 10th pregnancy I would still be scared because there are certain things that you're so not sure of but then when you have a peer who's also going through the same thing and then she validates your situation, it feels like I'm not the only one and I'm not the one at complicated risks or whatever. So even though the gynae says or assures you, the short time that you have with the gynae, like 5 to 10 minutes, is not sufficient enough to give you the validation what you're going through. So that kind of emotional support is very, very, very much needed during that period. So that was also a resounding yes from the EPICOS study results.

Yoann - 0:33:16 And maybe, you know, the last question, we discussed a lot about researchers that would be kind of engineers from a profile standpoint. What are the kind of personas or the profiles of researchers that you kind of came across in your different organizations? Would researchers be always engineers or with an engineering kind of background or have you seen different researchers with more like a clinical background for example like a mix because even yourself you're yes engineering background but it's much more than engineering in your situations right so like biomedical engineers so when it's a biomedical engineer we have exposure to a lot more on the science than any other engineers like electrical or mechanical or and so on.

Emma - So I mean I've studied like artificial heart and lungs and what's happening in the medtech industry like telemedicine everything was already taught to me in my undergraduate. So it's not something new for me. So I know these things exist already but maybe from an electrical engineer or a computer science engineer tell him it's like it is so cool I want to know about it Maybe when he's like doing research. But I already know about it these kind of things that I already know the things exist and from then how to move on or How to find a solution for that that should be a different mindset already

Yoann- I said it was the last questions, but every time I raise new questions coming If, let's say tomorrow, you would want to create your own lab, design your own lab, what are the profiles that you would want in terms of researchers that you would want to have part of your lab to ensure that, let's say, if you are working on a DTX, that your DTX would go smoothly to the process of development, validation, implementations? What are the profiles you would pick up?

Emma - 0:35:14 Someone with a strong tech background, yes, but I would form a team that's diverse. One, someone who is understanding the users like a behavioral person who is trying to understand what do we need, why we need it. And the second person would be what kind of solution do we need for that, that would be the tech person. And then I would also find someone who was working along with them, who was also looking at how do we implement the clinical trials and into the ecosystem and also the cost aspects. Because I think, yeah, the four people, these four people would make the perfect team to make sure that solution is successful. Because individually, though individually they have expertise in certain things, they should also have a passion that they want to drive the solution to the end, where the end user uses it, and not just a solution as a solution.

Yoann - 0:36:12 I see. And you know, you mentioned earlier about working with clinicians, obviously with the patients. Have you had any interactions with the hospitals and administrators, and do you know what they will expect if you come to them to move your solutions whatever the solutions and it's a pitch for solutions what would be their expectations so I don't know if you had interactions with them as one and two.

Emma - I do not have any interactions with administrators so the people I interact with is clinicians, patients because of the patient interviews and and the trial coordinators and the finance department who are running the trial, who are supporting the trial. So just these people.

Yoann - 0:36:58 So not much access, is it fair to say, not much access and understanding of the expectation that maybe hospital administrators might have on some of the digital health solutions.

Emma - 0:37:13 So in terms of administrators, are you trying to ask like decision makers?

Yoann - Yes.

Emma - No. So the closest decision makers that we have is probably the clinicians who have a bit more say because everyone around, everyone else are in the lower quadrant. So the people who are having a bit more access to these decision makes are probably the clinicians. So the influence on the clinicians would be, you know, if they say I really want a solution, then maybe the administrators could be a bit more convinced.

Yoann - 0:37:43 And what kind of power do or slash influence do we have to convince these decision-maker hospital administrators to validate or give the go-ahead of any digital health solutions? A lot of power, like basically if you have a clinician buying your whole good or is it still a 50-50?

Emma - 0:38:05 I think it's still a 50-50 because sometimes though the clinician approves of it because there are like certain guidelines and protocols and they have a SOP that they follow, sometimes they might not completely use the technology even if it's crossed everything and then the clinician approves to using it, then maybe it could be the cost factor that could be blocking it. So it's like a different step to getting it instrumented.

Yoann - 0:38:35 I don't have more questions. But anything else that we have not discussed that you would want to mention?

Emma - 0:38:45 I think as a researcher it's just these. Typically, I'm not sure if it's different in different parts of the world, but typically Asian researchers that I've seen so far, like whoever, colleagues, friends, friends of friends and everybody, the end goal of their research is a research paper.

Yoann - Publications?
Emma - Yes, publications. And I don't know how many of them see beyond that. Because when they publish, they try to find a better result and they publish in a higher impact. And their end goal stops there.

Yoann - 0:39:23 Like 80% is like, that's what drives the decision.

Emma - Yes, yes, publications. So that's why they're more focused on the technology, the efficacy, how good the tech is, and how beautiful it is, and what kind of unique problem statements they find. So the publications is what is driving them.

Yoann - 0:39:50 And that's maybe one of the reasons why maybe some of these cross-elements are not really considered, right?

Emma - Yes. It doesn't help achieve some sort of KPI.

Yoann - 0:40:00 So this could be a bias, because they are in academia, but maybe in an industry, R&D, this could be a very different game altogether.

Emma - 0:40:09 Cost could be one of the earlier factors that they consider in an industry, when you have a team of researchers, engineers working on a new product, all of the cost considerations have already been done, like all the market analysis, and all the segmentations, the positioning and how much. So it's just like, everything has been like kind of address all the questions have been addressed. That's kind of a step one, because if there is no viability of whatever is MVP from a market standpoint, then there is no R&D. When I feel here in academia, that's kind of the last step. And it's amazing, but it's kind of patient-centric in the sense that ideally you look at unmet need, clinical need, and so on, try to address the solutions or whatever gap that you have with the tech. And then later on you will kind of worry about the cost considerations when I think in the industry it's more kind of a portfolio management, right, and you're extremely thorough in the new solutions that you might want to incorporate in your portfolio or not, based on some of the cost considerations. Sometimes there are two ways to look at it. One, yes, it's because they want it's their portfolio and so on. Second of all, it's like, that's how the ecosystem is anyways. Because I've seen so many engineers, they develop the product, and then they cannot do all these market fit and so on. And they've wasted three to four years of their life trying to develop something that no one's going to buy.

Yoann - 0:41:52 It's the solution looking for a problem to solve, right?

Emma - 0:41:54 Exactly. So sometimes they think this is the problem, and they're trying to find a solution. And then four years later, they realize that's actually not a problem because that's what happened during my experience with these incubators and so a lot of solutions they have an idea this is my solution this is the reason why I made the solution for and then they come to this place and then they see the market phase and the market and they do all these analysis and they realize like I'm pivoting so I have a solution now I'm trying to find a market and they completely change direction I've seen so many of them do that. So that's why I feel like we have to have these questions way early at the beginning of the research. So that's why I always feel like maybe outside it's done differently than in academia.

Yoann - 0:42:39 So what could we do differently? I mean, wisdom is, and everyone is a bit different, but what could we do differently, more like traditional lab, to ensure that some of these questions are considered as early as possible. Any thoughts on that?

Emma - 0:42:53 No, like I mentioned, it's really, really individual interest, or it's a top-down kind of interest. If the PI says, I want this to be this way, and they would do it. Should not be the PI responsibility to kind of like challenge his or her own team on some of these aspects or in terms of like whatever is the mandate slash scope definitions or... Or maybe I mean it's like you mentioned it's important that we also have solutions that are fundamentally addressing a need and it's also important that our solution that are like getting into the market because this For example Amazon was there several years back several decades back, and then I mean not decades I forget it was there, but it's used now is so much more relevant Than then but doesn't mean it was a bad solution Cried so maybe it could be the time so The patient need me for example, the CT DNA test that we are doing right now, it's a disaster. But five years later, it could be the blood marker, I mean, the marker that everybody's going to.

Yoann - 0:44:15 But how up front do we, I don't know if it's, again, from a portfolio standpoint, but how do we kind of do some sort of prioritizations, or I think this kind of categories about, we know that these are some of the solutions that is just to address a clinical kind of need, and the cost considerations, might not matter much versus, we know that this would be like more like a B2C type of solutions. And so how could we know, is there a way to know early what sort of weightage you might have on some of these considerations, depending on the pathways that you might have to choose?

Emma - 0:44:56 Yeah, so one idea that I had was, so the robot that I said, the skull robot, right, it was meant for deep brain stimulation. But we know that it's a very, very challenging and difficult market to get in, because deep brain stimulation, anything got to do with brain, you have to do so many clinical trials, it's going to take several years to get there. And we thought, can we use the same device for other usage? That is like a low-hanging fruit that we can get into the market, get a bit more revenue, get a bit more familiar into the space, and then we move from there. So trying to find a low-hanging fruit, like curate can also be used for so many other indications. So, we can try to go for something that's light, get rid of space, and try to understand, and then move on to what it's being designed for.

Yoann - It's almost like defining for different kind of therapeutic areas, but the kind of type of tech that you might be some of the requirements, you know, regulatory, maybe reimbursement requirements and so on, that you might have to meet on the road, right? Defining like up front. So if you are like going into the WD space, then there are, you know, that there are maybe some sort of like predefined set of requirements that might be well defined, that you, that might guide your day-to-day and if you go DBS, that's maybe different set of requirements.

Emma - 0:46:27 Yes, yes. So I agree. That is exactly what I'm trying to say. Because as a medtech, one thing that I also realize is the more credibility we have, the easier it is.

Yoann - 0:46:44 Credibility, yes.

Emma - 0:46:46 Credibility in terms of confidence and evidence generation. Okay. So just because I'm going to the low-hanging fruit doesn't, it means that people know my product, people know my company, people know what I do, they know in the space that I exist. So from then on I can move to a bit more tougher, a bit more challenging segment and then you know get my confidence low while I'm also generating these evidences.

Yoann - 0:47:13 So, are you saying, for example, for a DTX, you do the tech development and that you might, instead of doing one, two, three tech development, clinical validation implementations, that some might just do tech development implementation, and then while they start implementing the solutions, then in parallel, they look at evidence generations.

Emma - Yes.

Yoann - Is this the way you would kind of take a detour?

Emma - 0:47:39 Yes. Because the typical route is going to take very, very, very long. Yeah. I feel the segmented route that I mentioned, this is just my idea. I'm not the expert here, but this is what I think works. Because we are generating so much evidence while we've already implemented the solution. So the moment you implement, you're getting your data and everything, like people's replies, people's responses, how they use it. So you don't need to set up a separate team to do the user study because your solution is there and people are already using it for something else. So that's a learning point that we have.
So basically getting to some sort of like POC, POV as early as possible and getting these beta versions in the hands of the end user as early as possible. Like iPhone 3, and now we have iPhone 13. There's so much difference. Every lab you know, we have clinical champion, but we should also have a “commercial champion”, like a point of contact.

Interview Transcript with Eva (P2)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:11:26 So thanks for the consent form, signing the consent form. So basically, you know, in the last paper, what we did, we asked, I think, close to 60, 70 folks on how some of the factors that we know that are going to influence the economic value of the DTx, how these factors are basically considered at every single stage of the tech development, the tech validation, so clinical trial, and on the implementations. Because the issue is that today it's kind of a sequential process. And you know when it comes to the go-to market, the implementations, whatever is regulatory approval and so on, you do your health technology assessments, you look at the economic value, whatever cost savings and so on. And then you realize that, yes, maybe it's a digital solution, but it might not be that cost effective or not as you would have hoped. And so before you come to that realization, is like, again, some of the factors, to give you like one example, you know, in terms of the health care resource utilizations, it's typically one of the factors if you need a couple of nurses, you need some physicians to be involved in the onboarding,

So it's kind of consuming more, or you might need more healthcare resource utilizations, and that might not help have a cost effective solution. So the question is, how could we, as maybe researchers, so engineer researchers, or more from the clinician, researcher clinicians, how could we maybe create a bit more awareness on some of the factors that we know are kind of going to be critical down the road, and therefore try to maybe when you know the day-to-day decision process, okay, you should prioritize this feature versus this feature or this one, then there is maybe additional framework or additional considerations that, oh, maybe I should take these factors into consideration when, as a team, we choose a product as a factor.

So it's really to understand more from yourself as a researcher, but also based on your experience, because you have been involved in every, sorry, every single step of the process. So you know what kind of matters, but also some of the gaps that we might have, and how we could do things differently. So it's just to pick up on your experience. So whenever you're not comfortable, not sure, that's also fine.

Eva - 0:14:06 I'm not used to discuss the economic value and I'm not just thinking about the economic value either. I think my focus is in more interested in the value of the investment rather than I look at it in a different way, but maybe that would be a nice takeaway from this interview, that maybe we should put more attention on that. So, yeah, I mean, I don't have the answer. So I think in a way, I would tend to say yes, I think, and I think this is not about just you, obviously, right. But I think, again, it's kind of a, you have a tech development and then we move on to the physicians, clinicians, and then it kind of move on to the implementations. So I'm not sure if, like I said, the clinicians and physician should not just look at the safety and efficacy, but they should also look at additional kind of potential factors that should be considered in the clinical trial, you know, in the validations.

Yoann - 0:15:08 As a researcher, should you consider additional kind of criteria and requirements, or maybe not.

Eva - I don't know. Maybe we should not change anything and we should just leave it the way it is. I don't have the answer. But let's see.

Yoann - 0:15:23 But to your point, what you just mentioned might be the takeaway, basically, that some of these kind of economic considerations or economic factors could be taken into consideration. But maybe before we continue on that, just for the purpose of having the context for the analysis of our conversations, you don't mind to share with me like your role, I guess, in

one wisdom, but also kind of your experience, because I think that would help put a bit of color on some of your answers.

Eva - 0:15:53 Yes, sure. So, currently, I'm a freelancer. I used to be a research fellow at N1 and WISDOM for over two and a half years, almost three years. My expertise is in neurotechnology. I have a PhD in biomedical engineering. And currently for N1 and WIsDM, I'm leading two digital health pilot projects in neurology. So one is the pilot feasibility clinical trial study, Cortex for cognitive decline post-radio therapy in brain cancer patients. And another one is the Lyric study, where it also connected to cognitive decline in patients that are at risk for delirium in the hospital. So both projects use QA-DX, which is in-lab developed digital therapeutic, slash digital diagnostic. And it's a web-based multi-tasking game that assess and train cognitive performance. So as I mentioned, either a user's diagnostic or cognitive training tool. At this point, we are conducting pilot projects, but there are many other projects that are running in parallel, such as literature review, ideation for other applications, and possibly assessing for RCT trials after those two pilot feasibility studies.

Yoann - 0:17:41 And maybe to come back to your earlier point about maybe not considering some of this like economic consideration. So you said you are basically involved in the tech development slash validations, right? To clinical trial, right? You had quite a few interactions you had quite a few interactions with different group of stakeholders. So obviously part of your N1 wisdom kind of time, but also in previous roles that you had. Did you in any of these conversations, interactions with any kind of stakeholders, did you have any kind of conversations about this economic impact or the economic value or just like what it might cost, you know, because sometimes we don't refer to these economic considerations about whatever is HTA or whatever is like, what it might cost for the solutions to be used or implemented. So did you have some of these kind of conversations with any of the stakeholders or not?

Eva - 0:18:47 Yes, so for the Cortex trial, when I joined it was already ongoing, so the patients were already being recruited. So this is considered kind of a late stage because, as you know, it first goes through an ideation, kind of concept development, only then you go for like reimbursement or literature review. So there is many steps before the clinical trial takes place. So in this case I was a little bit too late, so I did not have this kind of discussion. And personally at that point I didn't even know that we should consider that. However, for the second project I was involved from the very, very beginning, from the ideation phase. And I sort of started this pilot project myself. And at this point, there was a talk in the lab about the economic value, how can we assess it, and I tried to move this into the clinical trial design and into getting approvals, getting grants. So this was definitely on my mind and part of the process, especially that it was connected to the clinical needs. So the clinical needs for the delirium trial was that nurses have to do cognitive performance tests every day for every single patient at the ward in the hospital. And it takes them five minutes per patient every day. So it doesn't sound like a lot, but it's five minutes per patient, per nurse. So it takes time from the nurse, obviously, to do it. And if you have many patients in the ward, sometimes you skip some patients, sometimes you won't do it, so that means it's getting low. And it ends up not only challenging for the nurse to do this kind of test, but also it's not beneficial for the patients that might skip the test for that day because they seem okay in that, right? So they won't do the test. So in that case, we thought that, okay, if we do the digitization, if we do the test in the form of a game on the tablets and keep in mind the tablets are the same, so there's no cost to that. Patients are already playing the games in the tablet. So why not tell them like, if you have 20 patients in the ward, tell them, okay, now we are playing the game. So all 20 of them play the game. The nurse doesn't need to do anything. The nurse can do other things in the meantime. So time of the nurse and that saves cost of her time. And at the same time, if the delirium would be detected by this final test, it saves hospital... it's basically, we didn't calculate that, but we have knowledge directly back up on that, that if you detected the delirium earlier, the cost of treatment of the patient is lower than if the patient went on and developed a delirium. So you act early and you stay in this manner.

However, I would love to know how to conduct this analysis, how exactly, how much exactly is it in dollar values of this, I don't know. But I know it influences the cost. That's what I can say.

Yoann And the influence being potentially quite great, and correct me if I'm wrong, but that's the reason why you decided to try to look at ways you could minimize the involvement of the nurses, for them not to perform the test, but you have some sort of like economy of scale or look at the digitalization of the process, right?

Eva - 0:22:52 Yes, so for me as a researcher it's a win-win because as a researcher I mostly focus on effectiveness and patient-centric design, right? Not the economic value, to be honest. But if the tool is effective, there is a benefit for the health, for the patient, and there is a benefit, economic benefit for the hospital.

Yoann - And I think you mentioned something important about your kind of focus areas being on, you know, on this patient-centric design, and on the, not only the efficacy, but the effectiveness. Is this unique to you, Eva, because of maybe your background and many different reasons and who you are, is this something that you see typically across, not our team like N1 Wisdom, I mean you could obviously share about that also, but is this something that you see across kind of research institutes?

Eva - 0:23:55 Not really. No when I joined N1, I was actually surprised about the behavioral component. I didn't appreciate it at first, but now I see the importance of it. So at N1, there is a whole group that is focusing on conducting patient interviews, gathering qualitative data, which I hope wasn't number one fun in the beginning, but now I see that it has a lot of value. So, this kind of approach lets you create a feedback loop with the patients, but also with the clinical team, to gather their thoughts and their experience with the digital therapeutics, and assess the usability, engagement, and obviously assess and improve later on through the iteration and accessibility of such tool. So, in the beginning I was focused only on how effective is it in numbers, how much percentage of performance improvement is there in this mobile game. This kind of data show me that it's not only the performance is improving or decreasing, but also the patient's thoughts and clean call of health care providers, also nurses, clinicians can influence a lot of the patients on usage, if the patient is going to use it, and there is a big, big, big value to that.

Yoann - 0:25:40 So it's really looking at them as kind of influence, I mean them, the nurses as influencers, right? And in a way, would it be fair to say that working closely to the behavioral team can have also influence you as a researcher directly or indirectly on looking at certain factors that are important, but that also should be maybe considered through other designs, engagements, and back to your patient-centric design, right?

Eva - Exactly. So you can develop the best tool, you can have a tool that is going to improve the cognitive performance 50% in brain cancer patients, but then nobody will use it, right? That was the point. But then if you have the voice of the patient who's going to tell you, the colors are too dark, the font is too small, I need something bigger, something more intuitive. I don't understand the steps. And then we iterate, so the small iteration, and yet, it will make a lot of difference. Right.

Yoann - 0:26:48 And you know, you mentioned about what you did for the projects and for in terms of the solutions, in terms of, you know, reviewing the digitalization of the process and so on. You mentioned about efficacy and effectiveness. And I think this is quite new in a way, or that's quite unique. I guess we don't hear that much from most of the researchers. And again, I'm not here to judge what's right or what's wrong. But in your view, what will it take for researchers, like engineering researchers or clinicians, to maybe be slightly more aware of this effectiveness versus efficacy? And should every single research center have a behavioral team? That's maybe the way to bring a bit of awareness. Should we develop specific frameworks and tools for them, for the researchers, you know, if you want to consider, you want to learn more about, you know,

whatever factors or, you know, some of the considerations when it comes to the implementations of the technologies. Should we have like health economics, economics kind of individuals, experts being more available? Because I think one of the issues is like, when you're part of anyone wisdom, you don't know who to ask. You know that, okay, the cost might be important. And so like what you have done, you know, you take certain decisions, but to what extent and who might be the experts and so on, sometimes it's a bit difficult in the ecosystem to know who might be the right point of contact. So I don't know, what do you think will take to raise maybe the awareness on some of this effectiveness kind of considerations versus efficacy?

Eva - 0:28:29 Yes, so for my point of view, researchers like me, we are too focused on numbers and just our domain. And I love that N1 opened my mind and perspectives to see in particular how to fix as well as behavior. So I always knew that communication and stakeholders are important. You have to communicate with clinicians, patients, project manager, you know, advisory boards on this. But also, it's also so beneficial to look at the problem from different perspectives and to have as interdisciplinary team as possible. So, engineer, data scientist, behavioral scientist, economic scientist, every single person from different backgrounds. The more people you have from different backgrounds, the better for the projects. And digital health is very, very important for that, right? It takes very peculiar kind of experience and many different kind of people, backgrounds to develop a successful digital therapeutics. So I think, yeah, it will be great to raise awareness. It would be great to talk about these things. And yeah, I think the more we talk about it, the better. The more influence we have over it, the better.

Yoann - 0:30:14 I see. And do you think it's kind of like, you know, the chicken and eggs kind of dilemma in the sense that is this the issue might be like kind of a lack of general awareness or maybe skills, you know, like sometimes you know, but again, you know, you're training, you're specializing in certain areas. So you can't be, you know, this kind of Swiss knife and all this like multiple kind of expertise. But it's also to your point, I think, what we don't do much, and again, when I say we as a community, right, it's not our team. But what we don't do much is to try to fully understand the different perspectives of the different stakeholders that at some point are going to influence the development of the implementations, the usage, maybe adherence, patient adherence and so on. So it's kind of patients, clinicians at best, but we can have take their input. But in some of the conversations, for example, market access experts go to market, you know, obviously on the economic side, on the business models, on the regulatory. To your point, it takes really a multidisciplinary approach. So if all researchers, engineers, and all of the stakeholders would have such multidisciplinary approach, you know, kind of a 360 of the ecosystem, that might, on its own, might just address the questions of the economic kind of component, which is one of the many factors that should be taken into consideration, no? So it's, yeah.

Eva - 0:31:44 Yeah, yeah, so for me, what I, I might be a little biased because I have some startup experience, but for me, there is a clear difference between running a company and then running a lab. And lab is mostly like one direction focus, paper focus, and you stay in your lane, because your goals are different. So normally, not with domain one, but for my normal experience in the labs, the goal is to publish papers as many as possible, as important as possible, but then that's where the purpose ends. You usually don't see beyond that. You can license your technology later, but that's the other people's problem. License your technology or your discovery flow, worry about economic value and other things. Whereas in startup, you have this 360 approach. And you approach the problems from every single side. From the very beginning, you think about everything. At least you're trying to think about everything. You're trying to bring people from different backgrounds. Whereas normally in academia, you bring people from one background to make exactly what you need, like statistics, research, project development. So that's how I see it. a bit more to this approach from the companies, I think that would be great. Yeah.

Yoann - 0:33:18 And so do you think that it's like kind of the startups kind of environment and the industry folks that should learn a bit more entrepreneur in a way? Is this kind of both ways? Is it just one way? Or how do you look at this? Because again, you have the experience in both.

Eva - 0:33:49 Yes, it's both ways. I would say academia is a little bit more stiff to change. So it's not easy. But the community could obviously learn from those different perspectives. But then, the startups, those would be companies, are not focused on evidence as much as they should be, right? There are so many wellness apps, like the lifestyle apps that promise a lot, but then they tend to forget about providing good clinical trial, objective clinical trial, well-designed clinical trial, to support the claims. And I see it time after time after time, even huge companies like Neuralink, right? They have, they have people trial, but the regulatory compliance is not there, the communication with the scientists is not there. They have all this money, all this perspective, all these people working, and then the evidence for me, like this is like there as well. So you can be the most famous company in the world in the space and still not necessarily doing as much as you could be doing.

I think, yeah, it's a challenge. And I think it's maybe back to your point that we all have different kind of maybe KPIs and agenda at the end of the day. I think I guess for some of these organizations, it's maybe the next one of funding and whatever it takes, maybe it's patients kind of awareness/ tractions, you know, is like how many patients are going to use or customers are going to use the solutions and the evidence might be just like nice to have, but it might not be must. Again, depending on who are in your advisory board, in your investment board and so on.

Yoann - 0:35:34 But yeah, I think it's maybe we all have different KPIs. I don't know if it's...
Eva - 0:35:39 Usually, it's secondary. It can come later. First, you need money, right?

Yoann - 0:35:46 And do you see any challenges potentially for researchers to... assuming this is right, but for researchers to be more entrepreneur or maybe more innovator, any challenges that you foresee? If, let's say, we are asking our researchers to be a bit more aware or to take into consideration some of the maybe start-up stuff kind of considerations, do you see any challenges in them implementing some of being kind of exposed to some of these corporate world kind of practices?

Eva - 0:36:26 I think it's with the motivation. What's the motivation for the researcher to do that? Right? Because doing research is time-consuming as it is. So our reward as researchers is usually application. So why would we focus on something else? Why would we pursue some economic value or other considerations that are not necessarily our job to think about.
On the other hand, what can we do maybe is, like I said, open the minds of scientists. Like when I joined N1, it opened my mind to this kind of things. In being well-versed in the whole ecosystem, not just my area, and for the academic centers, and I wish more people would realize that, you know, you can be a scientist in the science, you can be a scientist in big corporations later, big corporation later. And big corporation really appreciate it. Yes, some business acumen, if you have this kind of knowledge, if you are open and kind of flexible to learn new things like economic validation and startup kind of Considerations.

Yoann - 0:37:56 So it's basically, correct me if I'm wrong, but it's kind of maybe a lack of appreciation of the two worlds, let's say the academic and industry. And industry, they don't fully understand what's going on and why it takes so long to do some research and why it's maybe not aligned with their KPIs and monetization agenda and whatever. and whatever, and maybe there's also a lack of appreciations of the scientific community to maybe some of the KPIs or what might drive a startup. So it's kind of a lack of appreciations of the tools, right, no?

Eva - Yeah, that's exactly it.

Yoann - 0:38:36 Okay, good. So I went through all the specific questions I wanted to ask you, Marlina. Anything else that we have not discussed that you would want to mention on these questions of, basically, if I can summarize, how could we, as a different group of stakeholders that are involved at every single stage of the early or earlier some of these factors, requirements that might kind of generate or support a DTx to basically generate economic value. You mentioned about healthcare resource utilizations. I mean, you have done it, right, without any framework, without, you know, maybe specific trainings is what you have done. But, yeah, I don't know if there is anything else in terms of comments or questions you have on how could we maybe consider as early as possible some of these factors?

Eva - 0:39:42 Yeah, so from what I've learned, something that is extremely important and also not very common in academia is communication. So communication, communication, communication. We are not really Yeah, we have some PowerPoint classes, like one hour during the study space, teaching us how to do a presentation, how to present your thesis, things like this. But we don't necessarily practice communication with each other. You go to a conference and you know how these conferences look like, right? Very dry data, very dry slides. It's changing a little bit now. But so my husband is from the other field, right? He's from sale. And when he saw what kind of presentations I had, and what kind of presentation was my thesis, like, he was like, so surprised your presentation is so boring. There's no pictures, you have so much text on your slides. And that's how it's supposed to be. It's supposed to be dry, to the point. Content driven. And you're supposed to read the words that nobody understands.
It has to be as complicated as possible. When you read the scientific publications, it's so unnecessarily complicated. The language that it's written with is really unnecessarily hard. So this is what we are used to as scientists. So I would say, I would love to see scientific community more open to a little different style of communication, to really understand different factors, different fields, and to more freely kind of just talk to people. How do you talk with nurses? How do you talk with clinicians? They have their own personalities, egos, goals. It's actually a lot of soft skills, right? To manage different kind of stakeholders. How you communicate your information. When I sent some slides to nurses, for example, they were actually much, much more communicative. And they straight away, honestly told me in a polite way, obviously, what they told me. They said, I don't understand this. This doesn't make sense to me. How would you explain in one sentence what you read it here? So I love that. I think this is how it should be, right? And yeah, to be open to communication, to tweak your communication a little bit more, to not be afraid to ask questions, to talk to different people, to talk to people from different fields. Because it's uncomfortable. For me, it was very uncomfortable to think about economics and because I have no idea about it. Just even to open this kind of discussion and be vulnerable enough to say, hey, I have an idea in this space. Can you tell me how to do it? So tell me, how can I start to learn this? This is a real lot. And I feel like it's very beneficial to open up to that.

Yoann - No, I agree.

Eva - And I think that's really important. I mean, the communications and I think, unfortunately, maybe like all the scientific papers are kind of in a way published for the scientific community but there are so many different stakeholders that should have access to the same knowledge. Maybe they would want to consume the knowledge differently, to your point, maybe through a PPT slide or maybe through a book or whatever it is. But yeah, I think that might also help, right, in terms of the communications, that whatever is the content, but just to have whoever is going to be the receiver of that communications, being a nurse or being an investor and so on. Yeah, that's a little bit of adjustment, basically.

Interview Transcript with Ezra (P3)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:00:00 So maybe to start, you don't mind describing briefly your role, part of a team, and what's your kind of day-to-day kind of activities, if you prefer.

Ezra - 0:00:13 So I'm part of the N1 Institute. I primarily work on a digital medicine platform called Identify. called IDENTIFY. It is used to optimize drug combinations for infectious diseases, including COVID-19, antimicrobial resistance, and many other diseases that currently do not have standard of care treatments.

Yoann - I see. And do you consider yourself as a research engineer? Or what's your kind of title or how, what's the best way to describe your role?

Ezra - 0:00:54 I was a graduate student, but now I'm more like a research engineer.

Yoann - 0:00:59 Research engineer? I mean, it's not about the title in the sense of like, from a hierarchical standpoint, it's more like a title that kind of define.

Ezra - Yeah, I'd say a research engineer.

Yoann - Okay, because, and why I'm asking the questions is like, we tend to use researchers, but to define and describe quite a different type of individuals with different skill sets between mostly the research-engineers and the research kind of more clinicians, also, typically. So you tend to be more in the research engineer kind of category.

Ezra - 0:01:33 Yeah.

Yoann - 0:01:34 OK. And could you describe your role in terms of tech development and tech validation. What are some of the steps, responsibilities, or how are you involved when it comes to tech development?

Ezra - 0:01:51 So, tech development, we have to, of course, from a technical standpoint, that it is something that's actionable and that it gives us the answers that we need, right? So for example, if we want to optimize a good drug combination, we want to make sure that our approach actually gives us the right answer that we're looking for. But at the same time, we also have to engage with other stakeholders. For example, like during the pandemic, when we're developing drug combinations for COVID-19, we have to consider the perspectives of clinicians, and not just clinicians, right? We also have to consider within the clinicians we're looking at, within the clinical team, like infectious disease experts, right? So we want to make sure that whatever we're doing is relevant. It's as if we pop something out of our research and development and it's not clinically relevant, or it's not useful to the clinical team, then the whole project wouldn't be meaningful.

Yoann - 0:02:57 And so to your first part of your answer, just to confirm, would it be fair to say that you're trying to look at technology to address kind of, let's say, clinical, I don't know if it's a gap, but kind of a clinical problem, so a clinical problem that you have, a kind of problem statement, and you want the tech to address this problem statement. That typically would be a clinical problem statement. So that's the, when you say actionable, that's what you mean is like addressing the capacity to address, for the tech to address this clinical problem statement. And by engagement, so mostly clinicians, you mentioned, and some sort of experts, are you interacting with different type of, various stakeholder groups beyond the clinicians?

Ezra - 0:03:48 Yeah, so, so aside from clinicians, we also have to engage with more like, more on the policy maker side, right? For example, like MOH, Ministry of Health, to make sure that what we're doing also address their perspectives. Because sometimes MOH, for example, what they're looking for, like in terms of pandemic preparedness, pandemic readiness, may be different from the perspective of clinicians. So we also have worked with, for example, NCID, right? They're more than just clinicians, they're actually like the people who actually come up with, formulate strategies to combat the infectious diseases, aside from, you know, like a clinician at NUH. They're actually the one who, you know, engage with MOH to come up with strategic plans to, you know, to overcome the pandemic.

Yoann - 0:04:50 And how is this kind of, what's the nature of the engagement? Is it like one-off kind of conversations, workshops, is it like proper qualitative interviews, is it just like on and off advisory capacity?

Ezra - 0:05:04 It's more like before we even start the experiment, we already engage with both the clinicians and the NCID experts to make sure that we're all on the same page. And throughout the experiment, whenever we have results, of course we engage with them too. For example, when we come up with a list of top combinations from our platform, we want to come up, we have a list, right? We have a bunch of them, but we want to prioritize the ones that are actually useful to clinicians and their perspective, as well as useful to NCID, the ones who actually formulate the strategic plans for pandemic. So we engage them throughout each step of the experiment, and even to the final step, like for example, writing this manuscript and so on.

Yoann - 0:05:57 I see. But is this, all these conversations is to ensure the clinical relevance, right? What about the relevance to from a hand user perspective, let's say like from a patient perspective, relevance about maybe looking at the feasibility from a more implementation side, or what are the various kind of considerations? Is this mostly about the clinical relevance, or are there like additional considerations?

Ezra - 0:06:28 Oh yeah, definitely. So like what I mentioned previously is more on like the clinical standpoint, right? I also want to look at like, you know, for example, user, like the patients. We want to, so the way we want to do it is like we want to prioritize orally available drugs, right? So that, so that patients, because for example, during the pandemic, there's the healthcare resources are very limited and hospitals probably cannot afford to hospitalize every single patient. So we want to prioritize therapies that are orally available so that patients can administer the drugs at home as opposed to, for example, an intravenous injection drug that requires frequent visits to clinic or hospitals, and that would be a burden for healthcare systems, for example, during the pandemic, right? So we also have these considerations. And not just pandemic, like many other infectious diseases that we have worked on, we also prioritize this for patients so that they don't have to make frequent visits to clinical settings.

Yoann - 0:07:33 So you interact with patients also throughout the process?

Ezra - 0:07:37 I mean, we, at least for my project, we didn't really engage with patients directly, but we considered from the patients' standpoint to like ensure that they don't have, they did like, drug administrations can be done at home, and that they don't have to make frequent visits to clinical sets.

Yoann - 0:07:59 So you're thinking about the end user experience, for the kind of workflow disruptions, and so on. And in any of these kind of considerations or conversations that you had with these kind of different group of stakeholders, would be the more implementation-driven type of considerations and thinking about the cost, on how much it might cost, or some of the factors that might be about the resources that might be required to support the deployment of the technology, or even just how much it might cost to the patients or to the system. Did you have in

any of these conversations such considerations about the financial aspects impact or mostly about the clinical and maybe some of the logistical aspects that we see.

Ezra - 0:08:49 Yeah, I think we have previously thought about the cost and benefit analysis. For example, if we can find a combination of drugs that are more effective, or even as effective as the standard of care, but at a cheaper price, that would be pretty beneficial not only to the healthcare system, but to the patients.

Yoann- But we only thought about it. Just a consideration, a theoretical consideration, but you have not conducted some sort of like kind of impact assessment or financial estimates on the various kind of combinations of drugs, right?
Ezra - 0:09:39 We didn't go that far, but we have previously thought about how, if we can find a combination that's cheaper and just as effective, or if not better, then like the standoff cure.

Yoann - 0:09:53 So, who do you think should perform such impact assessment? So you, as a research engineer, you describe what you went through, the process, the interactions. At which point, and who should come back and say, OK, I think these combinations financially from the economic impact to the system, so maybe let's say out-of-pocket type of cost and so on, might be more or less relevant. When do you think this should happen, this kind of analysis? And who might need to conduct such analysis.

Ezra - 0:10:28 Yeah, I think once you have, I think the very first step is of course you have to engage with clinicians. From a clinical standpoint, it has to be something that's relevant before you even move forward to other considerations. And once that's done, I think what happened to our previous project is that actually what happens is that we found a combination that's as effective as the standard of care, and it was a lot cheaper. The standard of care is a few thousand US dollars, and our combination is a very traditional drug, and it'll cost less than $50. It was, in terms of cost and benefit, it's a lot more expensive.

Yoann - 0:11:08 Like, spend it for one visit, yeah?

Ezra - 0:11:10 Yeah, but I think what happened is that we didn't have the expertise to really go through the rest of the consideration because you have to, for example, if you're given a combination of drugs, what's the schedule, right? How many times do you administer drug A and how many times do you administer drug B throughout the treatment, right? That's something that we didn't have the knowledge or expertise in, so I think in order to really understand the cost, you have to really talk to clinical pharmacologists or pharmacists to really understand how they typically administer these drugs and in order for you to conduct further analysis in terms of the finance.

Yoann - 0:11:57 And so I guess you're not going to kind of like you but any of the team members like kind of health economists It's kind of overnight right? I mean to your point you don't have the expertise in-house and but if You come across the right, let's say tool or framework or whatever might help you to maybe consider some of these factors. Is this, from your perspective, is something that you would be willing to consider, or is this just like another extra step and burden, and about maybe just out of your scope as a research engineer? How do you, because there are so many considerations, right, I mean.

Ezra - 0:12:43 I think I would love to include additional considerations because, I mean, at least for my projects, we're not just doing it for the sake of publishing, we're not doing it just basic science. We want to do something that's impactful and that could potentially be translated into real life that benefit the general public. So if we can consider as many considerations as possible, that would be great. So if we can work with someone in the lab or someone on campus or even other campuses to really consider these factors, I would love to.

Yoann - 0:13:22 And what you describe about being kind of more impact-driven, implementation-driven, on the translational aspects, and all these conversations you mentioned earlier also, beyond the more engineer-to-engineer kind of conversations. Is this specific to the team? Is this specific to the Singapore ecosystems? Or is this what's happening in every single lab out there?

Ezra - 0:13:48 I mean, it's hard for me to comment on other regions or labs elsewhere, or even other labs in Singapore. Our lab is pretty, we consider multiple aspects, like in terms of implementation or translation. Because I think that's the aim of our lab, of our institute, is to do something that could potentially be impacting the society. So I want to share something with you.

Yoann - 0:14:16 Let's maybe, let me hide this for now, I don't want to complexify too much. So this is the traditional process, kind of from a tech development. So here is about the digital therapeutics, right? But so there is the initial need identifications back to your point on the clinical aspects, then there is a product development, or you can have initial concepts, I guess. And but quickly, what should come is these requirements, definitions on how you're going to basically make that product or design or develop a product. Then you go to the design phase, you create the product, you validate, so the clinical validations and then is your commercialization. So this is kind of a high level, kind of simplistic view. Do you agree first of all with the flow?

Ezra - 0:15:15 Yeah, I think this is a pretty standard convention.

Yoann - 0:15:19 Now, what we have seen, that one of the assumptions I should say, is that this step, that you see here in terms of the requirement definitions, tend to be kind of done in-house within the in the team itself without much input from, to your point, maybe clinicians, policy makers, maybe health economics, potential payers, and so on, patients themselves. And that's kind of, this is not for wisdom or anyone, but this is kind of what potentially would be missing in some of the institute. Is this your understanding or so? Would you agree with that?

Ezra - 0:16:04 Yeah, I would agree with that.

Yoann - 0:16:08 And so what I've done is that you have a couple of groups of stakeholders that would be involved in the tech development, the engineers, clinicians, patients, and the relevant go-to-market experts. So in gray is what you see now, but basically what is happening and not happening, so typically this is maybe not happening much, and again this is not about wisdom because I think wisdom is quite unique compared to what we see, I mean, wisdom and one, right? And so as a research engineer, you kind of drive that process all the way to the clinical validations, and then you might drive or support the clinical validations onward. And the clinicians are involved, obviously, up front.

Patients, maybe, maybe not. And then the clinicians are involved, maybe, doing the design of a product. And then they take care of the validations. And patients are typically not involved much. And then when it comes to the commercialization, then your market access experts tend to come in the picture, but quite late. In blue, what you see is what maybe should happen. And this is where I would like to have your input to see if like, if you have a different perspective or if you want to do things differently, where as a research engineer, so this is again, not wisdom, but in theory, this is where he has, he has to be comprehensive to get a lot of different inputs from different stakeholders. different stakeholders, having the clinicians being involved more or less throughout the process, having the patients also involved throughout the process, and having much more input from these various experts at some of the kind of critical phases, I would say. Is this, I don't know, what's your initial kind of tech feedback? Is this as it's best to be, is this your understanding or so of the situations and how you think that things should be done?

Ezra - 0:18:11 Yeah, I definitely agree that engineers should be actively engaged throughout the process. But in terms of validating clinically the product, I would also assume that engineers should also be part of it, but just not as, you know, somewhat involved, right?

Yoann – So, you would say this is like really involved, right?

Ezra - 0:18:35 Not just like... Yeah, but like commercializing the product is like somewhat involved, right? But like validating the product, it should also consider inputs from the engineers or the scientists. Not just... because basically the engineers build the product, but then the clinicians will be validating the product from the perspective of clinical considerations. But sometimes clinicians may have suggestions on how to tweak the product. So in that case, the engineers or the scientists should also be actively engaged in this process to make sure that the communication between two parties are well-versed.

Yoann - 0:19:26 And do you see this as someone being in a driver's seat, leading, like from a tech development, you drive and you lead the projects, and then you get input from the clinicians. So the clinicians are kind of in the passenger seat. But for the clinical validations, will you see this as, okay, as clinicians, you drive the clinical trial and you need help, come to me, or you see this as more like working in tandem, like hand in hand, that you should, you, engineers and clinicians, should co-lead, co-drive the clinical validations to avoid being too clinically driven and not enough on the tech side. How do you foresee this?
Ezra - 0:20:06 Yeah, I would say it should be co-lead. Because ultimately, engineers will have their suggestions like how to improve the product, and clinicians will have their considerations. And then in order to build a successful product, then both parties will need to be actively engaged. And I would say they should both be leading this part of the process.

Yoann - 0:20:35 OK, I agree. Anything else in terms of how you would want to see additional groups of stakeholders being involved or how you want to get additional input from some of them. When conceiving a product, it's more like designing like a proof of concept.

Ezra - 0:20:59 Yeah.

Yoann - 0:21:02 I should maybe clarify this. I think, to be honest, I might just want to skip this part, right? To simplify, just like with the needs and notifications, then you need to define the requirements. And then when you move to the POC, POV, or like this kind of, you know, maybe prototyping, and then this is back and forth, basically.

Ezra - 0:21:29 Yeah, I think for the clinicians, I think I don't have, I agree with the blue line.

Yoann - 0:21:42 And so anything else on this graph?

Ezra - 0:21:45 Yeah, I don't have any more problem with this.

Yoann - 0:21:52 And on this market access experts, you mentioned earlier health economics and so on. Will you know part of NUS who you could reach out to, basically? Who might help you? Assuming you have the time, you have the bandwidth, you need some specific input, do you know who might be the right expert? You can just call and send an email, that could help you. Go on.

Ezra - 0:22:34 Beyond our team. Actually, I don't.

Yoann - 0:22:37 Do you know if there is a specific department for that, or that could help, or... Not specifically.

Ezra - 0:22:46 Is it probably the public health school.

Yoann - 0:22:50 Have you, I mean there is no right or wrong, right? It's highly complex. Have you heard on this, or have you seen or heard about health technology assessment, how it's done, or have you been exposed to such kind of methodology before? No, I have not. When you went through your studies including your PhD, have you had some courses on the health impact but also the economic impact?

Ezra - 0:23:26 No.

Yoann - 0:23:27 So, you know, I think Dean often mentioned that in one of his meetings with his team on the CTE side, the engineering side, that most of them didn't know about what is a quality. Is this something that you have seen in school? What is a quality? Have you heard of quality before?

Ezra - 0:23:51 What is it?

Yoann - A quality, like quality of life, adjusted life, basically.

Ezra - 0:23:56 Is this? Oh, you mean like quality of life in the context of clinical?

Yoann - 0:24:01 Yes, like the impact of your, is basically on how your solutions will improve the quality of life of the patients. And you use the metrics, the measure that is used is what is called a quality, which is a quality adjusted life years basically, that your solutions might improve. Clinically speaking, you might give two extra years to the patients because he or she is using your solution. Is this like in the engineering type of curriculum that you went through, limited exposure?

Ezra - 0:24:35 Yeah, limited exposure.

Yoann - 0:24:37 And on the clinical side, on just like, you know, you mentioned earlier about impact and I totally agree, but how do we define impact maybe from a clinical side? Is this something also that in school we cannot like share with you or is something that you are learning on the job basically with WisDM?

Ezra - 0:24:55 No, for my at least for my classes we didn't I think like I don't know maybe it's just me like most of my most of the classes I took they were more like tech heavy, science heavy, I don't think they ever mention anything regarding like translational type of work. So none on the clinical side and none on the implementation side basically. I think like more on the clinical side it's like, oh this could potentially do something. But it was a, never like anything regarding clinical translation, considerations for clinical translation.

Yoann - 0:25:42 Is this something that now that you're kind of more exposed to the reality of some of these technologies and real world environment, you know, patients, kind of adherence, and all these kind of considerations, is this something that you find exciting? Because I guess it's a bit new, maybe this is what, from the tech side, right, from what you have done and studied, is this something that is like interesting, exciting, or maybe out of scope?

Ezra - 0:26:10 No, yeah, no, I find this super interesting, right. Considerations of science is not just like, you cannot just make science work without having other considerations. It's more like a teamwork. Scientists, engineers are just a small part of this whole process. You could have the best technology, but if you don't work with other people in this whole workflow, your product wouldn't make it. So I think it's super exciting because this is very different from the research I had before. I never, never really thought about these considerations. And talking to a lot of

people, whether it's on campus or off campus, I feel like most people don't really have these kind of different…

Yoann - what do you mean specifically? Like how different, or maybe what was the nature of your role before?

Ezra - 0:27:26 Yeah, so I think what happened is like, I was involved in the very first curate, like the prostate cancer paper when I was at undergrad, right? So I think at the time we were talking about clinical translation, we were really focusing on clinical translation to make this into a clinic to help more patients. But we never really thought about engaging with patients. Yeah, sure, we engaged with the IRBs and more on clinical trials and so on but never really thought about like the user engagement like talking to other people in this whole workflow or at least I did. So you see the transformations of a team then? Yes, like more yeah yeah it's it's it's very different from like you know like how many years ago like six years ago seven years ago like it's very different.

Yoann - 0:28:29 You have been that long with the team?

Ezra - 0:28:31 Yeah, I was in 2016.

Yoann - 0:28:36 2016, nice. Good, so I went through all the questions I wanted to ask you, and thanks again Ezra for your time and these insights. Anything else you would want to add, anything else that we have not discussed that you would want to mention. So again, back to the topic of the context about maybe why and how researchers, I would say, like being research-engineers or clinicians, might need to be slightly more aware of some of these kind of economic considerations or implementation considerations and economic will be one of them as early as possible because you know the challenge is that we tend to to look at the process of the tech development validation implementation I kind of a c-control process the reality and as you mentioned earlier is that it really requires a multi-disciplinary team but approach with different stakeholders being involved, providing input, kind of more like much more dynamic and agile process. And we just want to ensure that if we know that, for example, the healthcare resource utilizations is a super, super critical factor that would define the economic viability of your solutions in like two years down the road, how as an engineer, how can we make sure that you're aware about such considerations? So therefore, if when you design and you prioritize certain features, then that you know that if I consume, I need like two staff, I need two nurses, or I could free some time from the GPs or whatever, whoever, then okay, that might make sense. And then therefore I should prioritize certain features over, basically, other features. So, on that topic, anything else we have not discussed? Or maybe questions you might have also?

Ezra - 0:30:36 Yeah, so, actually I don't have anything more to add.

Interview Transcript with Eisa (P4)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:00:00 Awesome, so I would try to not take too much of your time and so maybe to give you a bit of context I don't know if you have the time to to go through the consent form or did I share with you the consent form?

Eisa - 0:00:16 The consent form, yeah you emailed some documents.
Yoann - 0:00:18 I mean we could get a good through the details like when you are in the office at some point.

Eisa - 0:00:25 I'm so sorry, because I'm rushing for a grant call and I didn't realize that we need more data. So we are rushing through, like, the deadline is like on 17th May and then the first two weeks, I'm not around.

Yoann - 0:00:38 So, no, no, no worries. So basically, you know, so this is about the digital therapeutics, right? And we did a systematic review about a year ago to explore and understand some of the costs and factors that are going to impact the economic value that a DTX might generate. Whatever is a DTX or like let's say like digital health solutions that might generate for a provider, for patients or healthcare systems, right? And what we did, you know, and I asked you for your input about a few weeks ago on a second study to try to understand on how some of these factors are basically viewed as important by researchers, by policymakers, by HTA, Health Technology Assessment experts, and the different stakeholders that are basically involved throughout the life cycles of the DTX, from the product development to the clinical validations, all the way to the deployment and implementations, right? And then this input on how some of the factors are important, but also considered or not considered, we have seen some gaps and some assumptions, some hypotheses, I should say, that we are trying to validate. And that's the next paper, basically. So this interview is really to get your perspective on the process you experienced in DTX development and what has been your involvement, your input, and have more specific questions later on. Sounds good?

Eisa - 0:02:16 Yes, yes, good.

Yoann - 0:02:19 So maybe, if it's okay, I'm going to record our conversations. You're okay with that? Yeah, I'm sure. I'm okay, I'm okay. Can you hear me properly? It's perfect. No, no, I can hear you. No worries. No worries. So maybe, you know, the first question, and you let me know when you have to leave. The first question is, like, could you please maybe describe what's your role, part of the Institute, and what has been your experience with when it comes to DTX, like from development, engineering, yeah, whatever.

Eisa - 0:02:48 So in my role right now, because currently I just got recently promoted to a research fellow. So I'm actually overseeing the blood cancer trials. So mainly the two one, these two trials are multiple myeloma and robustococcal macroglutamate. Yep, so for multiple myeloma, we just started it long ago. So we currently have one patient in recruitment and we are expecting another one in one to two weeks time if the patient fits the recruitment criteria. And then for the Wilber Strong, the patient is already in this trial for 34 cycles, so it's 34 months. So as my role, it's more towards stakeholder management also, in the sense that I serve as a bridge between engineers and clinicians. So we are the one who developed the technology like Curate AI, and then when we run with the technology, we do the ideation, followed by the validation, and then when we propose it to the clinician, it's more of like a partnership. And then we serve as something like a bridge between clinical work and engineering work. So we are in, I mean, it's a very privileged position to do so.

Yoann - 0:04:06 I see. And the engineers are part of the institute or like, would be like external to the institute?

Eisa - 0:04:16 So, uh, the engineers are actually part of the institute. So we have our own QRI team who actually, uh, will come in to support the trials. Yeah, so in a more technical side, like how do you actually perform the calculations? How do you actually perform the dosing? And then when we provide a recommendation, we will have this kind of in-depth discussion with the clinician, right, which is actually covered by the DSRP, to see that whether it is clinically relevant. I see.

Yoann - 0:04:46 So basically, when we say researchers, they are researchers with more engineering-driven researcher. And the one that would be more like the clinically-driven individuals or researchers, you are in between facilitating the conversations, requirements, or translating some of the requirements into tech requirements or into clinical requirements. Is it fair to say that?

Eisa - 0:05:15 Yes, yes, because we are getting feedback from both sides.

Yoann - 0:05:19 And then we will come, and then we will find a common ground. I see. So you just mentioned about feedback. So what are your top priorities, in terms of your role, and you mentioned being involved in some of the clinical trial. What are your top two priorities for the two projects or the two trials you are involved. And therefore, the second part of the question is like, the kind of feedback that you are hoping and expecting from the different stakeholders.

Eisa - 0:05:51 Okay, so for the first, actually the most important thing is, is our tech, Curate, clinically relevant in the first place. Can we actually engage it in current workflow. But, then the second one, it would be more of patient safety, because ultimately this tech revolves around patient safety. So, first thing is whether can we actually, is it clinically relevant and second is actually patient safety. I mean, they are both of them, they are not totally like excluded from each other. But I think these are the two important criteria because once we meet these two criteria, we generate the confidence for clinicians to actually want to adopt this technology into their workflow. Because in their mind, right, their priority is patient safety first. Patient efficacy and patient safety. Yeah. So they can provide the best care for the patient.
So if we could generate that kind of confidence, provide that kind of confidence whereby the solutions, the technology that we're providing to them can actually serve as efficacy, it's clearly relevant and it's safe. They are more inclined to adopt this tech.

Yoann - 0:07:04 And you know, based on your experience in these conversations that you had with these clinicians, and I think as you said, the ultimate end goal is for your solutions to be deployed, implemented, integrated, but used also by these clinicians, right? So you mentioned that maybe their top priorities in terms of efficacy and safety, obviously, that the most, we must have. Any additional requirements are nice to have that these clinicians might have shared with you? You know, like, okay, you have to check this, tick these two boxes, safety and efficacy. Any additional requirements that was or were mentioned in the last few months in some of the conversations with them?

Eisa - 0:07:53 Actually, two pop up. One is actually a cost. Because to them, it doesn't make sense that if I have a very good current SOC at this cost. It doesn't make sense that your technology that you're proposing and that kind of solution is way more expensive. It doesn't make sense to them. And then the second one would be in terms of manpower flow. Because we know that the healthcare system is actually very, we have a very, the background has very limited manpower. So if our solution overtax them, right, they may weigh the pros and the cons, that okay, if the current, if this current solution you are proposing to us, in terms of efficacy and safety, doesn't deviate that much, but you're adding more manpower, resources, and all that, they may not be that inclined to take on this kind of, yeah.

Yoann - 0:08:4 So it's actually resource management and cost is to... So on the cost aspects, why would the clinicians care about how much would it cost to use your solutions?

Eisa - 0:09:01 Because there's not so much of the clinicians, because there's so more of the... Because some of these clinicians, they are also policy makers. just a general GP or a specialist that, okay, I see you, I'm that next patient, I've moved on. Some of them, they are really policy makers and they have to look at things from a cost point of view, so for the entirety of the institute. So, they will look from the point of view, it is okay, for example, right now, because I've, not an interview, I have a chat with a clinician in the past before. For example, PestMed. So there is this specific testing agent for prostate cancer. So a few years ago, it's not considered a widely recognized, a not widely used prostate cancer machinery to image for prostate cancer because this one actually has higher sensitivity compared to current, at that time. So the clinician will not like encourage patients to go for that unless it's absolutely necessary because first thing first, insurance is not covered. Because it's a new tech at that time. And if the current existing tech is sufficient enough, sufficient, it's able to inform them of the, provide them the sufficient information, they won't actually even go for that kind of high-end. Even though you have better measurements, better readouts, they won't. Because it doesn't make sense that if a low-cost CT can give me this result, it doesn't make sense that I request a patient to pay $1,000, $3,000 to go for another scan with better readout, when the existing tech already can give me the information I require. And so I heard this from radiation oncologist.

Yoann - 0:10:51 I see. And you know, so you mentioned that some of the cost element or cost considerations were mentioned in some of the conversations, but were these clinicians slash policy makers, did they elaborate on what's the ask specifically?

Eisa – It's just like what they would want to see or the kind of evidence or whatever data that they would expect from you, from the solutions to be able to kind of address some of the concerns they might have about the cost, or it's just like, please just be mindful about the cost. It should not cost more than whatever is the SOC at the moment, or where they're more specific about their requirements or guidance when it comes to the cost considerations. Okay, so this one, right, I didn't hear it firsthand. I heard it from, because my wife works in a pharma company, so this is what she got from speaking to clinicians in a pharma company. So, from their perspective is, right, you have, in order for them to really want to take in your solution, right, it has to have, like, a significant improvement, a significant improvement from the existing tech for them to have that kind of confidence. Because let's say if the current tech is very sufficiently good enough for them to use, there's no reason for them to change and add additional cost. Which is consistent with my conversation with this radiation oncologist.

Yoann - 0:12:20 I see. Yeah. And so in your day-to-day, considering these conversations and their priorities in terms of safety, efficacy, in terms of manpower, potential requirements, cost elements, and so on, how does this translate into your day-to-day activities, decisions, making for the true trial of the true solution that you are involved in? Is this something that, yeah, how do you take this into consideration in the day-to-day?

Eisa - So, okay, first thing first is QuretEye itself, right, is a very user-friendly platform. So, in terms of, and when we are running, because currently we are actually running trials on it, and then one of the manuscripts for the WM paper, you could see that one of the concepts that we are actually looking at is how much this tech actually potentially disrupts the workflow. So in the sense of a 3AI case, it's more of like a clinical, it's a CDSS, it's a clinical decision making support system, clinical decision support system, so CDSS. In the sense that it's actually an add-on to the existing workflow. It doesn't tax them further like, oh, you have to pay this extra, you have to involve additional manpower, So the first thing is, how would it change the workflow, but it does not disrupt the workflow, if you get what I'm saying. I see. Yeah, it doesn't over... For example, in the WM case, the patient comes in every month, and then the performer will have a follow-up.

And then, during this time, you actually use QAI to provide recommendations that will last one cycle, which is another 28 days. So this is really like an imbue to their follow-up system. It doesn't change like, oh, I need you to come in every three, four days, three more days, which is not part of the SOC. It's not common in their SOC.

Yoann - 0:14:44 And you know, you mentioned about the ultimate end goal is the kind of implementations of your solutions, right? In the clinical workflows. And you mentioned a couple of requirements slash considerations in terms of, you know, manpower, in terms of obviously the safety and efficacy in terms of evidence. You mentioned about the cost. Is there any additional kind of requirements that you kind of keep in mind that you know that, and you mentioned also about the stakeholder buying, right? That you need to have a clinician buying and input as early as possible. Is there anything else from an implementation standpoint that might help, might kind of facilitate or make it or break it in a way when your solutions come to the deployment stage? Any additional kind of requirements that you can keep in mind and that's the main kind of requirements we already discussed.
Eisa - 0:15:35 Okay, so I think one of the requirements, as I mentioned earlier, is that confidence, right? So how to generate confidence is really through validation. So in order to give the patients that kind of confidence, because medicine is optimally evidence-based, it cannot just base things on feelings. It's really mass evidence-based. So in order for us to actually show that our solution is actually sound, we have to validate it. So that's why we need to keep running trials, to validate its use.

Yoann - And you know for the kind of two trials, or the two solutions, and you could take one of the other, if tomorrow someone might ask you about, you know, what might be some sort of like cost, kind of like, you know, cost impact or financial impact, economic impact of your solutions. How will you go about it to answer questions that clinicians or policy makers might have about the cost? What, how, how will you go about this? Will you, yeah, how will you go about this?

Eisa - 0:16:39 Okay, first thing first is, at least I'll get us through from the context of our technology. So first thing first is our technology QA, I write, we are one of the few tech that actually provide those recommendation during treatment itself. Meaning to say we actually walk through the patient, go through the patient treatment journey, and actually provide actual dosing recommendations during the patient treatment journey itself. So we are one of the few techs. And that's how we actually personalize their treatment, using their own data. So that's how we sell it to them. And then on top of that is, we are also currently running clinical trials for this to validate. And if you look back, curate is not born overnight. It's not. It wasn't born like, oh, I wake up one morning and it was born. It was actually, it has undergone like a robust validation state.

So from 2011, the very first paper, when they first discovered a second order co-relationship from neural network models, they have used this second order co-relationship in vitro, ex vivo, in vivo, and then in more recent times, your retrospective analysis, meaning to say that we use patient history to model our study, and then follow by clinical trial. So it's a long, rigorous process. It's not something that was conceived overnight and we decided to run the trial.

Yoann
So it's been carefully and robustly studied, analyzed. I see. And you know, so far you mentioned kind of two groups of stakeholders that you are kind of interacting with on a daily basis, the engineers and the clinicians. Is there kind of clinician slash a bit of policy makers, but is there any other stakeholders that kind of influence over the last few weeks, months and years, the kind of some of the directions, some of the decisions that you and the team has made beyond the researchers and the patients. Anybody else that you had interactions with and that kind of influenced the overall process?

Eisa - 0:19:02 At the moment, okay, so for the WN trial, I think one of the important things is also the patient, because ultimately they are the one going through the treatment, they are the one

that the ultimate end user, even though clinicians are the one using it, but they are the one ultimately are the one reaping the benefits. So in this case, I feel like the clinician, the stakeholder, the patient has say to this kind of platform, because if the patient say, I choose not to believe, I do not want to be in this trial, I do not wish to be in this study, we cannot force them. Yeah, because patient autonomy is something that we take very serious consideration into, because, at least from the clinical point of view.

Yoann - 0:19:52 And you know, so I agree with you, but definitely at the end of the day, it's about the patients and what they would want, and the kind of appetite they might have for a couple of different solutions. Do you think that we should also ask them, but beyond the value, about how much would they be willing to pay for such value? Is this like, you know, back to the cost considerations and so on, how might we kind of try to understand what might be the right kind of cost consideration? So we see you have a standard of care and so on, but do you think that we should also have patients involved in some of these conversations, trying to find what might be the right cost and pricing point?

Eisa - 0:20:35 Yes, so, okay, this also depends on how well-informed the patients are, because we know that when a patient comes in, we actually look at patients not of one socioeconomic status, it's a wide range, it's a normal distribution. So, it also depends. Maybe some patients are slightly more involved, it's easier to perform this kind of discussion. But for some patients who are less informed, it's harder to have this kind of conversation to... For example, if this patient comes in, he's an 80-year-old man, and his formal education is maybe a junior high school or secondary school in this case, they may not be able to understand the full context in this kind of discussion. Because from their point of view, it's like, first thing first, if it's too expensive, I may not want it, but they may not understand the full benefit of it. Because sometimes when they think about, okay, cost, then I Yeah, so, and it is a possibility.

Yoann - 0:21:34 This kind of situation is a possibility. So, it really depends on how well informed the patient is. And, yeah. And, you know, so when we did the second paper, the one that, again, thanks for your help and your input on that, what we realized is that it seems that the researchers, more the ingenious researchers, they might not, they tend to not take into consideration some of the cost elements in the day-to-day, you know, in the tech development, whatever it is, the support maintenance, the features prioritization and so on. How do you explain that researchers slash engineers might not take enough, maybe into consideration, some of the factors and some of the costs that later on would impact the economic value of a digital health solutions, digital therapeutics. So, sorry, just to clarify, so do you want like how to actually inform them in such a way that when we design a thing we have the cost in mind? I think so that's maybe the next question. I think the first one is that, so when we did the survey, we realized that engineers, they do not take much into consideration the cost elements. So we know it's about all developing about the technology to address a clinical need, a problem statement, and that's it basically. Right? But it's not always about having the state-of-the-art technology or the best technology out there, because it always comes with a cost.

Eisa - 0:23:17 Yes.

Yoann - 0:23:18 Right? And so, what's the willingness of the system, of the patients to pay and so on? There are quite a few questions that you might need to answer as early as possible if you want to ensure that your solution is going to be basically deployed or implemented or maybe get some reimbursement. So, how do you explain, and you might not have the answer, it's just conversation, but how do you explain that the researchers, the engineers researchers, they do not take into consideration some of these cost considerations in the tech development.

Eisa - 0:23:50 It's like kind of a low priority in terms of requirements to them. Okay, so, because I personally train as an engineer, so my own train, one of us that may not be representative, but at least from my point of view, right, is that it's not that we do not care about the... I'll use the word I

because I'll be... It's not that I do not care about the cost. It's more of the point that, because at this point, for example, our tech is at a development stage. It's considered a prototype. So my focus right now is to actually make sure this prototype is workable, is clinically relevant. Then, before I talk about upscaling, because when we talk about upscaling, that's where all the main costs and that's how we were thinking about how we can actually manage the costs and all that. So, I will not say that I do not care about the costs, but it's not a priority during my development and prototyping stage. I will not consider, because it's more whether can I make the thing work. Once I am able to make it work, the next question will be,
okay, now I'm thinking of upscaling. And that's where I will start factoring cost and all that and see if there's any way that we can actually make it cost efficient. Okay.

Yoann - 0:25:01 So you would consider some of these like cost elements later on part of the process more towards the clinical validations or after the clinical validations?

Eisa - If the clinical validations, because the purpose of the clinical validation is to make sure that it's actually clinically relevant, so I would say that I'll usually, I will start, actually I will start thinking about it during the clinical validation stage, it's not like separate, I will start thinking about it, but the, if you really want like an actual thing you do, this sitting down and then discussing with the stakeholders about how to upscale it, that will most probably be after the feasibility validation and all that.

Yoann - 0:25:40 I see.

Eisa - 0:25:41 Yeah, at least that's for me.

Yoann - 0:25:42 Yeah, no, no, I mean, and thanks again for sharing your perspective on that. And what do you think you would take for, let's say for you or the researchers slash engineers to maybe take these cost considerations slightly earlier in the process, even before you go to the clinical validations. You know, when you look at the tech development, there are a couple of decisions about whatever infrastructure you might use, whatever platform, some of the mechanisms, some of the features, and so on. What would it take for you, engineers, researchers, to maybe increase kind of the level of priorities of these cost considerations?

Eisa - 0:26:26 I think it is by education. Like it's easier to get this kind of, to raise the awareness because for engineers, right? First thing in our mind is we have to provide solutions. You don't give the solution first. So maybe you could just educate that, okay. Part of the solution process, the solution finding process is actually also cost, cost is also one of the factors that may affect whether people are willing to take this technology in or not. So maybe educating it at an earlier stage will help informing them because when we actually emphasize on this more, people may start thinking in this direction. That's my take on it.

Yoann - 0:27:17 Yeah, sure, and I think part of the kind of educations in a way, I think it's also for all of us, all the different stakeholders involved, is to realize the importance of certain elements, certain factors, right? But my kind of later make it or break it, I guess as an engineer, and correct me if I'm wrong, but you want your solutions, you don't just want to develop a new solution. You want your solutions to be used and to have an impact to patients' care systems, right? And for that, I guess if there is a higher level of awareness of some of the enablers slash buyers, and the cost would be one of them, that might help maybe to kind of rethink about, okay, how I'm going to prioritize certain features in view of these kind of elements, right?

Eisa -0:28:13 Yeah, yeah. So maybe we could just, yeah, we could always educate and just emphasize on the part that is there a way, right now we are prototyping this, could we actually, for example, when we think about this solution, is there a way to, in the meantime, reduce the cost into R&D is actually quite high just to get the prototype out. And then from there, we want to downscale it, right? We may come back to the drawing board sometime to start thinking, okay,

how can we upscale? So, maybe we could just like educate in a sense that, okay, maybe we don't have to come back, like make a discount. Okay, this is my personal thing. In the meantime, just put cost-saving planning as part of the monetizing phase. Because if you think long-term, longer-term.

Yoann - 0:28:55 And you know, there are a couple of mechanisms that also might help. I will just share one with you. In some of the grants, especially in Singapore, they will ask you to provide some sort of high-level cost analysis of your solution. So you know, as a clinician, as a researcher, if you want to submit whatever application for whatever grant, some of them will already ask you some sort of high-level kind of data and insights on the cost considerations. So, which I think is a good mechanism to kind of start to kind of like, maybe the top down, but to kind of start thinking, to be forced in a way to start thinking a bit early about some of these cost elements. Is it a good one or not? I mean, that's not the topic, but are you aware of any mechanisms that might, or any incentive that might help researchers think about these cost considerations?

Eisa - 0:29:54 Good question, because currently right now I'm applying for grants, so I'm aware that there are fine prints saying that is there a way that we could actually do this study locally rather than we outsource some of the work overseas. So, ultimately, for engineers, we will come in and then we will weigh the pros and the cons. Because, for example, if we realize that, okay, maybe even if we outsource it locally, right? We pay the lower cost, but ultimately the work that is going to come back, like for example, if it's going to be frequent enough and the work is going to come back and then it's going to involve so many stakeholders, it complicates the process. But when we outsource it to a foreign company, and they provide that kind of service, it shortens the project time and it's more efficient also. Even though at a slightly higher cost, some of us may actually go for that route and then we will try to justify. So it's ultimately still a pro and a con. It's not a very straightforward like, oh, because it's cheaper, we should go for it. Just because we need to provide justification, we have to definitely go for the lower cost, because we still have to factor in the non-tangible time, manpower involved, etc. I see.

Yoann - And maybe, last question, how would you define or break it down or what are some of the elements that you would say that, yeah, when I looked at the, when I consider the economic impact of such solutions, I would think about A, B and C. What would be this A, B and C? You mentioned some of the elements earlier, but I think just maybe to concrete these conversations, yeah, how would you define the economic impact of such solutions.

Eisa - 0:32:01 So economically speaking, right, for, first thing first is, for CURATE, right, so we actually put, okay, so for QRI, on Paxil, as you have also been involved in the WM paper, you realize that the overall drug dose that we actually administer to the patient compared to SOC is actually lower. So in overall, we actually kind of have a lower cost for the patient. So on the outset for the patient personally, it's already like a lower cost solution. Yeah, of course, we are not trying to say that we are trying to aim to always low dose the patient. That's not the intention, but it's rather to avoid toxicity if you do not need to go that high.

Because how clinicians actually administer drugs, right? We will administer at the SOC. If it doesn't work, we move on to the next line. But some patients, right, because of toxicity and all that, we move on to the next slide, but some patients, it's not because the drug is not effective for the patient, but it's because we're giving it the wrong dose. So if we, and QRI actually attempts to pinpoint this kind of optimal doses to provide recommendation to the clinician. And sometimes this recommendation is actually a lower dose. So, this overdose actually overall in terms of QRI, it actually helps in terms of costing economically. But if you look at from the hospital point of view, if we see trends like this, it can actually save a lot of... Because we are not talking about one patient, we are talking about maybe a lot of like hundreds of patients in this setting, it's just quite big.

Yoann - 0:34:10 So you know Eisa, you shared quite a lot of insights, extremely insightful conversations, so thanks a lot for that. Is there anything else that we have not discussed when it

comes to this topic of the economic impact of digital health solutions, and how do we consider as early as possible some of these elements, some of these factors that are going to impact the economic value of digital therapeutics or digital health solutions. Anything else that we have not discussed that you want to share based on your experience or any feedback, anything else?

Eisa - Yeah, so another thing is, actually I'm very curious, is what the pharma company, what their thoughts on this? Because ultimately, right, they are the one, because to them, it's a company, ultimately they're looking at profits. So I'm actually very curious, actually, because this I'm not really very sure, I have no idea what's their takes on solution if you can actually optimize dosing for patients, because ultimately, we are not dosing patient at SOC, we are actually dosing them at a slightly lower dose. So from their point of view, it's okay, we may end up selling lesser drugs. So I do not know.

Yoann Yeah, but you see, that's why I think your question, I think it's extremely critical, because it's the kind of questions that it's fully aligned with, you know, spot on in terms of the conversations we just had. I guess for them, safety and efficacy of receipts are most, whatever it's insurance, pharma, and so on. But I guess for them, the economic considerations are a must to have, right? The safety and efficacy is just like, is a given, right?

Eisa - I don't want to even talk about this, but you have to demonstrate and that's it, we move on to the next kind of priority and it's about the economic consideration. So I think for us, and that's just my view, but for us to be able to demonstrate the relevance of the feasibility of a solution such as CURATE, we will need to do some sort of like analysis on, okay, we have like, to try to extrapolate data that we have, let's say if we look at specific cancers, specific therapeutic areas, whatever interventions, private versus public systems and so on. If we extrapolate some of the data that we have, what might be the potential return, return on a clinical but also on a financial perspective?

Yoann - Because the challenge, and I think is what you, Dean, and the team, what we have said so far, is not about to low-dose every single patient out there. Right? But I think the shortcut is that, oh, you're going to basically use less of our drugs and therefore that economically doesn't make sense, right?

Eisa - But I think the point is you think, if you have a slightly different approach and you think that, okay, maybe we are going to low dose or we are going to optimize the dosage and it's going to be lower for let's say 20% of the patients but these 20% are going to be more adherent and compliant for maybe twice the period that they would have been overrides on a higher dose, then it's maybe 2x in terms of revenues for the pharma company or whatever companies, right? So I think this kind of economic analysis based on the initial data that we have, I think some sort of like simulations, you know, that would help to justify why a pharma might want to be king because it's not only about doing the right things, but I think, I mean, doing the right things for the patients and clinically speaking, but I think economically, it could make sense also, because you know, all these side effects that patients might have, that might trigger some re-hospitalizations and additional costs that none of us would want, right?

Yoann - In terms of the providers and the pharmas and the healthcare systems. So if you take, if you have a comprehensive and holistic view on all these cost elements, the cost savings, the cost avoidance, the adherence, the side effects and re-hospitalization and so on, I guess if you take all of them into consideration, I would tend, that's just my assumption, but I think it should be a win-win for everyone, for the patients, the healthcare systems providers, but also for the more commercial entities, the private entities, such as the pharma and the insurance. I guess it's going to be a win-win for everyone, but we need to come up with some sort of initial analysis and some of the assumptions that will need to be demonstrated.

This is just my assumptions, but that's what it will take to be able to convince the pharma that we're not trying to load those, every single patient out there with drug A versus drug B, right?

Yeah, so because in some of the trials that we are not involved, I mean like in trials in the hospital also has their own other trials. So sometimes when they partner with the pharma companies, right, the pharma company when they want to test their validity of their drug, they have to run clinical trials. And sometimes they partner with hospitals. And when they actually run through the trial, the drug is actually free. Because it's a trial. So the pharma company needs the kind of data to actually back up whether their drug actually has the efficacy. Is it safe? So, as I mentioned, ultimately the solutions that come together may potentially, if you look from a holistic point of view, involving everybody, it may actually benefit everyone economically.

Eisa - 0:39:49 Correct. To your point earlier, we just need evidence. So this would be right on the clinical side, but on the financial side too. Are slightly more advanced and open from a kind of mindset standpoint. You know, like for example, Novartis, and this was maybe three, four years back, they had this new heart failure drug, Intestro. I don't know if you heard. And they were so convinced, so confident about the drug that to establish this kind of comfort or confidence from the providers in the drug. Initially, the business model that they had was like outcome-based models, right? You would pay the drugs based on certain outcomes that you would expect and you would see, you know, the lack of real hospitalizations and so on. So really like, it's not about you get my drug and you pay like 50 bucks for whatever dosage, but it was like outcome-based. And I think from a pharma coming with such kind of disruptive business models with a drug, which we knew, I mean, from the evidence in clinical trials, we knew that such drugs would reduce the risk to the patients of the heart failure patients. It was pretty innovative from a business model standpoint. So this is the kind of pharma that might have the willingness to have some of these conversations and say, okay, let's try to do something kind of at scale in a way or to try and have some sort of feasibility study and see what getting some chemical, but also some financial data. But yeah, that's a different conversation, basically.

Yoann - 0:41:29 Anyway, Eisa, thanks a lot. I don't want to take too much of your time. I know you have some experiments to run, but thanks a lot for your time and sharing your experience on this important topic. I will let you know on some of the next steps and when you are in the office I will ask you to sign the consent form if it's okay.
Eisa - 0:41:48 Thank you for involving me. It is not a one-way thing that I share, but from your perspective, because from my engineering, I will not see things from a health economics point of view. so focused on results that sometimes we actually kind of forget about the larger picture of health economics. So I think for sharing a perspective also, I really, I think this is what makes our institute so unique, right? Because we come together to give a holistic, it's not just about solution, but we also look, just solution, just solving the problem, but how to solve it efficiently, effectively, cost-efficiently.

Yoann - 0:42:26 Exactly. I think the setup of our institute is definitely quite unique, but I think for every single digital health solutions, tech solutions, and healthcare systems, it really requires a multi-stakeholder approach, right? And I think we are quite fortunate to have quite a few of these stakeholders and expertise in our institute, but some institutes might not have, and I think this is where having this multi-stakeholder, multidisciplinary approach is so critical. To your point earlier, if you don't have a buying from the clinicians as early as possible, then it's just going to be another tech sitting somewhere. Anyway, thanks for letting me. I'll let you run your experiments. Thank you, and I'll see you at some point in the office.

Interview Transcript with Elisabeth (P5)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:06:15 Maybe the first question I would have for you is if you don't mind to describe your role, at N1, wisdom, what was your role and how involved were you when it comes to DTx, basically, from a DTx development or validations?

Elisabeth - 0:06:57 I was wearing a couple of different hats at WISDM and one of them was on developing the solution internally and supporting it from the technical but also clinical validation standpoint, the general communication of that research, what I have in mind is specific to CURATE.AI. Another role that I played is I was involved in the behavioral research and understanding the motivations, the barriers, and the enhances of digital technologies in general, including DTx, what role they can play from the perspective of the target population, from the perspective of the physician, from the perspective of the caregivers. And then I was involved in various community activities, which would include conversations or exchanges with policymakers, with startups, with individuals from the medtech scene to speak also with individuals that work specifically in terms of specific interest of the DTx's go to market. I lost you, maybe, maybe. That would be very specific to APAC. So my very last sentence was that that may involve some of the stakeholders are very specific to DTx and an example that would be Pitchfell.

Yoann - 0:09:35 I see. Good. And so, you know, when, maybe, let's start with, you know, when it comes to the development of digital therapeutics, so more from a tech engineering kind of phase, I guess, what were your key priorities? Some of the considerations in driving your decisions, when you think about, OK, DTx development as a research engineer, these are my top two or three priorities for the development of the DTx. And then I will ask you also about your top priorities when it comes to the validations of the DTx. But maybe when it comes to the development of the DTx first, what were your key priorities as a research engineer?

Elisabeth - 0:10:26 It definitely will be the technical capability and the clinical value. I would love to say that it was a market fit, but I think that would be untrue. The priorities would be focused on technical performance and the clinical value this solution can have.

Yoann - 0:10:53 I see. And if I ask you the same questions when it comes to the clinical validations with, I guess, a different set of stakeholders being involved also in that process, were your priorities being the same or slightly different?

Elisabeth - 0:11:05 It would be different. I think from that perspective, yes, there's still the medical value, but it's also the workflow fit. And the human factors more broadly considered. Patient journey, where the solution is, the physician's decision making, are the nurses involved?

Yoann - 0:11:31 So because you brought the point about the market fit, I have to ask you that question some specifically. What do you mean by market fit and why in a way? Why are you mentioning this point specifically?

Elisabeth
Yeah, I brought it up because this is the big challenge for DTx and one of the critical items that are recognized I think in generally in product development, not only digital health, but in general in product development. And as part of a research institution that has its own mandates, that's not necessarily can be a product owner, this market fit is not really considered as strongly as it could be.

Yoann - 0:12:26 This would be in specific to the team, is specific to like research institute, academia, or in general, across public and private organizations?

Elisabeth
I will say academia probably is the furthest where [market fit is not considered] I can generalize that type of a statement and where however in academia there are very particular initiatives that would bring in that topic a little bit stronger or there would be an emphasis on commercialization, go-to-market and more business-driven innovation. It is not the rule, however. This would be an exception from the rule under the specific initiatives within the rule itself.

Yoann
You have the theory and the practice, the kind of day-to-day reality, but you mentioned about the implementations and some of these kinds of considerations. How do you think that, again, as maybe research-engineers or for any stakeholders involved as early as possible in the DTx kind of life cycles, how some of these implementation considerations do you think should be taken into consideration? Are they taken into consideration? How should they be taken into consideration? What technology do you think you should use?

Elisabeth - 0:14:15 There are a lot of things that can be done by design. But I suppose everything starts with outlining what is the objective of a certain development. In some settings it's very clear, you know, if it's a start-up and an objective is a commercial success or an impact or social impact driven by commercial success. I don't think anyone plans to lose money but in an academic setting this objective is not necessarily set as a commercial success from the start or it may not show up at all.

So perhaps first that would need to be specified. What is the certain innovation and when it comes to then talking about the implementation then there's a set of other questions that come into in what physical setting for who the users are, who are the payers, who are the endorsers, who are the influencers, who are the five Ps from that our book. And then after that, you can see which components should be incorporated at which stage of the innovation, also not to overburden some of the early thinking. And it will be different for different type of products. We have security by design, we have all of this outside in thinking or market access by design, all of these different elements that can be incorporated early, but I don't think they all can be incorporated at the same time.

Yoann - 0:16:13 And they can't all be incorporated because of the complexities, because of what might be the reasons why all these considerations can't be kind of taken into consideration.

Elisabeth - 0:16:29 Yes, I believe that even just having the relevant expertise in the same room investment both of time and of money for you know, basically a blank page if we wanted to have all of these expert pieces in the same time present however, I incorporated all of these things they can be pre... ok, now I'm thinking about it, perhaps in this early innovation there should be an awareness, but the depth of all of these different aspects, that's something that needs to be timed. Awareness of all of them should be there from the start.

And maybe to your point about maybe raising awareness, maybe about some of these considerations that might be specific to the clinical validations or that could be specific to the implementations stages or related stages, I would say.

Yoann - 0:18:04
Do you have any examples or suggestions on how such awareness might be kind of created as early as possible toward the life cycle of a DTx?

Elisabeth - 0:18:10 So far what I have seen is the lived experience of the founding team or of the researchers that are going into that space or individuals that are aware, or they are aware because of their prior experiences of the complexities and also different factors in the healthcare system seem to be doing quite well in having that awareness first and then building the capabilities later. It could be then, you know, having the diverse but small team at these early discussions and the project conception.

Yoann - 0:19:10 I see. And you know, part of the implementations kind of considerations, I would say, you know, the topic of our research is on the on the economic impact, right, of a DTx, which may be one of the many considerations. How will you define that? How do you define the potential economic impact of a DTx? What's your understanding of such term?

Elisabeth
It can mean a lot of things. But let's start slighting and dicing. It can be the cost effectiveness of rolling out a specific solution. So that can be both what type of revenue it can generate and for whom. It can be for the solution owner, it can be for the healthcare provider, it can be for the payer probably not as much, but for the healthcare provider they can, it can unlock certain reimbursement capabilities.

It can be also about cost saving when the solution offer to reduce the hospitalizations in one example. And then if we talk about the economic impact, we also have the social tool. Economic impact, so maybe that's where the payers are more interested, at least the public payers, to see less time out of work, to see on the national level or on the whatever area that they are overseas. Less healthcare spending, so more healthy life, yours. Yeah, I can see these three from the top of my head.

Yoann - 0:21:30
And in your kind of specific role, you know, as a research engineer, when you were involved, part of a team as a researcher, did you consider any of these specific considerations that you just mentioned, being the cost effectiveness, in terms of you mentioned about health care resources, utilizations, and so on. Did you consider any of these specific points in the development and all the clinical validations of the DTx?

Elisabeth - 0:22:06 Yes, but it was rather abstract consideration. So not very deeply. It was something that we were aware of. We had some assumptions around the potential impact, the cost effectiveness. The one example could be that the whole immuno-oncology project for CURATE.AI was started with that idea in mind that it might lead to lowering the cost of rolling out the immuno-onco. The same for the irrutinib. We had that idea in our minds that perhaps there might be a lower cost to the patients and to the payers if the doses are lower, the doses of the tract. So there were some economic assumptions of the positive impact, but they were not scrutinized. They were not... It was not a rigorous thinking.

Yoann - 0:23:24 You know, to your point earlier, you mentioned that definitely there are many considerations when it comes to the implementations, right, that might enable a DTx to be successful from a deployment adoption standpoint, the economic related considerations are just one or a few of them. And do you think that this good enough approach is okay?

Elisabeth - 0:23:49 Is from looking at the academia and the research side, we can't factor everything. I mean, maybe this consideration should be taken into consideration later. So is this kind of good enough approach

Yoann
Do you think that we should maybe create or generate a bit more awareness on some of the specific factors and considerations?

Elisabeth
It depends on the objective. So the stuff that I mentioned earlier, what's the objective of the very specific projects or very specific initiatives? Maybe this is where more clarifications could then support this type of thinking on what, to what extent, where is good enough, to what extent the implementation factors are critical. So then the claims that are made about the solutions match also how the solution is being developed.

So quite often what happens in academia is that the initiative is driven from the technical and clinical curiosity, or there's a technical capability, there might be a clinical need, and there might be both of them happening at the same time, that is a very nice connection.

But only later on there are some claims made about those solutions. So, for example, that it's going to solve this problem and for this many patients, no rigorous attempts on actually answering the question if those patients would indeed be interested in using a given solution and they were not represented in the research itself. So I think it depends on that objective. Then quite often you have research that does not have an ambition to make those type of applied claims. It's more, we are demonstrating now this improved technical capability, and it's up to perhaps the next stage of the initiative or the altogether different team to take that and now start looking at those implementation factors, knowing that this technical capability exists.

Yoann - 0:26:26 I see. And you mentioned earlier that in your role, when you were part of N1 and WISDM, you had many interactions with different stakeholders group. You also mentioned about the five Ps. So in any of these conversations and interactions that you had during your time at NUS, did these considerations of these like economic impact considerations, cost effectiveness, whatever it is on the kind of economic impact of the potential solutions, did you have any kind of decisions or any of the stakeholders that mentioned or brought the point in one of your interactions about this as a potential requirement or potential considerations?

Elisabeth - 0:27:10 Yeah, definitely. This is a very, very present thinking in the field and understanding of the challenges in the field. So, the monetization of the solutions, commercialization of the very specific products, getting traction, getting reimbursement, supporting new policies that enable this reimbursement or nationwide reimbursement in different countries. Yeah, it's a very big topic.

Yoann - 0:27:46 You know, let's say, let's assume that, or let's assume that we want to create a bit more like awareness on some of this implementation related considerations to different group of stakeholders such as, for example, researchers and the clinicians, right? What kind of challenges do you think that they might face when trying to integrate these considerations of let's say, cost effectiveness into the early stages of DTx development and or clinical validations?

Elisabeth - 0:28:27 Oh, definitely it's the technical expertise. It's not trivial, this type of thinking, this type of process. So I think this is going to be the first challenge from moving from awareness to incorporating. And then in raising the awareness of cost effectiveness or just the economic component, the challenge is that it also fights for the attention with many other aspects that specific individuals or specific professions might consider of a higher priority.

Yoann - 0:29:19 Did you know, when you were looking at tech development and you mentioned earlier about, you know, you might want to kind of have a small but diverse team that could help, support from someone on all these kind of more implementation related kind of considerations, including the economic considerations?

Elisabeth - 0:29:55 I know you and you would be my first point and through that and through this first connection I suppose there could be other individuals that could be found but it's not it was not something that was as highly present and accessible to everyone. So yeah, but maybe the access in itself could be considered a barrier.
I suppose if I didn't know you, I would look for the contacts in the business school. But it does feel like a mission in itself. Identifying the right person probably I would expect that it would take me you know a couple of Attempts or leads or emails before I have an opportunity to talk to the right person, and then I'm not entirely sure if they would be interested.

Yoann - 0:31:06 So your experience what you're sharing now is really specific to your experience at NL1 WISDM. Do you have, have you been exposed, or do you know how the

different research institutes across countries might view or approach this kind of implementation, this kind of considerations? Do you see any kind of differences with us, I guess, or do you see similarities? Or are we unique, not unique in a good way, in a bad way? How do you look at this beyond the NUS kind of ecosystems?

Elisabeth - 0:31:48 Yeah, I think NUS is already doing things well. There would be many schools that are much more siloed when these conversations are not happening or they're not experts in that space. There are also other academic clusters that might be doing it better. So I know that there is the Digital Health Initiative across three universities here in Switzerland. One of them is ETH, another one is St. Gellin, which is a business school, and the third one is either Lausanne or Lucerne, I don't remember, but you can already see that there is the business school actor there that I presume is supposed to include that, provide that access to thinking around commercialization which inevitably is going to be a part of the economic values of the solution. I suspect there might be a similar initiative in the UK and there should be something like that in the US itself too. I know that MIT has a dedicated healthcare digitization team there but how much of the cross-sector is.

Yoann - 0:33:43 I'm also like watching the time, so I'm quite conscious of your next appointment. So, you know, on that topic of looking at the economic impact and the different influence a DTx to generate some sort of economic evidence, I guess. Anything else that you would want to add that we have not discussed, that you want to share on how research-engineers might consider some of these considerations, or might not, or what should be done? Anything else that you want to add on that topic?

Elisabeth - 0:34:21 Yeah, it's a little bit tricky. I almost feel like the engineers are not the best people to drive that because by by nature the engineers are engineers in an academic setting they look for the technological improvements or you know Yeah, the technological Capabilities and this economic considerations, they may or may not, but quite often they may, solutions or you know shiny engineering innovations and favor things that are much simpler and they are not as interesting from the engineering or technology standpoint. So in that sense I can see a little bit of a misalignment in the incentives. To some extent of course I don't want to say that these things cannot go hand in hand, but then it would require the engineers to consider an option that their interesting way of, So, perhaps again it will be all about aligning on that one objective of the initiative or the solution on that North Star and understanding what role the technology will play. And perhaps it's for the engineers to settle on what's good enough to support the clinical outcomes and then the economic effectiveness, you know, making things cheaper. Also from the computation, like, yeah.

Yoann - 0:36:32 And to your point, let's say we are all aligned in kind of the end goal of the product, you know, the Northstar and so on. And do you think that this still should be like a engineer kind of driven process for the early stages of the process with just in a way some input from different stakeholders, obviously the clinicians, the patients, but let's say market access experts. Is this the process in theory that should be the process that you think is like, when you think about the best practices, that should be the way to be like engineering kind of driven with a different input? Or you think that some of the stakeholders should be more, you know, having some sort of like co-leadership, co-driven type of initiative

Elisabeth - 0:37:21 Well, I imagine that it would be more product driven and engineers have a role to play or engineer. Engineer can also be a product person, but then they need to manage their own hats and how to approach it. So market access experts or any input from the implementation should be more like coming from an advisory capacity or early on in the process to ensure that, maybe to your point earlier, at the end of the day, it's still research in the academy, maybe slightly different agenda. If you have too many constraints on day one, you might not have the same level of output from a research standpoint, pattern, and so on, I don't know.

If you have an initiative that is engineer-driven or technology-driven, you will check boxes for a good few different incentives you are, or different objectives that are very important in academia like publication. Because that's what you publish, you publish technological innovation, publish SMS-based, I don't know, triaging solution that can be extremely, from the economic perspective. So that's why I'm coming back to what's this North Star, the objective is for the academicians or for the research institution. And how do you balance the academic output with the product output, if that's the goal.

Interview Transcript with Sasha (P6)

Raw Data Prior to Atlas.ti Coding

Sasha - 0:03:01 Okay, so basically when it comes to digital health, I just started to work less than two months ago [in this current team]. So my role is still somewhat evolving. I believe my role currently is to have a substantial input when it comes to the factor of eventual implementation of digital health solutions. Because in two settings, namely in preventive care and outpatient care, it's one key component of the success and final impact of any product is how people, the patient and other stakeholders will approach it, whether they comply with the recommendations, whether they follow everything or whether these solutions will have any distortive effect on their behavior. So they might be influenced by perceived expectations, they might ignore instructions, there are many possible deviations. If we need to account for this in the design and in the evaluation part, we need to distinguish what kind of deviations are driven by these factors, what is driven by incentives that we willfully or accidentally provide to them, and what is the literal clinical impact of the interventions.

Yoann – As you said, you just joined the team just two months ago. Do you want to share a bit more about your overall experience in the field, including your previous experience or some of the projects that you have been working on, maybe.

Sasha - 0:04:55 So, I'm a social scientist before? So my background is microeconomist. I did my PhD eight years ago, and gradually I shifted my field toward behavioral and experimental economics. These are mainly randomized control trials in which we examine the effect of some kind of incentive or behavioral intervention on people behavior and strategic interaction between people. The behavioral intervention is more relevant to the setting. I started to work on health-related and health risk related projects during the COVID-19 pandemic. I designed field and online studies to examine the effect of preventive measures on risk-taking and preventive behavior and that shifted my interest toward digital health.

Yoann - 0:06:01 I see. Great, thanks a lot. And how will you define what might be the economic impact of a solution, a technological solution? It could be a digital health solution, it could be a digital therapeutics, it kind of doesn't matter in a way, but what is your understanding of, or definitions of what might be the economic impact of technology core solutions? How would you define it?

Sasha - 0:06:29 I think there are two parts to it. There is one, the individual impact, that is easier to approach, also in a clinical study. The second is scalability. I believe that in general, DTX has a potential to provide scalable solutions because there are a couple of factors, a couple of components in healthcare that are conventionally done by clinicians or by human resources. That is, and DTX is able to replace a man who potentially improve them. And that means that both on the, on both sides, both in benefit and cost side, there will be changes. When it comes to benefits, it's possible that there will be differential impact. In some factors, they might be better because AI has immediate access to a larger library of information, but their precision, their trust, stakeholders' perspective, they might be different. We cannot exactly predict how this will work. On the other hand, the skill side, we expect, right, that they will scale well. Because simply the marginal cost of scaling up will be much smaller than adding and training and organizing a larger crowd of clinicians in a program. I think these are roughly the components that I would consider.

Yoann - 0:08:18 And so you mentioned about some of the costs, some of the benefits. Who is, who should be responsible to deliver those aspects of the solutions? Because you have the engineering part, you know, the technology, you have a clinical part, and at the end of the day, the different pieces of the puzzles we need to deliver, in a way, you know, this cost and benefit. So, who should be responsible, especially for the financial or the economic potential benefits or slash the cost?

Sasha - 0:08:58 Right. So sometimes there's a misunderstanding of what economists are doing. So, to be precise, that part of it is not my expertise. So when it comes to scalability, this is usually done in different cost-benefit analysis methods. This is actually more accounting than microeconomics. So actually that's a separate later stage, so that's the implementation stage. At the point I'm working at, it's not before that stage. I think that's simply a separate field and very separate methodology. But they do need our input. Why? Because all cost-benefit analysis methods are linear. So they work with inputs, outputs, and prices. In other words, you can only do this if you have an understanding of how scaling might work and what is required. So you need to understand the stakeholders. Just to give like a trivial example, you have a hospital level study, you implement a new screening method, then you need to be involved in training the relevant clinicians. But if you scale it up at the national level, you need additional levels, because you need to organize the training at a larger level, the ministry or some kind of national level organization is involved, and you need new kinds of inputs that you need to take into consideration. Actually, there will be different kinds of resources. That's not exactly the scope I'm working on. Sure.

Yoann - 0:10:46 But your role in a way, or maybe you had the opportunity earlier, but it's to work with such economists to maybe to help them to provide such input or information that will be required for them to be able to perform this health technology assessment, basically, right?

Sasha - 0:11:14 I can provide parts of it. I think there will be just several parties collecting the necessary information. I think I'm a part of the puzzle.

Yoann - Okay, and have you been involved before in some of these projects where you were providing such information in view of assessing the economic impact or performing an HTA for some of the solutions?

Sasha - 0:11:43 Not in the short term. Not in practice. I mean, indirectly, yes. Like, I worked on a project assessing the impact of a procurement system for highways.

Yoann - 0:12:00 I see.

Sasha - 0:12:01 That's just such a different field that I don't think is directly applicable. In that methodology, it's directly usable in healthcare.

Yoann - 0:12:12 It's just too different. I see. And so when it comes to the tech development side and some of the projects that you've been working on, how would you summarize what are your key priorities? You know, it's always like, or maybe how success would be defined for you.

Sasha - 0:12:31 Oh wow, that's, yeah, that part is a bit difficult, right? You mean my success or the project success?

Yoann - 0:12:38 So, less about your personal success, but I mean more on the technology. Let's say, as a team, we do work on a tech development, right? We develop a new tech and we should validate through a clinical trial the technology. How would you define success from your perspective for this technology? I give you a basic example, you know, like the clinicians, for them success would mean the efficacy of a solution. Could the solution deliver those clinical outcomes? That's it. Engineers will tend to look at success metrics more from the tech standpoint, more on the performance of the solutions, but not maybe from a clinical perspective. And so that's why I'm like, on a typical project, and you are free to take a specific one if you want, but how, and as you said, it's kind of a multi-stakeholder collaboration, you know, yourself and the different stakeholders, and we all define success differently. So that's why I was quite keen to understand, from your perspective, on a typical project, or a specific one if you want, how will you approach and how will you define success?

Sasha - 0:13:55 Okay, so when it comes to the outcome or the impact of any kind of new technology in health. What I want to understand, and I think this is very important for any kind of new product that is used by several stakeholders, is that you might want to understand what impacts the success. So there is a clinical side, and again, there's a behavioral side. But that has a differential impact. Consider the Blue Zone Study. So for instance, when it comes to the Blue Zone Study, we understand that it's necessary to analyze the impact of the diet on biomarkers. But what else we do then? We provide them free food, that's an incentive for them to actually have this kind of diet. You might not be able to scale this up, so you need to see how these incentives work, and you want to see how exposure to a certain kind of diet have a prolonged effect on people, right? So there's the kind of behavioral impact. So what I work on, for instance, there I work with a so-called behavioral stock model. So how that works, what you do, what you purchase, and your choices are partially driven by your past experiences. So there is some kind of direct, it doesn't matter if it's consumption or literally just some kind of adjustment, right? So here, what you expect is that dietary choices will be influenced by all these factors. And you might want to disentangle them because in the end, that's not what you will do. You will not provide free food for a prolonged time at large scale because it's not sustainable, right? So you want to understand these mechanisms separately. If you use the right design, this is possible. And the more we are able to understand this, the better it is, because we are able to make predictions. I see.

Yoann - 0:16:22 Have you had any conversations with any stakeholders in the healthcare systems or not about how the behavior of individuals for any solutions might impact or influence the adherence of the participants or more on the economic impact of the solutions. What I mean by this is that, for example, if you have a solution that is out there, but nobody is using it, or if you have the solutions and participants of patients are not compliant, then the solutions cannot deliver. Hi, Roger. Is it okay? Yeah, we are doing an interview, but we'll move to a dentist office you don't mind we just need to a dentist office okay you're good yeah yeah yeah so what I'm trying to understand is like the kind of conversation that you might have about how the behavior of an individual might impact the output, the performance of a solution, including on maybe the economic side.Have you had such conversations with some of the stakeholders?

Sasha - 0:17:51 Yeah, I mean, I had most conversations with physicians. Physicians. Yeah, because of family reasons, because I have a daughter in the family. It's my sister, she's a gynecologist. So she describes medicine, she performs surgery. So when it comes, I think what she does, the most relevant part was lifestyle and medication. So medication is the common part, and lifestyle also matters because for instance she takes care of pregnant women and then she tells them please don't smoke, please don't drink and gives them like a little bit actually quite simple lifestyle advice. What she said and and what other physicians told me, they were mostly Hungarians, this actually matters because of cultural reasons, translate to the terminology that I'm using, is that most people have a rigid personal profile that drive their behavior, and they believe that interventions with digital technology will be ineffective. But this is their professional opinion or personal belief, I'm not sure how to put this, but they did not have any direct experience with digital health. So they just extrapolated from their professional experiences on what they expect. What I learned from this is that from the clinician side, we might need to face skepticism, possibly sabotage or some kind of other form of self-resistance against this technology. We need to influence their beliefs and not just their knowledge. Right.

Yoann - 0:19:52 And so, you know, in what you mentioned, and I think it's critical in the overall adoptions of digital health solutions or any technological solutions. So, it's back to your expertise, which is about the behavior of individuals and how do we change some of these behaviors. So, we know that this is critical in terms of adoptions, in terms of compliance, and is obviously critical when it comes to, again, coming back to the topic of the solutions to deliver an impact clinically and financially maybe, right? So in your view and your experience working with different teams, different researchers, engineers, clinicians, how is your expertise or the behaviors of the change

of behaviors that will be required by the participants, how is this taken into consideration by researchers? Is this something that they understand and they take back into considerations? And that's the reason why they have conversations with experts like yourself. Or is this kind of a really late considerations that we do work on the tech, we go to clinical trial, or by the way, nobody is using the solutions. What should we do about that? So how what are kind of the best practices have you seen or gaps and is really your expertise the behaviors of individuals taken into considerations throughout the life cycles of any solutions?

Sasha - 0:21:22 Okay, this is a quite long question. Yes. So let's start from the from the beginning. So before I moved here I actually had a limited interaction with non-economists. So if I just consider this last less than two months, I think where my input lies is getting clear to me. Like when it comes, so in several projects I join in, you know, in a minor or a larger role in the planning or design phase. And what I noticed is that it's not obvious in research design to other researchers, what are possible pitfalls when it comes to compliance or behavior. And in some cases, I saw some kind of naivety when it comes to this. Like the design, when it comes to interviews, it assumes that people are telling the truth. It assumes that people have sufficient, pay sufficient attention to the questions that they will be engaged. I challenge this. So when it comes to, for instance, the Bluestone study, the reason I pushed for this seemingly elaborate similarly elaborate and convoluted method to perform like an auction against a computer as opponent, it seems like unnecessarily complicated. Because I know that from my professional experience, literature and other factors, is that for these reasons, they don't tell the truth, they don't care, they are not paying attention, the data will be seriously tainted if you just ask them straightforward questions.

Yoann - 0:23:20 If I summarize and correct me if I'm wrong, but you can have a lack of considerations, but also understanding of your field, basically, and how your expertise, or some of the pitfalls, as you said, could be, should be taken into consideration as day one when it comes to the design of the research, right? What do you wish that researchers, part of the team, but in general, generally speaking, because I guess what you just mentioned is not specific to the team, but it's maybe specific, it's like in any research institute. So what would you wish that researchers would do a bit more or a bit less early on in the process to address that pitfall you just mentioned?

Sasha - 0:24:11 Right, I think when it comes to human factors, what people should do less is working with hypotheticals. Okay. Okay. So working simply with questions or ask straightforward questions such that, you know, how much people appreciate something, how they perceive something. Thinks very best if there are decisions and the decisions have consequences. More if this is not possible. Then we need to make sure that the type of questions that we ask them, that usually these kind of questions replicate. It's possible to ask questions that people in general give honest answers. It really depends. But without this understanding what kind of questions we can ask, or what are the cases when asking is pointless. You need input from the literature, you need input from someone who's been exposed to this. When it comes to this, I'm extremely skeptical, and that worked out for me so far.

Yoann - 0:25:31 And know every single research team out there might not have the chance to have all the expertise in-house in a new part of the team, right? So what would be your recommendation to these teams for them to make sure that they take these considerations or they take whatever you just mentioned now, these recommendations, into consideration as early as possible? What could they do? What kind of tools would you recommend or knowledge or what would be your recommendations to them?

Sasha - 0:26:04 I think the most critical part is the study design. You want to make sure that the study results have external validity and when it comes to the implementation stage you will find a similar effect of the implementation part and people's health outcomes as a study. And in this respect, I think design is the most critical part. So these kind of factors that I mentioned that needs to be taken into consideration, you will be seriously misguided if the study doesn't provide

the kind of exposed data that you need to have to understand. So you need to focus on the designs at the validation stage that replicate the actual clinical stage.

Yoann - 0:26:59 If I take the specific examples of like a team, let's say you have a team of engineers, just engineers, and they start working, developing a technology, right? They might not have the background and the knowledge to understand what might be a robust study design. And so I'm trying to, I might want to get your opinion or perspective on that, on how could we help them. Because again, they might not have a possibility of having all the expertise under one roof. So are there specific tools out there that could help them confirm that, yes, I've done the right steps or I'm taking into consideration the right aspects or to proof check, maybe the study designs?

Sasha - 0:27:54 I think when it comes to like return or any kind of impersonal toolbar, it's a little bit difficult to obtain because there are so many things in human behavior that are context dependent. So, when it comes to my contribution, some things are based on actual studies that I can refer to that are sufficiently similar to what we are doing here, but in other cases I extrapolate from really related things. I look for contextual cues that are similar. So there's plenty of guesswork there. And I also question my opinion that is it, will this replicate or not? And I start, I'm also trying to be skeptical. I think the best way is to acknowledge that and maybe draw in someone with this kind of background as kind of like a co-author or at least in some consultation role. Let me give you a very simple example. You have a good understanding of incentives and microeconomics that people move towards cheaper, people move toward better, or at least they don't move in the opposite direction, right? So if I, for instance, give you chocolate, it doesn't, maybe it will not change much how much you will eat of it because it's chocolate. You understand that one of them is better, but it will actually not matter. But if the chocolate is worse, you will not eat more of it. But when it comes to motivation, things can go in the opposite way. Do you donate blood?

Yoann - Not as often as I should.

Sasha So there were studies that tried to see how people would behave if that was paid. Because of ethical reasons, usually those who donate blood, they're not paid for this because it's human tissue. That's not the only reason. So what they found is that when they pay for this, there will be fewer people donating, and the quality will be worse. This is the so-called crowding out effect. That is one of the most counterintuitive things in human behavior, is that once you provide incentives, there will be a countervailing effect, is that you lose the drive to actually do something. How can you possibly predict this if you don't know about this specific thing, but you have a good general understanding that incentives matter, you will get it backward.

Yoann - 0:30:59 I see. And is this connecting the dots between what you just said, but you mentioned earlier about the lack of scalability, or the importance of the scalability of some of the solutions. Is this the reason why most of the solutions are not that scalable? Is it because you think they are maybe not that evidence-based early on, and not having the right study designs, not validating the right assumptions? And I don't know.

Sasha - 0:31:27 It's a possible reason, I think. I'm not sure that it's that simple, because scalability can fail at. It's complex, and it can fail at many points. It can be for instance organizational, it can be market driven. So for instance market driven explanations like for instance Uber and Grab, they were previously struggling to expand. Why? Because although the technical part scales well, the transport system of cities are completely independent. And what you do in one city will not influence what you do in the other city. Right? So there can be many points of failure. Scaling up is difficult.

Yoann - So maybe let me rephrase my point just to see if you agree, by considering some of the aspects you mentioned in terms of behaviors, behaviors of the participants, of the end user, that might increase the likelihood of a scalability of to scale a solution, basically.

Sasha - 0:32:41 I believe, yes. Because it's, let's just say that it's, if it doesn't replicate, then it will fail at an earlier point. It might fail actually before you try to scale it up. Yeah. Because you put your technology in a critical setting and it immediately fails. Yeah. Then that's like the first step of scaling up, right? So you will not go on national scale right away. So you go from validation to implementation at large, and you immediately fail because it fails to replicate.

Yoann - And maybe you know, I think we more or less all, as kind of researchers, clinicians, and so on, we are aware of that challenge that is the implementation, is the adoptions, you know, is the adherence of the end user. Is this, do you think, the reasons why we are so focused on kind of the short-term? Maybe priority that if nobody is going to use the solutions of this is not going to be successful Is this the reason why we are maybe not that focused into the potential? Economic impact of the solutions. It's kind of more like let me try to address the the first issue which is implementation and adoptions and once I got there, I get there, then I might want to focus on additional challenges, complexities that could be the economic impact. Is this, do you think, the reasons that we are addressing or looking at this kind of a sequential process that fixing issues after issues?

Sasha - I'm not sure I understand the question.

Yoann - So you know when you look at, you were just mentioning that when you implement a solution in a clinical setup, most likely it's not going to work out. So implementation is an issue, and adherence, adoption of a technology is an issue. Let's say implementation. And so is this the reason why we know about that? So is this the reason why we, as a community, we are so focused on tech adoptions, that we tend to forget additional considerations, such as the economic impact of the solutions. That would matter to the payer. That would matter to the insurance. But we just focus on the first issue, which is like, let's make sure that the tech is being used by someone. The rest of the considerations, I'm going to kind of, this will matter later.

Sasha - 0:35:12 I think that the problem might be simply in general, like lack of overarching expertise. So simply at every stage here, we are required very different kind of expertise. Like scaling up from hospital to national scale, that's actually organizational matter. If you don't understand how a ministry works, if you don't understand how the administrative part of hospitals work, this will be very difficult to understand what can go wrong. If you don't know the clinical side of things and how different departments of a hospital function, how their training system works, then you will fail at an earlier point. You cannot have everyone at the same institute. So I believe that you draw in clinicians at an earlier stage of the study might be useful because they can point at possible points of failure. Yeah, like involving everybody and forcing all kind of possible problems. I mean, good luck with that.

Yoann - 00:36:21 Good, so you know, I did cover all the questions, the topics I wanted to discuss, but is there anything else on that topic of digital health solutions, kind of impact from a more like economic perspective, is there anything else that you would want to add, any observations from your experience working with a couple of different stakeholders that we have not discussed yet?

Sasha - 0:36:54 I think there are some aspects of digital health specifically that are really unique. I think one thing is the current rapid progress that we observe. you know, how do you call this? Disruptive. If you think about the time frame of a single project, disruptive technology might pop up, what do you do about it? The other thing I behavioral aspect that things change so fast that there is very little time for the general population to understand what's going on. Like, there are a couple of things that you need to understand online to function properly so that, for instance, you

don't get scammed. People learn how to identify phishing attempts, right? But now phishing will get more sophisticated. The other day, I get an email from a colleague and I believed it. Believe it or not, it made sense because the style of the letter, the content of the letter actually overlap with something you might expect from the person to receive. It was a scam. I didn't reach the point that it would make any kind of further stamp because the following emails made no sense. Yeah. But the first one kind of, yeah, good enough. First one was good enough to make me engage.

Then I obviously using common sense, then I realized that this is a scam or a phishing attempt. I think in the end it was something like this. Now when it comes to, we talked about this actually regarding I think the perspective article and chatbots, that what kind of emotions it triggers, it might be influenced by that it's a robot, right? But robots keep sounding different. The output keep looking different. If you look at AI generated images from one year, even one year ago, they improved so much. They are becoming more and more deceptive. They are becoming more and more realistic. You can expect that this will absolutely have an impact on whether they work or not. Like a chatbot, very soon, will sound more like a human. And even if it's salient to you that it's not a human. That, see what I'm getting at? Which, the line could be blurry sometimes. It can be blurry. It will be more and more, yeah.

Yeah, but this is a completely new aspect. So something that is salient to you, that is not a human, but it sounds like a human, I don't, I'm just guessing. I'm just guessing how that will impact people's perception, attention, trust, you know, because there's no prior evidence. Previously this was impossible. I'm just guessing. Now, we implement a chatbot that currently, and you start with a technology that doesn't sound human, but writes grammatically correct sentences that are actually correct. Do you expect people to behave similarly? Because maybe by the time you want to implement it, they will be different, they will be better. Right? In conventional studies, conventional technologies or nanotechnologies or in-person interactions, this is not a problem.

Yoann - 0:41:15 Good. Anything else you want to add on that topic?

Sasha - 0:41:19 Nothing on the front of my mind.

Interview Transcript with Sara (P7)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:08:56 Thanks a lot. Any questions at this stage or any clarifications?

Sara - 0:09:00 So maybe just one very basic question. So when you talk about economic value, is that a very narrow interpretation where you say basically the achievable price per product in the market? Or are you taking the usual more broad perspective where you say, okay, can we save costs in the traditional therapy? Can we avoid more expensive therapy? Can we close gaps? So just for me, in the back of my mind, how do you see economic impact or value of the DTX in the context of your study?

Yoann - 0:09:42 So thanks a lot for asking the questions. It was one of the questions I wanted to ask you. So I will kind of answer in a way to that question, but when we had conversations with the researchers, we typically refer to the clinical value is kind of like understood in a way, safety and efficacy or effectiveness. And on purpose, we didn't want to be too narrow or strict on how do we define the economic value, because it kind of means more or less, it could mean a different things for you as an expert versus a clinician versus engineers, for example. And so in short, we are taking more of a broader definitions of what might be an economic value.

And what we realized is that most of the researchers, clinicians, they tend to think that they are not taking into consideration the potential economic value of the solutions in their day-to-day decisions, but because we speak different languages. So for them, they would look at the economic value more in terms of like, to your point, like the efficiency gains, right? Like cost savings, cost avoidance, healthcare resources, utilizations, the number of nurses that I might need to deploy the solutions. So all these factors would play a role, would impact the economic value when you do your HTA of a digital therapeutics.
But to the clinicians and engineers and researchers, this is not about the economic value, it's more like some deployment considerations, right? So it could be any of basically of the kind of definitions of aspects you mentioned. So it's really more the broader economic value kind of definitions from a digital health or digital therapeutics, basically.

Sara - Okay, sounds good.

Yoann - And so maybe to start, if you don't mind to put, to have the right context, if you don't mind to describe your role and how do you interact with, I guess, digital therapeutics kind of innovators slash researchers. Yeah, that would be a good maybe starting point to ensure we have the context.

Sara - 0:11:56 So, one of my main jobs is I'm a healthcare management professor. So I teach, and one of the areas I teach in is healthcare financing and also health systems development. And in both of these areas, you know, economic value and also innovation plays a big role.
And I think in terms of the digital technology, I think on the one hand, a part of my research interest is to work specifically on acceptance of digital technology because we do have, as you know, in Germany, we have the space where it's, I think, quite possible to get solutions having access to the market. But then we do see still a lot of acceptance barriers, technical mindsets, the different, different things. And that's what we work on and also on adherence. So as soon as patients get convinced to take on the solution there's still this initial excitement and then it trickles down a lot. So that's one of the two things that I like to focus on. And then also I interact with clinicians at some point, building up some research studies and I'm active in the marketplace to some extent, understanding how the innovators, the manufacturers think and what struggles they have getting their solutions on board. So it's different aspects of it, but it's mostly around research and teaching.

Yoann - 0:13:33 Anyway, congrats on your recent paper with Florian also that was just published a few weeks ago. It was kind of an insightful paper. I had a conversation with Florian about a week ago and I told him that it was a good timing because we are about to publish the paper too, so I managed to basically include your paper as a reference basically to support some of the assumptions that we have. Because if I'm not mistaken, in your paper, you identified the cost as cost slash reimbursement and who is going to pay for the solutions as kind of one of the concerns from the physician perspective, if I'm not mistaken, right?

Sara -Was one of the topics.

Yoann So I think we are aligned on some of the gaps that we might need to address. So maybe to follow up on your questions about the economic value kind of definitions, there are multiple definitions. And do you think that we should have, we should define the economic value differently for each phase of the DTX lifecycle development?

Sara - So when it comes to, to maybe clarify, when it comes to the initial stage of concepts, kind of prototyping, mostly driven by the engineers, then we should have maybe, I don't know, like a simplified, streamlined, uncomplex definitions of some of the considerations of some of the economic value. And then when it comes to more the clinical validations, there are a couple of endpoints that might be kind of relevant also, and we might have slightly different definitions of economic value. And obviously, when you do your HTA, kind of a bit more complex, more broader kind of definitions. I don't know.

Yoann - 0:15:21 Do you see this as kind of a need for us as the different stakeholders involved in the DTX development, or should we stick to have one single definitions standardized across the different phases and across the different stakeholders? What may be the right approach?

Sara - 0:15:39 I think there's a lot of value in having standards around definitions. And I think it's probably a little bit of both. As you said, at the beginning, you have a rougher idea, and then you start refining. So it's probably not having different concepts, but it's probably having refining, you know, having more refined, more detailed concepts from your initial prototype, where you define, this is my market size, this is the type of therapy I want to develop, and this is maybe the current treatment gap or the current standard of care that I want to get into. And then as you move towards clinical validation, where you say, okay, is my primary endpoint, you know, keeping the situation constant until there is that space for face-to-face therapy, which is a very different endpoint compared to, as you know, improving mobility or something, depending on what you want to do. And so it does, I think it does get more refined as the process evolves, as far as I can see.

Yoann - And maybe, I don't know if there is any right answer to that question, but who might be responsible for the economic value of a potential DTX? What I mean by that is that, you know, when you look at the DTX lifecycle, you have a lot of different experts, stakeholders that are involved and should be responsible slash accountable to ensure that the DTX at the end of the day, at the deployment stage is going to deliver economic value to a system or to a payer? So who in the development process should decide or should define?

Sara - Sorry, maybe you can repeat.

Yoann - 0:17:39 So what I have in mind is that when we have conversations with a different group of stakeholders, ensuring that the DTX will deliver economic value, most of the time is that that's not part of my job scope. Right, I'm here as a part of the engineer, I'm just here to ensure the performance of the product. And then as a clinician, I'm here to ensure the safety of basically of safety efficacy of the solutions. But then when you do your HTA at the end of the life cycles, I guess, or at the end of the road, then you realize that unfortunately, your DTX might not deliver the economic value that might be required for approvals, reimbursement and so on. And so do

you think that it's kind of a co-shared kind of responsibility across the life cycle that each of the stakeholders, you might be a clinician, you might be an ingenious scientist and so on, and it's a shared responsibility that we all have to ensure that a DTX in 18 months down the road will deliver economic value, or is the responsibility of a few group of stakeholders be kind of maybe the commercialization kind of experts or go-to-market experts. I don't know what's your view on this kind of responsibility.

Sara - 0:18:49 I would probably, I would tend towards the latter, because I think it's very challenging I think from somebody who's clinically or technically focused to assess this. I would see it rather, compared to what I've seen in other, like in medtech development, in other fields, is that coming from the market, you say we are in a space like there's a lot of comparable pricing in the German market for cognitive behavioral therapy apps for example So you could come from the commercial side and say there's a high chance that if this is one of the markets that attracts us and if it's one of the first markets that we want to get Into we would be in the price range of from there to there So we need to make sure that our development costs, you know, assuming certain payoff period and investment cycles, wouldn't exceed a certain amount of money. So I think it's more like an input and then the technicians would be aware when they make decisions in terms of complexity, in terms of, you know, does this therapy need an adjacent medical device, for example, to be considerate about these things. If we have a market the same as any other requirement where you say our competitors generally offer this type of technology, this type of convenience, this type of integration opportunity, I think it's just a requirement as everything else. And then the clinicians have this in the back of their mind, just knowing, okay, we're hitting a certain target, and then if they start creating more complexity, or they're creating a product that requires more backend support, that they start talking to the business, say, I think we are, if we make this decision, it might increase our cost down the road. So that's how I see the interface, personally.

Yoann - And as you interact with a lot of these different stakeholders for across different projects, I guess. Have you come across any specific kind of best practices of some of these groups of stakeholders, let's say maybe more the clinicians or the researchers, the engineers, that could consider, that would consider as early as possible, this kind of economic considerations. I don't know if you have like some best practices of like teams that you know, you may be surprised but early on just at the concept stage that they will kind of anticipate some of this.

So looking at the economic value, but so often is about the kind of implementations related kind of considerations, right? It could be about potential reimbursement and so on. So I don't know if you have seen or come across any teams and any kind of best practice, best best practices that could be shared basically, non-confidential, about teams trying to include these considerations as early as possible.

Sara - 0:21:44 So I think the advantage of this whole market, at least from the space that I understand a little bit better, is that it's still quite small, so the players are quite well connected. And so the developers or the companies, building these MVPs and putting them out there, they're very well connected with, let's say the associations for digital medicine in Germany, that in turn is quite active with working groups and bringing these different stakeholders together, also advocating for changes in the economic landscape. So I think the advantage is that it's not as siloed as you would maybe see it in the big pharma industry. So I think the interaction and small teams and just bringing the startup and software development mindset to medical tech development is, I think, in itself already, you know, creating faster loops and better connections between the business and the development side.

Yoann - And so, and maybe if I like, phrase the questions differently, you know, when you have a team of, let's say, like tech, I mean, digital, DTX manufacturers, slash developers coming to you and say, look, professor, we want to consider potential implementations, you know, DGAU in the German market and so on, looking at HTA considerations. Is there anything that you wish these teams could have done before coming to you, basically, and trying to understand what's next

from a go-to-market model, from an HTA perspective? Is there, typically, will you see that all these teams will have the right kind of data, for example, the data to support the right research to support also their business plan, or I don't know, if there's anything from your interactions with these teams, more than manufacturer, anything that you wish they had done beforehand?

Sara - 0:23:54 I have is pretty low threshold, but it does, for entry, but it does require companies to prove data security or data safety, patient data safety. There's some hurdles there, which Germany is very big on. interoperability with our health tech infrastructure that we have, and it needs to work with all the systems in place. So if those two things were not considered, then there's no way these products can start.
Then they would need to rework and get these certificates. Also registration as a medical device, class 2A, is a requirement. Those are just hard requirements that if they're not considered, and they cannot be implemented, then the product cannot be launched. The approach that we have, as you know, does not require full clinical validation upon market access. So instead, the manufacturers usually come in with a smaller data set, proving they're either a clinical value of some sort or a process or structural improvement for the health system. But in reality, I think it's 95% or even more are using the clinical value rather than improving the processes. Because I think that's the safer route and the more attractive route for the market.

And so that these data need to be at least you know strongly suggestive of there being a clinical benefit for the product to then be able to you know be on the market and be reimbursed. Then as you know there is a you know one to two years period where the companies are on the market they're also you know they can basically call their own price in certain ranges and then they have to collect clinical data or finalize their clinical studies, which then have to stand the test of both, you know, is this product clinically successful or beneficial enough to then be given access to the market. And then also there's going to be price negotiation or often case arbitration to set the reimbursement price for these products. So it's mainly these regulatory safety things that are hard problems, should have been considered, and then also collecting initial clinical data sets, which typically is not the hugest problem because that's usually a big that's how these projects start often, you know the other regulatory constraints are important.

Yoann - And in that process you just described, looking mostly at the clinical value and the clinical benefits right to the systems and to the patients, what role would these economic considerations play in any of the decisions about go ahead, not go ahead, reimbursement or reimbursement. And so the role that these economic considerations might play today, but also how you see these economic considerations in maybe like five years on the road as we get more and more, hopefully, solutions being available to the patients, to the physicians. How do you foresee these economic considerations playing a role over the next kind of few years, I guess, as a trend.

Sara - 0:27:36 Well, in my opinion, I would see business cases mature and also companies mature. Mostly, I don't know how it is in other markets, you know much better than I do, but it feels like the established companies, so the established players in the healthcare market, like Pharma and MedTech, and even the IT companies, so to say, they're not the biggest players. They're not really entering this business at relevant rates. So it's a very innovative and young business that is playing with these huge market projections. If you attack a market like depression in a bigger European country and you see that patients are waiting for I think 18 to 20 weeks to access a human psychotherapist. I mean there you have a huge opportunity to bring value and then to argue that in a business case. So there is, you know, pharma has very established models on how to prove clinical value and how to demonstrate additional value compared to existing products. And I feel like seeing that a lot of the digital health companies in Germany are accepting, you know, are settling their prices in arbitration, which means it's not really, you know, that the cases they bring today are not as convincing as they should be. So, I think as we mature and we understand that okay, this is the revenue projection which gets more realistic, but we also get more mature in negotiating or arguing for the quality and the impact of the product, I think we will see some adjustment on both the reimbursement price and also the market value projections.

So it would become more and more a bit more like sophistications of the market. Yes, that's what I would assume.

Yoann - 0:29:50 Okay. And if you might have like, let's say, one advice to someone that might kickstart a new concept, a new DTX concept, being clinicians or being engineers, in a way, will not matter much. But what would be your one advice when it comes to the economic considerations that you might suggest him or her that this economic consideration should be or should not maybe taken into consideration? But I don't know what might be your advice to someone about to kickstart a new DTX kind of development when it comes to the potential economic considerations or HTA that might be required in two years down the road?

Sara - 0:30:35 So I think the biggest piece of advice to really solve a problem and because the, so not like I have this idea and it would be nice, but to really look for problems in the current landscape. So to give an example, I don't know how it is in France or in Singapore, but I'm imagining it's the same. We always have very strong cracks when we move from one sector of the health system to the next.
It's a very classic situation is we have a hospital stay and then the person gets released home. Maybe there's not the right infrastructure to receive them. And then by the time they reconnect with their GP things have gotten worse. So that transition time is a huge problem and you know work on things like that or as I said the gap between you know having a diagnosis and getting access to our face-to-face therapy. So really look for problems that exist and then also are connected with as you said an economic value you know avoiding that patients go back to the hospital after 30 days because their depression scores have gone down and they haven't been picked up by anyone that could help them. I think that's one piece of advice. And then, the big hurdle that we see, other than engagement and acceptance by the patients with the tools themselves, that the clinicians or the physicians are the main influences whether or not the product is accepted. To really have a product that can be accepted by the health professionals and also have a concept for them to prescribe it in a way that works and it doesn't overburden them. So always consider the healthcare professionals and how it would fit in their process. I mean, if they only have the typical seven minutes per patient, then they have to spend ten minutes to explain to a patient how to install an app and how to use it, then they have to meet the patient every week and they don't get extra payment. And that, of course, is not helping us getting these products out there.

Yoann - 0:32:45 Exactly. And on that, and this is more like out of curiosity, but now with the DGA could a physician charge for his or her time in terms of like patient on-boarding Is there a cost for that?

Sara - 0:32:57 There is a very very small fee, but since there is not good guidance on how to spend the time I think if the physicians would be more used then it would be sufficient But right now it feels like it's not reimbursing them well.

Yoann - 0:33:15 So there is no, not the extra incentive basically for them to consider these new tools in a way. Maybe one of the last few questions I have here is on the, what, I don't know if you have seen a couple of literature on what they call mini-HTA. So you don't have your full HTA that is done by HTA experts, but there are kind of streamlined HTA versions, what they call like mini HTA, and just looking at kind of assessments of just a few factors and dimensions. Do you see this as a, I don't know if it's a best practice, but will you recommend basically DTX manufacturers slash researchers and clinicians to consider as early as possible some of these tools and frameworks that might help them ensure that they are taking the right steps and decisions towards obviously the clinical value but also the economic considerations. So MiniHTA is just one of these potential tools, but do you see this as kind of a solution or it might be too technical in a way for most of the entrepreneurs out there? I mean, you would probably,

Sara - 0:34:29 I mean, if you look at the big HTA, I don't know specifically what these would entail, but I would probably think they would, they would consider clinical effectiveness and then probably safety as the key component. Yeah. I think it would make sense, coming back to what we discussed before about, you know, sophistication and, you know, creating better arguments for these solutions. And I think it would make sense to start getting into a routine of assessing the value that one creates and also using a framework like this possibly to decide how to move the product along. I think that would be good.

Yoann - 0:35:19 And are you aware of any tools slash frameworks, checklists, whatever could be evidence-based that might help this early stage kind of published or I don't know. I'm not aware so that's why I'm like asking.

Sara - 0:35:47 No, but that doesn't mean that it's not out there. No specific frameworks, no.

Yoann - 0:35:59 And do you see... What I would probably... What probably most manufacturers would do if they wanted to enter our market in Germany, that they would probably look at the requirements in those dimensions that are minimum requirements that are met typically by competitors that have passed over it or that have moved on to permanent acceptance stage and then, you know, backwards develop.

Sara - 0:36:31 So it's almost like having kind of like case studies of, okay, these successful technologies, organizations, you know, they've gone the upwards reimbursement and you can have a reference kind of a case or case studies for these organizations. And to be honest, I mean you know our process, right? But this phase of having one or two years where you can charge, be used as a medical device and not having proved your full clinical value, that causes a lot of criticism among the healthcare providers that feel like, you know, we're putting so much scrutiny on other products that we prescribe, we want to be able to trust that the data is there. So there is, in my opinion, a possibility that this gets more difficult, or this initial play phase may even get removed, and then it has to be, you know, they have to be much more switched on in having these models in place faster, which then again, to your point, means they would need to start working on the much earlier development.

Yoann - 0:37:41 I see. Okay, that's really interesting because, you know, in the industry, let's say, all these like fast track kind of processes, like the one you have in Germany, are perceived to be pretty obviously new, but as really interesting, right, from a DTX kind of manufacturer perspective, because you might not have the next like 15 years to do all your clinical kind of validations, RCTs and so on. But your point is that from more of a provider side, is that, is this good enough, right, and from a safety efficacy, that's some of the concerns that might not help basically from an adoptions standpoint, right?

Sara - So it does dilute the quality, you know, and then you have to argue, yeah, but there are products that are permanently listed and they have proven. Then they say, well, then I'm not going to prescribe anything that's in that in-between phase. So it's, I mean, it's hard to predict because I think it has huge advantages to get products out there fast. And they're also, I mean, level 2A medical devices are not, you know, there's nothing invasive, there's nothing toxic, so it's really, there's not a lot of risks for them to be used. And so I see it as a great route, but as we move up the safety scale with like Nexus 2B, with telemedicine, and a bit more complex medical devices, then there might be a point of saying, hey, we have to have more evidence for them to actually be prescribed to possibly 70 million people.

Yoann – So you will not be surprised if the DIGA gets refined for some of these aspects and evidence required in the next year?

Sara - Yeah. Okay. Because, I mean, I agree with you, it's kind of product category specific, context specific, obviously, efficacy, but the risk into perspective. But I see some of the

organizations, I mean, DTX, going from Germany to France, you know, because now in France we have this new kind of pathway too. And obviously, yes, they have all the level of evidence in the German market and context, and obviously safe and effective, but it's also, you need time to prove the safety and efficacy in a different context. So I guess, and I'm hoping, there are not too much differences between the two markets in terms of the populations. But yet, you still need the additional evidence. So I guess this is some of the products that should be good enough from a provider standpoint, and also maybe the risk that should basically be considered.

Yoann - 0:40:20 But OK, it's interesting to see on how the DIGA and some of these kind of regulatory pathways might evolve over the next couple of years. So, let's see.

Sara - 0:40:31 I mean, from that perspective, it would also be interesting, I don't know if you're aware of the UNETA process on the European level for market access. I mean, I haven't checked in a while, but last year there wasn't much there. If there are specific discussions about, you know, making the regular framework unified work unified for Europe and then having similar standards for this type of new technology because as we see with pharma, maybe with the exception of orphan drugs, it's very difficult to harmonize these very established processes that then feed into local HTA pathways and try to find common ground on the European level.

Yoann - 0:41:13 Yeah, and also, like you, I'm kind of following, but halfway, I would say, and many years of conversations on the HTA specifically, and in view of potential harmonization, standardizations, the challenge is that at the end of the day, you will still go back to your local HTA guidelines and pathways. independently of what we might have at the European level, to get most of our countries on the same page and changing their national guidelines, that will take some time. But this is moving in the right direction for, I mean, obviously, DTX manufacturers, but I guess I'm thinking also about us as a potential patient, right? And that you might want to have access to this solution. Maybe last question, because I'm also conscious of your time. And so we went through all the few things I wanted to discuss with you, Sara. Is there anything else on that topic of DTX and economic value that might need to be demonstrated at some point? And how early stage, kind of more researchers and clinicians, engineers might need to consider some of these considerations. Is there anything else that we have not discussed that you would want to share, or any questions, anything else you want to share on that topic?

Sara - 0:42:38 So maybe one point, or one topic, that we're going to look into in a bit more detail is adherence. So if you look at the funnel, you have your potential patient base, and then you have those actually signing up, getting the product, then you have those, the doctor is convinced, prescribes it, and then the patients actually manage to install it and start working with it, and then after two, three weeks, we see user rates dropping, I mean, this is across apps, and across technical products, and then, working on designing these products in a way that, you know, using the opportunity of making them maybe more personalized, or, you know, focusing on how to get patients back, you know, using all the learnings we have from other technological fields that interact with people, and really getting the patients to stay on the product. And then, because I think that is moving on towards value-based healthcare, and we have payers increasingly asking for, you know, value to actually be delivered, not just therapy to be initiated.
I think that might be a fact that if you are a company, it can say, hey, I understand that there are five reasons why my patients drop off from the app, and this is how I work with it, and this is how I built in measures to get them back online, and to reward them, or to let them start without feeling like they've jumped off or made a mistake, and you just work with these concerns and specifically dedicate time to increasing adherence, I think that's a big factor, at least from what I'm seeing with these technologies.

Interview Transcript with Senna (P8)

Raw Data Prior to Atlas.ti Coding

Yoann - Thanks a lot, Senna. So maybe let's start with the first question to understand a bit more who you are, what's your role, and your involvement when it comes to the DTX, basically, from which stage of the life cycle of DTX are you involved, the nature of your role when it comes to DTX if you don't mind.

Senna - Yes of course, so my work predominantly is in the health systems and policy side of things. When it comes to digital therapeutics, I am more so focused on the implementation and reimbursement side. In the sense that it does come up in my work, but it's not a focal point of the work that I actually use because it comes, so the development of DTX comes in the form of how policies create measures that affect the development of DTX, rather than actually following the lifeline of a DTX, if you will. So for instance, a very concrete example of this is a paper that I wrote two years ago, where I highlighted a number of policies in Australia and Canada that had specific measures on how digital technologies were to be developed and what kind of stakeholder engagement was required at each level of development. So this is kind of my take on the development side of things. In terms of implementation, I mean, implementation of digital therapeutics and health systems is something that I'm interested in and I work on kind of no longer on a day-to-day basis.

Yoann - Could you just share with me some of the key, maybe, some of the gaps, basically, maybe that you have seen, you mentioned about the development of the implementations, some of the gaps that you think that we as a community, I guess, including policy makers, that we should address. policy makers that we should address? And the second part of the question, and you could answer these two questions into one, you mentioned about some of the stakeholders that might need to be involved when it comes to the development, the validations of the implementation. So what are some of the key conclusions or guidelines, basically, from your papers two years ago on that point?

Senna - So, I mean, I would actually point you to another paper that I wrote, published I think July last year in the JMIR on mapping factors that affect the uptake of digital therapeutics in health systems. And in that paper, one of the key kind of points was that the perceptions of both patients and health professionals and of other stakeholders as well actually that were less prominently named. They are very, very important because this kind of goes back to the stylistic difference of digital therapeutics as opposed to biomedical interventions is that digital therapeutics require a certain engagement in order to reap the benefits of them, which is not necessarily the case for biomedical therapies. I suppose mental health is the most stylistically similar. And that is even part only parts of mental health. I mean, we're not talking about psych, like medication for psychiatry, for instance, but like the cognitive behavioral therapy or EMDR therapy, you know, stuff like this, this is stylistically more similar to what the digital therapeutic can do, or right now, I suppose, mostly does not exclusively, I mean, there are some very good examples for instance in, what is it, in a chronic management of chronic conditions, especially diabetes, where there are some very nice digital therapeutics that automate the release of insulin and all that stuff. Anyway, the point is that there is a stylistic difference, and it requires participation, it requires trust, and this paper that I published, there we talked a lot about stakeholder participation, we talked about the need to have patients engaged, the need to have health professionals engaged, but I've come to realize, as opposed to what I wrote in that paper, is that when we talk about patients and health professionals, we're already too late. There's an upcoming paper, hopefully in the next couple months that I can share with you, that talks about patient engagement and using their health data. And the point kind of spans with digital therapeutics as well, is that by the time that we get to the patients and the professionals that we're too late. We need to engage citizens in their healthiest state so that they're sensitized for the eventuality that they become patients. And I think this is a factor that is very much underrepresented in current development policies, in

current, even guidelines doesn't have to be hard policy, but in the current lifeline of a digital therapeutics, we only think about, well, the health professionals has to accept them. The patients have to accept them. But there is a shift in patients. I'm relatively young. When I look at my father, for instance, he and I share nothing when it comes to digital competence in terms of ability. Well, we can both navigate a computer, but the level of comfort to work with digital technologies is vastly different. But both of our perspectives in our healthy states are important to dictate what a diminished version of that capacity is capable of in a ill state, if that makes sense. Makes sense, yeah. And I think this is where involving patients is great, obviously. Involving health professionals, great. But let's also acknowledge the fact that patients of today are not the same as patients of tomorrow, are not the same as patients from yesterday. So we need that healthy voice as well. Because a, I mean, this might sound a bit condescending, but there is the argument that a healthy person can offer different insights or maybe in some cases more clear-minded insights into their preferences than a patient who is currently being afflicted by a health condition that they want to have treated. In this upcoming paper, I talk about if you are only going to teach a patient how to use their health data by the time they're ill, you've lost them. Because by that time they don't want to learn something, they want to be treated. And the same principle kind of applies to the development of DTX. Obviously we need patients to understand that their needs are met, but we also need healthy professionals to understand that kind of, I suppose from a more longitudinal point of view, that their needs are met across time and geography.

Yoann - I totally agree with you. And you know, in all these different conversations that you had and through your research and the different papers, you know, we talk quite a bit about the clinical impact of what you described, looking at the outcomes, and that's why we are looking also at patient's engagement patients' engagement, adherence, has no compliance in view of delivering these clinical outcomes. So from this conversation that you had, how are the economic value and the factors that might impact the economic value of DTX, how are these considered or not considered by the different stakeholders that you had interacted with? Is it a must? Is it not a must? Is it nice to have? It doesn't matter much? What's your view and also which might reflect the view of these different stakeholders?

Senna - I suppose my view and the view of different stakeholders differ slightly, so I'll try to do justice to both. Stakeholder views, the consensus of stakeholder views is that clinical outcomes are important to measure, and I do agree with that. Clinical outcomes are important to measure. We need to know that what we're actually putting out in the market, what we're developing, and what we're advocating for from a policy lens actually does what it's supposed to do. So there is no, there is no kind of competition there. Where there is a slight deviation, this is I suppose where I take a slightly more holistic lens than many of the HDA experts, I suppose, that I interact with, is that there is the schism where you can either build better DTX that starts, that output better care than the treatment as usual. That's one way of going about it. And I think, of course, we should aim for that wherever possible, right? But in light of the problems of our health system, I don't think that is the right approach, personally. Again, this is where there is a slight deviation. My stance is that DTX need to be non-inferior, not superior, because we don't need better care, we need more good care. And when we then talk about the economic impact of DTX, this is where I suppose I'm trying to poke the bear a bit, because I think if clinical outcomes must be comparable to some extent, like we shouldn't put an inferior product on the market, let's put that out there. Nevertheless, I think that by measuring only clinical outcomes, we do DTX injustice. Because I'm a part of a project called Label to Enable. You might have heard of it. It's a quality standard for health apps. And one of the sentiments during those roundtable discussions was if you measure a fish's ability to climb a tree it will forever think it's stupid and I think that is exactly what's happening with DTX we're trying to cram it into the existing HTA process which is not built for it because oh sweet irony health systems are drowning so we So we need to be able, it might be an oversimplification of what's going on, but I don't know how to convey it any more clearly. We need to be able to capture the essence of what DTX does, and what DTX does is able not only to reach the strands of community that are typically underrepresented, but it allows a person to reintegrate into their daily life, whether that be education, employment, or just social life more earlier. You can fire them from a hospital, or you can, sorry, discharge, I suppose is the correct terminology,

can discharge them from a hospital and use remote monitoring capabilities of digital health technologies and I suppose even administer certain treatments through digital therapeutics to complete their treatment process. But what we currently don't measure compared to the treatment as usual is what the economic benefits are of discharging someone say a week earlier. We only consider the clinical outcomes but during that time their mental health and well-being can improve because they they are able to reintegrate into the daily life into their society, their financial situation might improve because they might return to employment, especially in countries with less robust employment protection laws. They might be able to return to education and therefore mitigate some of the developmental delays, especially at early age, if that would be possible, if that would be necessary. These are all kind of factors that are so pertinent to digital therapeutics and we talk about them all the time, but for some reason we kind of ignore them when it comes to health technology assessment. And I think this is also why a lot of the economic evaluations that have come out in recent months, I suppose, found that digital therapeutics aren't economically, like, they aren't cost effective. But yeah, of course they're not, because you're only measuring 20% of what they're doing.
Yoann - So, yeah, and once again, I totally agree with you on that point. So do you think that it's a, I'm trying to understand why, why are we having such a such a issue or maybe deficit Because of the HTA framework that, to your point, maybe not been developed for measuring the economic impact of value of a DTX per se. So it's a framework kind of issue with a couple of constraints and deficit. It's maybe from a policy and guidelines standpoint where we don't really define well the kind of economic value that would be expected from a DTX? Is it a combination of both? Is it maybe additional reasons?

Senna - I think it's definitely all of the above. So on the one hand DTX are a newcomer on the block and they need to carve out a space for themselves and that just you know historically by you know theory of market competition they need to prove themselves in a competing market. There is... that's kind of the basic basics of how the market works. But the problem then becomes is that healthcare, as opposed to some other fields, is uniquely change-resistant. We, like, as a culture, I mean, I'm not talking about population and public health, but even there, it's not great.

But healthcare specifically is incredibly change resistant. As a result, I mean, let's take a step back from DTX for a second. Let's look at patient reported outcomes and experiences, pros and cons. We've been working nearly 20 years, especially in large parts of Europe, to get these things implemented to no avail. Why? Because clinicians don't want to. Because there is a lot of resistance to actually start using these things, even though their benefits are clear. But it's a matter of perception. It's a matter of getting people convinced that it is useful. And this is kind of as simple as getting someone to fill out a couple questions on their patient reported experience and outcomes. DTX kind of exacerbates those problems to the nth degree because suddenly engagement becomes not a side question to treatment but engagement becomes treatment and I And I suppose this kind of build, this becomes a two-sided problem where health professionals are resistant to do it, patients are not incentivized to do it, and maybe are in some, in a good amount of cases, not informed how to do it.

And I suppose that's a bilateral relationship. If patients really want to, they can incentivize the health professional, the health professional really wants to, they can inform the patients. I don't know where the chicken and egg lies there, but there's both are relevant. But at a policy level as well, there is nothing advocating for the inclusion of patient reported outcomes. Even in the upcoming European health data space, it's not fair as far as I can tell. Whereas quite honestly you know you have an electronic health record system how easy is it to have a standardized form pop up or an email being sent from that system saying hey would you mind filling out these questions to kind of enrich your treatment trajectory or can you review your treatment trajectory or however you want to put it. It can be completely automated with no additional burden to health professionals, but because health professionals oftentimes don't see the value of prems and proms, they won't use it. With digital therapeutics, that's not just a health professional problem, that is a problem of all. And there needs to be, I mean I'm beating an old drum when I say there needs to be capacity building. And I suppose the paper, the implementation framework paper that

I mentioned earlier, it kind of goes into that. It also highlights some policy models or some policy factors such as having a sandbox where people can gain experience.

Because that is the other part of this all, right? Digital health, kind of as an umbrella concept, only shows its value after you've used it. Yeah. Which is counterintuitive. So you can only convince someone to use it after they've used it. And I don't have a solution for you there, but it's paradoxical and we should probably look at that as to how to go about that. And it kind of all loops back around to trust. We need, I mean, trust in medicine. I hate to bring COVID into this, but COVID has done a number on trust in science, trust in medicine. And part of what we're experiencing, aside from the fact that healthcare is uniquely hesitant already, is also a kind of population level kind of like, oh my, there's this new type of health care, we had a new type of vaccine that got an immense backlash, there's a new type of health care, yeah let's see about that.

Yoann - And you know, you mentioned about the importance of the kind of buying of vaccine from the clinicians on some of these whatever is probes or whatever is the new systems, new technologies and so on. And what we see is that in some of our conversations with like policy makers and even for grants, grants, you know, when you want to apply for grants, they will ask you now, they can have some sort of like economic impact that your digital therapeutics or digital health might have. So it's just like high level, but it kind of force you as a scientist, as a researcher, as clinicians, to kind of to think early about this kind of economic impact kind of considerations. So back to your the clinicians, like, what will it take to, for them, let's say, if we focus two minutes on the clinicians, what will it take for them to be slightly more aware of the importance of such technologies, not only to be safe and effective, but also to not come with additional costs. Because at some points, you know, like, it might be the best tech, but if it comes, which is like, we don't have much budget, we don't have much resources. And these economic considerations are becoming more and more important, right? So what will it take for our clinicians to, yes, slightly be more aware of the importance of this economic value through and thinking about these considerations through the clinical validation stage, maybe?

Senna - I mean, it's a good question. And I suppose clinical validation is one thing. Because, I mean, we talk about economic value at two different levels here. On the one hand, it reflects the economic impact of a clinician having to make sure that they're able to prescribe the DTX, you know, whether that be licensing fees, whether it be purchasing the necessary hardware, the necessary software, however, you know, there's a whole kind of thing going there. So it has an economic impact at the delivery stage, but I think what we're, or what, not necessarily you and I, but kind of in the valuation community, what we're in, like, almost accidentally doing, is we're trying to compare the cost impact of a clinician with a societal return of investment. So we say, okay, great, if something costs 100 euros, dollars, whatever the Singaporean currency is That's great. And if that return if the return is 150 Great, but the return is not 150 for the clinician The return is societally. Yeah, but the clinician still has to pay the hundred. Hmm, so this kind of goes back to Again, I don't have an answer for you there.

But it goes back to how I think financing of clinicians under certain health systems needs to be modified. And this is also where part of insurance comes in. So for instance, I suppose that the English NHS has easier pickings because it's all national level. I mean, yes, they have their integrated care boards, or perhaps Germany is an even better example where they have the social health insurance fund. The moment that that fund has a digital therapeutic, all public health professional, all public primary care professionals, let's put it that way, they can prescribe it. Therefore, there isn't really any costs in terms of they don't have to purchase the license. That happens at the insurance level that the doctors are affiliated with, which kind of cost pooling becomes the number. Even the Netherlands had a particular incentive, I think last year, maybe even this year, I don't know if they continued it, where they allowed insurers and health professionals, might be insurers. But basically, at the delivery side, they allowed a number of stakeholders to pool together their funds to mitigate the cost, the immediate cost, in fact, of purchasing the hardware and software, as to kind of make it more appealing to invest into these

digital solutions, I think partially because we don't know the societal impact beyond the clinical level, exactly. And I don't think we, and it's quite unfortunate, but we don't, I don't think we know how to really fully measure and assess the long-term impact of the DTX, and which is really unfortunate because, back to your point about diabetes and so on, I think it's like the value economic as well as clinical of a DTX is not in the first one month, but is in the lifetime of the chronic disease of the patient, right? Maybe like in the 10 and 15 years. But anyway, it's a different, slightly different topic.

Yoann - I wanted to ask you, you know, there are a couple, like back to the questions about the framework, recently over the last kind of two years plus, there are new frameworks that have tried to address, you know, some of the challenges that we have seen with the more traditional HTAs, and there are some like mini HTAs that you could kind of apply as early as possible, I guess, in the tech development. Are you aware of some of this framework and have you heard any kind of approaches kind of at a baseline what they're trying to do.

Senna - And I do think that there is something there. I won't go into great detail because again, I'm fully read into it, but from the parts that I've seen, they do fall into the same fallacy of trying to measure the ability to climb a tree when the tree is only a stump, you know, instead of a full-blown tree. Great.
But it's still measuring only a fraction of what's going on. No, I don't want to be too specific, I will call them things. So what are the few things that we should basically assess, let's say when it comes to the tech development, and what are the additional ones, maybe different, maybe coming from a different perspective that we should kind of maybe assess when it comes to the clinical validations, and that all of them, that might impact the economic value of the DTX.

Yoann -How will you approach trying to look at these considerations as early as possible?

Senna - So from a tech perspective, I think that's really interesting because getting, I mean we talk about scientific boards, I agree Project has a scientific advisory board, but what about a citizen advisory board? I don't hear that ever. And I think that is as important if not more important where you pick a random selection of 15 people off the street. Not literally. But yeah, you pretty much grab an equally weighted number of people as are in your scientific advisory board. And you treat them exactly the same. Whatever the scientific advisory board does, the citizen advisory board also does. It's not necessarily a tech, as in, this is what I would do technologically, because I'm not an engineer. I have no idea. I don't have the first clue about how to go about that. But kind of making sure that the technology succeeds, you have in your scientific advisory board where you have your health professionals, your patients, your, you know, the usual suspects, I suppose. That part works great. But let's expand it, let's give it a counterweight and include the general citizens as well. And you have some joint sessions, you have some separate sessions, and you're able to provide a much broader view in terms of you know what's going on during the development. Now in terms of what things need to be done from a I suppose more policy lens I guess or HTA lens or whatnot I think cross-pollination is the name of the game because you know measuring economic productivity or measuring productivity is a concept new to health, but not at all new to the field of economics. I think having more kind of, I think having more exchanges with other fields such as even humanities, understanding cultural differences or cultural components much, much better within, you know, will help the uptake of DTX and the evaluation of DTX. For instance, there is a startup, sorry, there's a startup in London called Talatrive, I think it is, who focuses on culturally competent care. And that, I mean, it's not a DTX, but the principle of giving health care, where the kind of cultural biases, and I don't mean bias in a negative way, but just the cultural perceptions of someone's, you know, lived experience are being taken into consideration have a much higher degree of retention than kind of a blanket statement CBT trajectory, for instance. I suppose including these parts, these components, even so much as imposing them from a regulatory paradigm that this needs to be considered is a big step forward. Now that is the humanities aspect, the economic aspect, which is to find indicators by which we can measure this social impact. You know, all right, someone is discharged a week early, we can monitor them in their own environments. Okay, does that have consequence within that week?

Does that have consequences in the following month? Does that have consequence six months later? And to your point about chronic conditions 10 to 50 years, sure. I mean, once our data longitudinally actually spans long enough, we can do those types of analyses. But we can't if we don't start thinking about the indicators now, because we need to start collecting data now to actually get to that point. And you know, we discussed about the economic impact, but I think it might be great to define what we mean by that, or maybe by impact slash and economic impact specifically. You mentioned earlier, and so I want to ask you basically, how will you define the potential economic impact of the DTX to, let's say, a system, self-care systems?

Yoann - 0:42:21 So you mentioned earlier a few points looking at engagement, looking at the productivity, looking at maybe some additional cost savings or cost avoidance such as what if we can discharge a patient like a week earlier, there is a huge cost savings of assistance, how do we capture that, anything else that you would want to hide in these definitions of the economic impact for digital therapeutics? Economic, I mean it's really broad which is you know hence the side that I made earlier. So I suppose at baseline it is cost impact you know like at the very very before treatment even starts is how much does it cost to actually use the data? How much does it cost the patient? How much does it cost the health professional? How much does it cost the health system? Health insurer I suppose. You know how much what is the development cost although depending on the country of course this all has to be contextualized within a country setting within you know developing something in Myanmar has a vastly different cost associated than developing something in the United States. So it does need to be kind of... I think the name is purchasing power parity. It needs to be able to be compared across time and location. At baseline, there is that, but kind of the economic impact.

Senna - 0:44:00 So I would say financial impact is a subset of economic impact. The economic impact is more of a discussion on how a DTX can positively affect the economic determinants of health, the commercial and economic determinants of health. Financial literacy, not so much, but kind of financial stability is one.

How does DTX, I suppose financial stability is the most easily digestible one. How does, you know, can you only get access to the DTX by means of paying for it yourself, which might lead venture into the field of catastrophic health expenditures if left unchecked. But at the same time, that is in the input stage and the output stage, how much income is a person able to regain within an estimated period of time due to the fact that either they're monitoring happens automatically and they can have longer follow-up monitoring Not really an additional cost or at a small additional cost of that offset each other or how much Economic How much financial gains can they have? By re-entering into the workforce earlier again in interaction with the employment protection laws. This is an embryonic field. I will admit that. I don't have a very clear, a very clear goal, which is also part of the problem why we focus on clinical impacts so much. Why we have a lot of trouble moving away from it. Because the concept of commercial and economic determinants of health, both inward input and output is pretty novel and it's only been picking up speed in the last year or two. But that doesn't mean that we should shy away from it. It only means that the work is a lot more conceptual still and not as readily available. But honestly, in my opinion, a bad indicator right now is the starting point to getting to a good indicator later. So even if you say, okay, look, we just measure how many, you know, time to, instead of kind of time to time of admission to the time of discharge, we have time of discharge to return of employment as an indicator. It's not a great indicator, I know it's going to be replaced. But as a kind of embryonic indicator, it will show us more than we know already.

Yoann - 0:46:51 Right, initial proxy. And you know, we were sharing the results of the current study that you're working on, but you mentioned about, for example, the financial stability and some of this determinant. How important would, let's say, if we take financial stability or some of them in this, that would define the access or not of someone like you and I as a patient to a DTX, how important are these considerations from your experience?

Senna - Well, that is going to be incredibly context-specific. And this is where I would advocate very much for a preference study or a study of relative importance. Because, for instance, I mean, I hate to use the United States, but it's just a really good example. In the United States, there is very poor employment protection for a good part of the population, so return to workforce there is probably ranked incredibly high, whereas in the Netherlands, we have proper, we have one of the best employment protections, I want to say, on the planet. So that return might, you know, we would rather spend another week at home. And we're like, oh yeah, but we are taken care of. You know, we have a safety net. So I suppose what you might find is that it's inversely proportional to the safety net that is available, which is interesting, because that does give some level of indication as to what particular DTX should focus on within different countries. Nevertheless, I mean, I can only give you a speculative answer. And I do think that this is, yeah, we need to ask the citizens this. What do you find more important?

Yoann - Yeah, right. No, I agree. This is where that citizen panel comes in. At the end of the day, it's a context-specific thing here. You know, and that's maybe my last question, but in many of the conversations, and this is one of the assumptions we are working on, I didn't want to share this with you, but it's not going to be a big surprise to you. But definitely, it seems that most of the researchers, like engineers and the researchers working on the development of the technologies, they do not consider some of the cost considerations and some of the factors that we know would impact your HTA and the economic value of your DT etc. And in the second paper that we are going to publish soon, we see a clear gap on how researchers, such as the engineers, how do they value and consider some of these factors versus industry or let's say policy makers. And there is a huge gap. So how do you explain that this group of stakeholders working on the tech development, they do not consider some of these important cost considerations? What are some of the assumptions that you might have on that to explain this?

Senna - 50:13 That's a good question. I've been to a number of AI conferences lately, AI and health conferences, and what I saw there is that if developers hate one thing, it's regulation, because they just want to build things. That is an oversimplification and a pretty interesting stereotype, isn't it? You know, developers want to build things. I mean, I'm a researcher. I want to analyze things. Like, I know better, you know, it's just different. But, nevertheless, if your prime concern is not, you know, we need to make this usable, but rather I want to build a fun thing, that is a Fundamentally different starting point with which you employ because you just want to make the most You know, you just want to make the most pretty thing that you could possibly come. Hmm You don't care, you know I wonder if you want to make the most aesthetic for it you've ever seen me don't you don't care that you can't eat soup with it Again it's an oversimplification, but it does help to bring the point home of we don't you know developers are, to the experience that I've had, are uniquely desensitized to the context that they're developing something for. They just want to develop something, which means that the ask is actually in the one giving the assignment. Because I don't think you can change the developers per se. And also, I don't blame the developers per se, but I think they need much clearer instructions. Maybe, I don't want to go as far as to say a guidebook, but for the sake of the argument, let's say so.

Instead of, I want to have a DTX for, I'm going to stick with mental health because that's one of my fields of interest, I want to have a DTX that is fitting for to complement treatment of anxiety in the context of Singapore, especially for For non Singaporeans, yeah, you know the the people from Let's say Myanmar or What? Thailand Indonesia Thank you. Yeah, exactly. Because these are migrant workers, assisted migrant workers. Because that requires them, you know, you can make a very pretty app, but you know, when you say, okay, but a migrant worker from Thailand needs to be able to use it, that already puts a much more kind of more dedicated lens to it. And I think this is where the UK actually has a couple of examples in their early value assessments. They just highlighted a number of priorities that said, all right, look, for digital health technologies, if you focus on these areas, then you're eligible for an early value assessment. And whether the early value assessment is fit for purpose, that's a whole different discussion. Yeah. It's just the mere virtue that a health system imposed prioritization is available. And they might even go a bit further and say, okay, but we want an app for this specific community for this region. That's not a

bad thing. Because I think we need to start very, very specific in order to get to the more general stuff.

Yoann - 0:54:00
All about the requirement, basically, definitions, I agree with you. Senna, I'm watching also the time, quite conscious of the time, I don't want to take too much of your time. Is there anything else that we have not discussed on this topic of how do we consider and how do we consider some of this like cost of the economic value of the DTX as early as possible in the overall life cycle of the DTX? Is there anything else that you would want to share or any questions?

Senna - Yes, there is one actually, because we've kind of implicitly touched upon it, but I do think it deserves to be explicitly mentioned and that is the concept of risk. Because when we talk about the valuation and the follow-up to valuation is reimbursement and financing. We touched upon financing a bit. But reimbursement and financing, especially from a health system point of view, they are kind of rooted in the concept of risk mitigation. You want to mitigate the financial and the health risks of an individual by spreading it across the population, which works. It's great. The problem is that as opposed to, again, biomedical treatments, the risk of non-adherence in DTX is kind of proportional to the engagement of the person, if that makes sense. The more the person engaged, the less risk there is that the treatment has no effect. I'm not saying it has the same effect for everybody. But it's more so the fact that at least some, I suppose within the 95% credible interval, I guess, you'll find that effect size. From a reimbursement point of view, it's also a matter of Alright, do we need to? Do we need to? And if so, how do we need to find a way to spread the risk so that the non adherence of the person is not reflected on the costs of the system? So in a way that if I'm prescribed something and I don't adhere to it, great. But then also I carry part of that cost.

And this is where so-called outcome-based, I suppose, maybe not so much value-based, it is a part of value-based healthcare, but this is where outcome-based reimbursement policies can come in. I reimburse proportional to the outcome that I achieve, which incentivizes professionals to make, or to which incentivizes developers to develop apps that actually do something to, so this also partially answers your previous question. If you make the reimbursement, and therefore part of the market uptake contingent on the outcomes that a DTX can achieve within a population, then the market will automatically shift to accommodate that. So this does then, you know, require a proper understanding of exactly what that value is.

Yoann - I agree, you know, like before joining the kind of academia, academic space, I was, I spent two years in insurance. So, yeah, it's all about the risk, risk mitigations, I guess, which is was really, really interesting.

Senna - 0:57:23 But yeah, there's deductible, you know, can we say, OK, great, you know, a DTX costs 100 and will reimburse the full hundred. However, if we notice that by means of validated metrics, mind you, you've only completed 50 percent, we reserve the right to deduct up to, I don't know, 33 percent of the reimbursement. Yeah. As not to say this is not a copayment but it's more of a like it's a it's a reward system for someone getting through the treatment completely and there needs to be a margin like if you miss one session sure we're still gonna reimburse the full thing it can happen but if you if we notice that at some point it just stops or it becomes too patchy, that, you know, then you can start tinkering with the reimbursement mechanism.

And that way, similar to a treatment, like a biomedical treatment, I suppose it could be the same way, it's just that we don't have a way of monitoring whether someone takes all their pills. Here we do have a way to monitor if someone goes through all the steps of a DTX. So suddenly we are unable to do this. The question is whether by policy we need to be able to use health data for insurance purposes. But from a systems perspective, that should... Some countries allow it, some countries don't, but this is a risk protection from the individual that is still there. But if they don't, you know, we don't touch that. However, if they don't, if we prescribe them treatment and they don't take it, then we shouldn't have to pay for it all.

Because the onus is on them to do it. They still can get the full health benefits and be reimbursed for the totality of it, right. But in order to mitigate some of the implementation and some of the functioning costs of DTX within the health system, we need to be able to share this cost across citizens and system.

Yoann - 0:59:52 Yeah, you know, I strongly believe that KPI, KPIs drives behaviors. I don't think, yes, yes. And I think whatever it's patients, clinicians, but I think it's a must. And in theory, it would be great to use whatever data we could get from the DTX from the patients, interactions, or the lack of interactions and so on, towards some sort of like level of coverage, reimbursement and so on. It's quite a stretch, I think, from a data protection, privacy and so on. But I think one of the issues that I have when I look at most of the DTX, I don't know what's the percentage, but most of the DTX today, they don't leverage enough this kind of real-time real-time evidence that they get in terms of data from the patients to really personalize the interventions. I've seen too many DTX that you and I are going to use the DTX and we more or less get the same level of care, interventions, without much localizations, without much personalizations, you know, the time-sensitive type of nudges and reminders and whatever, the activities, interventions. And I think this is where DTX could do much better to be able to really personalize the interventions that it would make it relevant to the patients and that would sustain the engagements of the time. So that's something that, as a DTX manufacturer, they can do easily, right? I mean, obviously insurance would be the next level, from a complexity standpoint, data privacy and so on, but there are already quite a bit that could be done within the existing regulatory context, right? Without crossing any red line, I guess.

Senna - 1:01:33 So allow me to bring you in touch then with this startup on culturally competent care, which is based in Australia, actually. Because I do think that this concept is very important for non-attrition, for adherence, and something that can be, especially with AI-powered GTX, can be included much more feasibly.

Yoann Yeah, what's the name?

Senna - If you build an algorithm, it's called Palitrive, but I'll bring you in touch with their CEO. Okay. I suppose the one who set it all up. She's a delight to talk to, and I think it can offer some really nice insights. Thank you. But to get back to the reimbursement and financing portion of it, there is also a point where we need to acknowledge that it doesn't necessarily mean, you know, someone who does, over the course of three months, you know, someone who uses it every single day versus someone who uses it five times a week. Like, at some point of utilization intensity, if you will, there is a diminishing return. You're not gonna get more out of it than the DTX is able to do. So I think then we need to be able to say, okay, there is an ideal number of uses, that there is a minimum requirement of number of uses, which is probably a little bit less than there, you can derive enough of the effect to warrant full reimbursement. And then, you know, it's, it's a matter of patient engagement, if you want to give everything out of it, you can keep using it, great. I mean, we've already paid for it anyway. But if circumstances prohibit you for whatever reason to do it, that's fine, that's okay. I would look at it kind of like a, almost like a, what is it, a logistic distribution. You know, there is a, you know, we need to, the cutoff for reimbursement is somewhere at the, somewhere after the, kind of the exponential increase has happened. You know, if someone decides 80% of the total thing is enough, great. But that's still 80%. That's great. But if someone only puts in 40% of the work, yeah, okay, that's a bit of a problem. So we shouldn't interpret this linearly. And I hope that some of my work in the next few years is actually able to do some of this modeling for instance because that would be really really nice to do. I just don't have an idea of how to go about it but overall yeah I mean it's I do think that there is a nonlinear relationship that we need to use the F word to make them fair. Yeah, we are still early in this process, but there's definitely quite a few exciting papers ahead for your team and all the experts in this field. So it's going to be quite interesting.

Yoann - As you said earlier, we are just at the beginning of this journey. So, but thanks a lot, Senna, again, for your time, sharing your experience and expertise on that really important topic. I will keep you updated. Let me stop the recording.

Interview Transcript with Shiva (P9)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:01:32 Could you briefly describe your role part of the lab slash NUS?

Shiva - 0:01:40 My role, well, officially my role is head of clinical trial innovation and senior research fellow. So yeah, but basically my tasks are mainly conducting clinical trials where we test the DTX, specifically Create AI, which is an AI-derived platform for treatment and personalization.
You know, it can be optimization of drug dose or treatment intensity, and it has been tried in cancer immunosuppression, cognitive performance, so it's indication agnostic. Apart from that, we have other more out of the box trials, which would be more, I mean, this is, the curate also, of course, it's an innovation, but then we have also some things related to blockchain and it's these where we try to find, you know, new ways of mixing technologies for the good of clinical trials, and personalization of clinical trials and PAs. I also design clinical trials, and I take care of the regulation, the regulatory procedures.

Yoann - 0:03:04 So, would you see yourself as a researcher? How would you describe it from a title standpoint or not from a hierarchy standpoint, but more as a, yeah, would you describe yourself as a researcher?

Shiva - 0:03:25 Exactly.

Yoann - 0:03:27 Okay. And so you shared about the group of stakeholders that you tend to interact with beyond our team, the Wisdom N1 team?

Shiva - 0:03:46 I interact with physicians, with clinical research coordinators, with institutional review boards and less often with HSA.

Yoann - 0:04:09 And so you said you are involved in kind of the two initial phases of the DTX, the development, but also the validation. What are, from your perspective, what are the kind of key priorities when you think about, okay, we are going to develop a DTX. These are my top two priorities as a researcher involved in these projects. And Sam, when you're looking at the clinical validations, these are my top two priorities. The top two priorities, when the design and the development of a technology, which is a bit more like the tech-driven part of the process. And then when it comes to the clinical validations, again, what are the top two priorities? And if we don't know it's fine, right?

Shiva - 0:05:10 I mean, when designing is probably, you think about the utility of this product. Is it going to be useful? Is there a need for it? Then once you identify the need, is it going to have a real impact? This design, you know, is it going to be, to have, let's say, efficacy?
Mostly efficacy. And then it's going to be, it's going to be adopted by the end user, but the end user can be also physicians or nurses or patients, but is it going to be adopted by the whole ecosystem? So is it going to be useful? Is it going to be adopted? Then is it feasible to deploy it in the system?

Yoann - 0:06:22 And what do you mean, could you kind of break down this feasibility of deployment or deployment feasibility? What are some of the factors that you might consider to give you some sort of like initial indications that yes, potentially we might be able to deploy, to implement this technology because of A, B, and C, or we might have a couple of challenges that could be D, E, and F when it comes to the deployment. How do you assess the deployment feasibility?

Shiva - 0:07:00 Well, I would say that we do it, of course, in collaboration with the physicians and with the medical team. So, in that way, it's easier to know that you are not doing something, you know, that it's irrelevant. Because it's either facilitating their practice, it's helping, you know. Helping them save time and effort, and it's on top of it, it brings value, right? It can be the DTX, either in the way of, you know, more granularity in the data that they get, decentralization, you know, like being able to, let's say, control the status of the patient at their homes, things like that. So, yeah, I think, yeah, I think taking into account the opinion of these people, even from the design, from the design part, let's say, starting from the design.

Yoann - 0:08:27 I see. And you mentioned about interacting with quite a different groups of stakeholders. You also mentioned about this aspect of utility and who is going to use it at the end of the day, right? So when you are exploring these considerations, would the questions of who is going to pay for it at the end of the day, or the questions of business models. Is this something that you discuss or that are part of the conversations with any of these groups of stakeholders? Is this something that would be considered or explored?

Shiva - 0:09:03 Well, at least in my experience in the conversations I've had, it's not like a priority. It's not the main consideration. I mean, during this early phases, it's true that we calculate the costs of conducting the research, that is all. We have a budget and then we know, we have, we need this amount of money for paying, I don't know, the tablets that the patients are going to use, or if we need extra time from a research coordinator, or we need to hire an extra person, these kind of things. So we know that the cost of the research is obviously taken into account. It's reflected in a written agreement. agreement, but then, yeah, in the trials, in the ones I have been part of, there is some costs. Well, it's not like a full cost effective study, but we compare the cost of the experimental treatment with the standard of care, or with the projected standard of care or with the projected standard of care costs in the case that there is no standard of care arm. And then we conduct qualitative analysis which can inform about potential adoption, but it's not like hard numbers about the cost.

Yoann - 0:10:43 And so just to confirm, so part of your clinical validations, you would also look at the cost, how much is it going to cost to deliver the interventions versus what is the standard of care, is what you mentioned, right?

Shiva - 0:10:58 Correct, yes. In the case, for example, of DTX, the cost is mainly, I mean, yeah, you can count on the cost of the hardware, for example, and then the software, well, I don't think we can say that it's, I mean, once it's done, there is no cost to use it.
And then, the cost, I mean, what we have done, for example, in our studies, compare, what would be the cost of delivering, what is the cost of the drug, okay, regular dosing compared to curate dosing. So these are the cases where the drug is very expensive, which sometimes it happens in cancer, then you can save a lot of money.

Yoann - 0:11:53 I see. And just to confirm again, is it fair to say that the cost that you are exploring is only the cost of delivering the intervention, meaning that whatever is the cost of the software, the potential hardware, that you are not looking at what could be the potential cost savings at the systems level. So for example, digital health solutions might be, let's say, more expensive to deliver, but might generate more cost savings versus the standard of care, right? So you purely look at the cost of delivering of implementations, but you don't look at what is going to be the return on investment of the return on such cost. Is it fair to say that?

Shiva - 0:12:40 Is it correct? All right. Yeah. So we look at the cost of just the patients involved in the trial, let's say. And yeah, we don't do any kind of projection beyond that.

Yoann - 0:12:56 I see. And is this like, because you mentioned about HSE also, in any of the conversations that you have with them, is this something that will become part of the conversations about some of the costs or just ensuring that you get some initial data point on

that, on the economics aspects, or so far, not much, basically, to your earlier point. This is maybe not a top priority, basically.

Shiva - 0:13:23 No, we should just say my directions have been basically about, you know, when we need clinical research material or notifications, or, you know, for medical devices that are not registered in Singapore for example or for documents what kind of documents would we need to start yeah you know to start investigating a drug that is not registered for example.

Yoann - 0:14:02 I see. I'll give you maybe two, you know, I'll give you two specific examples of like specific costs that we know are going to impact the economic value. And you tell me if this is some of the factors that you consider when it comes to the tech development or the tech validations. So the first one is on the healthcare resources utilizations, right? So if tomorrow you deploy a technology, you might need nurses, you might need physician's time, so you might need to consume basically healthcare, kind of, HCPs, healthcare professionals. So this might drive quite a bit the potential cost that would be associated with a DTX. So healthcare resource utilization is one. The second one would be, let's say, on patient adherence. You know, whatever technology you might have, whatever it's a drug or digital health, if patients are not compliant, then obviously, they're not going to see the right outcomes, benefits, and then it is not going to drive much cost or cost savings. So these questions of health care resource utilizations and patient adherence, are these two factors, factors that you consider or that the team would consider part of a tech development or the tech validations?

Shiva - 0:15:17 Well, definitely we, yeah, adherence is usually one of the end points in trials. So this is that can give you an idea about, for example, acceptability or, as with other technologies, if they are not going to use it, then it's not. Then about the hiring of the providers, I don't think we have considered how many more people you will need for technologies.

Shiva - 0:16:08 But I think it's because in our case, at least for now, it's still a clinical decision. I mean, it's a clinical decision support system. When there is a human in the loop, it's not purely AI-driven. AI driven. So, yeah, it's been that we assume that for example for QA you need at least one person to do the calculations and then one physician to accept them. But then okay the physician we can take for granted or it would be logical to think that it's going to be there no matter what, right? And every patient will have a physician. Then regarding the person, which are the researcher who is helping with the calculations, yeah, this, well, this is something that we are now talking about, you know, getting doctors, physicians to be more educated in the mathematics of the subject. So maybe in the end, it wouldn't even be necessary to ask. You know, once it's explained and it's easy and fail ever in a fail proof, then in our case, maybe there will be no extra cost. But yeah, in our studies, we don't, as far as I remember, we don't consider this cost.

Yoann - 0:17:43 I see. And you mentioned earlier about the adherence, patient's adherence or participant's adherence. Could you share a bit more on how is this measured or defined? How is it defined? Yeah, I mean, what are some sort of metrics that you are considering to try to get some sort of proxy on the adherence slash compliance of the patients to your solutions? Are you looking at usage on a daily basis, some sort of patterns, analysis, or the number of time the participants would click on a button, or I'm not sure, yeah, what kind of metrics you are.

Shiva - 0:18:27 Yeah, we look for example, data submission. If they have to submit their, you know, their measurements, for example, in blood pressure. So they have to submit that. So that's a way of measuring, like, are they being involved in it? So then that becomes a metric, which I think we call exactly adherence to the protocol.

Yoann - 0:19:02 I see. So it's adherence to the protocol. And you mentioned earlier also that for some of the trials that you are involved with, you look at the usability or you have some qualitative interviews with the patients. Is this where you try to understand also some aspects that will be related to the implementations of the usability? So maybe not about the cost per se, I guess

you're not asking like the willingness to pay, correct me if I'm wrong, but I guess you're not asking about the willingness to pay for a solution, but you would try to explore some of the potential concerns and bias enablers that these participants might have is it is it correct to say that?

Shiva - Yeah, I think it's more related to the To how comfortable they feel How safe they feel right? How much do they trust it? Yeah, concerns with the technology. So then, yeah, concerns with AI, concerns with... So, and this is any kind of stakeholder, right? So patients, doctors, whatever. So yeah, it's not exactly asking them about would you pay for this, no. So it would be indirect, let's say.

Yoann - 0:20:31 And you know on the adherence, you said you're measuring, and sorry I'm doing a bit of back and forth, but on the adherence, so you're tracking adherence, which is the protocols adherence, right, adherence to the protocol. From your experience, how this could be used as a proxy to define what might be the adherence in a real world environment? Is this kind of good enough, kind of indicators, or this will not tell you much, basically, on how patients not in a clinical trial kind of settings might basically be compliant or not to solutions?

Shiva - 0:21:10 I think it can be a good indicator, at least in the case of, for example, the hypertension trial, because the patients are in a setting that is very similar to the real world scenario, I would say, because they are doing a normal life, they are at home, they take the measurements from home. So I think it depends on the type of trial, basically. But I would say it's a fair indicator.

Yoann - 0:21:49 Okay, and I think I just want to highlight this and to make sure I capture this part of the recording. I think the important point you just mentioned is about how you design the trial also, right? I mean, if it's purely in a clinical setting versus if these patients are like already using the solutions at home, I guess you are as close as possible from the design of a trial of what might be a real-world environment, basically, in this clinical trial, right?

Shiva - 0:22:23 Exactly, yes. So if you design it in a way that resembles as much as possible the real world, the real life, then I think the more significant it would be that indicator.

Yoann - 0:22:34 I see. You mentioned the different stakeholders, you know, the clinicians and HSA or patients, having a strong influence in some of the decisions, whatever it's on the tech development or the tech validations, or it's more kind of a consensus among the different stakeholders, or is that purely clinicians driven, whatever the clinicians say, that's the way to go and that's it. What's your experience on that?

Shiva - 0:23:19 Well, in my experience, at least in our platform, in our type of platform, I think the main design comes from the researchers. Then I think it's more in the trial phase, starting from the pilot, where you start to maybe make adjustments to it. But I think it's more maybe logistic adjustments than adjustments to the tool itself.

Yoann - 0:24:05 I see. And I know earlier you mentioned that the cost kind of considerations were maybe not a top priority. Could you explain why? Is this because of the academic kind of settings, you know, non-private environment? Or why would, because maybe we are like hurting the overall life cycle of the tech development or how would you explain that these cost considerations are maybe not a top priority? And maybe because it's not, I don't know.

Shiva - 0:24:42 Yeah, I think that's a main explanation, I think. The academics. It's an academic environment. So, I think in academia we are more like identifying a health problem. And then we found a solution for it and we tested it. But it's not, you know, it's not a commercial mindset I would say. So I don't think that, at least from the start, there is the objective of bringing this to the market as a person, you know? So many projects, I think, end up being like proof of, you know, concept, maybe. But then, when you identify health problem, it is relevant, it can happen to be a

problem. A health problem that creates an excess of expenditure. So maybe indirectly it ends up being a good solution. So you identify health problem, which happens to create the use of resources and if decision makers then become aware of this tool, the first promise, then they will push it forward. They will push it to the next stages. thought, what will it take for the team to be a bit more like implementation driven, and to maybe consider some of these cost considerations on day one, you know, like, you have patients involved, and you have like interactions, like you have a behavioral scientist, you know, part of the team to try to consider some of these more like implementations kind of considerations as early as possible.

Yoann - 0:26:48 What else could you do or could the team do to kind of maybe consider also some of these cost considerations as early as possible? Should we need like additional expertise part of the team? Is additional like KPIs or different mandate or what are your thoughts on that?

Shiva - 0:27:06 Yeah, yeah, I would say we would need, I think we would need, you know, a health economist probably or someone who has been, who has experience, you know. Then I think we would need, you know, like guidelines, guidelines from NUS regarding the first steps of trying to develop a new technology has to comply with this or that. Yeah, and then I think actually the universities is already setting these things in motion because yeah, we do research but we also have a responsibility towards the citizens. And then bringing something material, valuable.

Yoann - 0:28:16 And sorry, I come back to one of my first questions about your role, part of the Institute. You know, when we tend to look at researcher, we look at engineers, so research-engineers or research-clinicians. Sorry for asking you this question, but how could I categorize your role as a researcher? Do you belong to the research-engineers, research-clinicians, research innovators, research regulatory experts?

Shiva - 0:28:45 I don't know, or just researcher? I think of myself as a biomedical researcher. Not engineer, because I'm not an engineer. Biologist by training. So I consider myself a biomed researcher, let's say.

Yoann - 0:29:14
Okay. And maybe for the last questions, I would want to show you something. I'm going to share my screen because I've done a couple of interviews so far, and I just want to get your input. This is a line of your. Do you see my screen? Yeah. So I just want to see if you have any thoughts on that framework, which kind of maybe summarize what we discussed also. So on the top you have the process of any tech from okay we look at the gaps, the patient needs, the product development, you know what are the requirements, we design the product, we create the product, is the validations and then it's the commercialization, right? So some kind of high-level steps. And then you have the engineers, clinicians, patients, market access experts and maybe I should create additional categories. But in gray, what you see is like who is driving or who is involved. So you see that engineers tend to drive the initial part of the process. Maybe we don't have today these requirements that are well defined, taking the different experts into consideration. But you can argue that this is really well defined. I could just had a gray line basically here. Then it's about basically the engineers that drive the first part of the process.
The clinicians, they tend to be involved more and I don't know why this is blue, it should be gray. But the clinicians tend to basically look at the clinical validations. But ideally, and this is not about just wisdom, but it's like, you know, in DTX research in general, that clinicians should be involved in every single part of the process. Patients are somehow involved a bit sometimes up front, but the reality is that they should be involved throughout the process. And the market access experts, you mentioned about health economists earlier, they are not much involved. They come quite late in the picture. But somehow it would be great to have them, such as also HSA maybe and some additional expertise, regulatory experts, to be quite, you know, I mentioned regulator here, should be quite involved early on. What are initial thoughts when you look at this? Is like anything's kind of not correct or anything else that or anything that you would want to kind of modify or that might not represent your understanding of the field or and how I think it's quite accurate.

Shiva - 0:32:12 Yeah I think it's accurate. Yeah? Yeah, right now I can't think of...

Yoann - 0:32:18 Any gaps or... I can't think of any gaps. So you will see yourself as, you know, this is the regulatory aspect, you will see yourself as an expert, as an individual, more in this market access experts, or you think that, because the role that you have is really unique, right? I mean, yes, you are regulatory experts, but I tend to see yourself more as a researcher, like a research engineer, you know, being quite driving basically the overall tech development and validation, right?

Shiva - 0:32:59 Yeah, well, that's because when I came to the team, I was just doing, you know, regulatory stuff. Then later on, I started also, you know, doing research. So yeah, I think I'm in the middle. But now I think at this point I'm more like similar to the engineers. Yeah. Okay. But I agree that market access experts I mean, either as consultants or in some cases, it might be needed to have someone in the team.

Yoann - 0:33:41 And do you think that we do this, like, you know, the requirement definitions, taking these different inputs from the different stakeholders, is this well done as we speak by the different teams involved in the DTX development? Or do you think that there is room for improvement? To define the... Well, I mean, as you have it, it's like...
Shiva - 0:34:05 Basically, according to this figure, nobody is doing it. Correct, correct. I think that's probably... in defining the handbags properly. Yeah, I think it might be true. So this is, I mean, we tried to, I guess, the most similar, the closest we do to this is consulting maybe HSA, but we don't do it very regularly.

Yoann - 0:34:59 I see.

Shiva - 0:35:00 So I think we should definitely, it should become more of a standard.

Yoann - 0:35:08 Yeah, as a team, we do it. But I think what is not clear here on the graph is that this should be the result, the output out of the process. And that process should involve different experts as the market access experts, regulatory experts, and so on.

Shiva - 0:35:32 Today, I think it's done internally. It's really like engineer-driven, more tech requirements without maybe taking these different clinicians and different stakeholders kind of input into considerations to be able to define this design and these requirements and stand out basically. So that's what I might have to modify.

Yoann But thanks, Shiva. I've gone through the different questions and things I wanted to discuss with you. Is there anything else, Ravier, that we have not discussed on these questions of, as a researcher, how could we potentially consider as early as possible the economic impact that a solution might generate down the road? Is there anything else, any questions you have, any clarifications, any experience, anything else that you would want to hide?

Shiva - 0:36:29 I'm not I think, well basically, I think maybe, you know, researchers should have, should complement their, their, you know, their expertise with, with more like economic cost-effective analysis, cost-utility analysis, more and more refined, you know, in-depth studies. I mean, and if there is no time for that, then maybe we should, you know, we should have more of this type of figures. You know, I mean, in the same way as now, medical, the medical field is going to be knowledgeable in AI. I think in Singapore, this is going to be expanded in the university. So medical students are going to have, you know, to study AI, have solid knowledge at least of what everything means and maybe not at the level of programming but whatever. So yeah, maybe we should have more, you know, to understand the economic landscape and have a wider perspective than just what we are doing now.

Yoann - 0:38:24 I see. And from a HSA or Singapore perspective, there is no official guidelines or requirements when it comes to this cost analysis or whatever health technology assessment that should be done and performed for any regulatory approvals, no? Are you aware of anything on that?

Shiva - 0:38:48 I think, so, from what I remember, there isn't. It's basically safety and efficacy.

Interview Transcript with Surya (P10)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:03:00 So maybe the first questions I would want to ask you, Surya, is maybe to understand a bit better your role, your involvement when it comes to interacting with different of different stakeholders that might develop or validate some digital health solutions or DTX, if you could share a bit more about what's your role and when do you basically help and support some of these teams?

Surya - 0:03:25 Yeah, so I mean, I've been involved in these things as a health economics expert, health economics person. So for example, I was on a European Union project called AdLife, which was about developing an app for people with a lot of chronic conditions. So as I recall, heart failure was one of them. And I remember also, also put it into a proposal for UK funding for innovation system funding UK technology board or something like that and that was for pregnant mothers to support their mental health so it was a guided doctor who had this idea for a technology which would automate out of the support that he gave and provide a one-stop shop for young mothers who were experiencing mental health problems. Yeah, so I mean these are a couple of examples and there have been other things which have come my way.

We also used to, when I was previously at the University of Strathclyde, we also used to host the Digital Health Institute, which was Scotland's main digital health hub. It was part of the interdisciplinary university research, part of the management, I guess, of the university interdisciplinary research, health, everything center or whatever it was. So we used to interact with those guys quite a lot and did interesting conversations with them about the financing and business models for digital health solutions generally.

Yoann - 0:05:39 From the few examples you mentioned, will you tend to come in the later part of the process when there is already a solution? Please, go ahead. When there is already a solution, initial kind of concept, whatever, it's a beta version and so on, you come maybe later part of the process to look at the go-to market, business models, the economy considerations? Or will you tend to be involved on day one, from the concept stage, basically in the get-go?

Surya - 0:06:08 I tended to be involved by the later part, because at a certain point, people realize that they have to demonstrate the most effectiveness of their technology, and not when they start thinking about moving in some money. So it's not necessarily the way I would want it because, you know, often I would have questions which I want to ask up front, but I don't normally get that opportunity. You know, I mean, what happens with technologists is that they are driven by passion, right?

Yoann - 0:06:45 So... Correct. And I think, you know, what you said is that you summarized in one sentence exactly what we have seen from a data standpoint and what the researchers basically told us. But you said they come to the realization that they need to maybe demonstrate some sort of like cost effectiveness. What are some of the triggers? At what point would they realize that maybe they have to demonstrate it?

Surya - So having to get external funding is one of the big things that makes people realise that. So then they have to put together a business plan and then they have to tangle with the reimbursement system. And I think that's often a harsh realization for them because, like I say, they're driven by passion and they think that they have this thing which is going to add a lot of value. But then you get into this question of, well, how are you actually going to demonstrate that to someone else? How are you going to, how are you really, really going to market it? I mean, there's also this, I mean, the comparison that I always have at the back of my head is with pharma because, you know, in pharma, pharma doesn't do anything, like, especially big pharma doesn't do anything. They don't move until they have a sense of what the end game is. You know,

they really, really, you know, when they investigate a molecule, they really have an idea of how that's going to go, how that the different ways in which that might play out. And they have a sense of how they're going to realize commercial value from this investment. And a lot of digital health feels much more like a kind of, I don't want to say a kind of hobby thing, but it tends to be like, you know, wow, I have this good idea, you can do this really cool thing, look at this interface, and then, you know, we could do this and that. You know, and then they get a lot further down the development journey before they actually start thinking about what the business plan is.

Yoann - So once again, I totally agree with what you said. You know, in some of the conversations, some of the interviewees mentioned that sometimes academic researcher might need to think a bit more like the private kind of startups where they need to kind of think about the business models, the go-to-market, as on day one. And I just want to confirm, because you mentioned about these examples about pharmas, and I think in a way you are kind of saying the same thing. Are you saying that maybe as academic researchers, I don't know if we should or not, but if we might think slightly more as a pharma trying to understand what might be the potential opportunity on day one, should we get closer to the pharma model?

Surya - So I think digital health will have to get closer to the pharma model. I mean, the thing I find really frustrating with digital health as a space is you can see you can see the potential of the technology because about the technology, you know, because so much of medicine is informational. I give you information, then you give advice back to me, maybe you prescribe a medication, but basically that prescribing medication is just releasing the instruction to someone else to hand the medication to me. It's not that way. It was a complex physical thing. I mean, obviously, there's surgery, you know, which is a whole different story. Most medicines are purely informational transaction, and a lot of the information processing could in principle be done much more efficiently by machine than it could be done by person. I mean, doctors, GPs, bless their souls. You can see they really struggle with all of the information that's available for a single patient. You know, I mean, I could give you examples, you know, from my own personal experience of things which are quite important just aren't picked up because the information isn't structured in a way which makes it easy for people to retrieve it and then, in a way, GPs are very busy. So, you know, there's this huge, huge potential for digital solutions to really improve care and take out the cost from health service delivery, which is, you know, significant significant as a share of the economy. But we don't have the innovation system which is going to deliver that. And the story of Power Mac has been that because of product liability issues, you really have to make sure the technologies are safe. You have to really, really invest in making sure the technologies are safe. A lot of development is making sure that the technologies are safe. And then there's a whole bunch of other costs, which is the marketing costs, which people seem to bother people about. It doesn't really bother me so much, because it is very difficult to sell into healthcare.

It should be difficult to sell into healthcare. It's difficult because you've got sceptical purchasers at the other end and purchasers should be skeptical because they're trying to, I mean one of the things they're trying to do is they're trying to safeguard patients interest. So you have all this cost which goes into developing products which is all making sure that everything checks out. And, you know, no one would invest in a digital technology at that level of intensity because they're not going to see, you know, even if this thing is used, you know, at scale, there still isn't a story about how you realise the returns. And so we're trapped. I do think we're trapped in this kind of weird equilibrium where we have potentially transformative technologies which aren't being developed or maybe they're being coded up and nobody is actually doing all the additional insurance work around them in order to make sure that they're acceptable to the marketplace.

Yoann - 0:14:26 Absolutely.

Surya - 0:14:28 And because of that, I used to talk to Digital Health Institute of Innox and they said, you know, the problem is that the way the way the way the sales side works is that you're

not selling these things as a medical technology, you're selling these things as IT. So you're selling into hospitals IT departments and hospitals IT departments are all concerned about how do I reduce costs. They're not concerned about how do I make life better for patients or how do I improve the efficiency of the organization even. by keeping the business just about taking over without spending too much and whilst avoiding, you know, ransomware attacks and other catastrophic failures. I'm sorry for rambling on about this. I feel I've used up a lot of the interview time. I'm sharing you my slightly ranty opinions.

Yoann - 0:15:29 No, no, no, it's highly relevant, Alex. So please, you can continue if you want. I have a lot of questions for you, but you can continue if you want. It's not an issue.

Surya - 0:15:41 So let's go to your questions and see what that produces.

Yoann - 0:15:44 So, you know, I wanted to maybe follow up on something you said earlier. You mentioned that, you know, so some of the teams might come to you at a related part of a kind of process or stages, and that you wish you could have asked them some questions earlier in the process. What are some of the questions that ideally you would have wanted to have them earlier in the part of the process?

Surya - 0:16:07 Yeah, so normally people have an idea of prevalence. Normally people have an idea of disease prevalence, and that's kind of their starting point. And their starting point is like the maternal mental health problems and then you kind of work out what is the annual birth cohort and of those, so and so, of those how many are going to have mental health problems and going to be customers for this app. So I think, you know, I mean, from the point of view of the School of Public Health, I mean, that's a good public health framing, right?

So we start off with what relation we need, and that's very important. I think there's there's there's a bunch of things that you could add on to to that, though. I think it's. I think it's good to kind of segment the potential market place a little bit more. I think it's nice to think about, you know, who are the people who might be prepared to pay edge of their own pocket if you are able to reach them and how would you market to people who are able to pay out of their own pocket. I think that gives you a sense of what the purely private market might be before you start thinking about marketing through the public system. Because if you can sell to people who are paying for your app privately, then you can build a bit of an evidence base which you can then use to sell into the public system which tends to be a bit more sluggish and a bit more evidence driven. So thinking about that sort of staging, how could I reach out to a smaller market which which I could then use to generate evidence and buzz to reach the larger market. I think that's a thought-provoking question at least. And now, relatedly, I think there is a question for entrepreneurs, which they often haven't thought through about pricing and you know if you if you one of the problems with digital health is that well you're the general issue with a lot of health care you know the marginal the things cost is quite small. So you have to think about how are you going to, and this leads back to the market segmentation, so how are you going to price and what sort of commercial benefit realisation do you have to have to convince someone whom you might want to I think people don't think about risk. And I think that's a common, again, that's something which goes back to, goes back to Pharma, because Pharma is normally very good at thinking about risk. I've had a, I have a friend who's an entrepreneur and I remember asking him, what do you think the probability that your product will fail is? And he said, the probability that my product will fail is zero. Because I will do everything in my power to make it work. And that's okay, but that's like, I mean, it's good that you're driven, but that's not rational, right?

So you have to, and so it's like, you see this with PhD students as well. What do you think the probability is that you will finish your thesis whilst working for a full-time job and starting a family and volunteering as, I don't know, volunteering as like a volunteer constable in the community or something like that. Oh, well, I will certainly finish my thesis, even though I haven't been able to

finish it in the last 10 years. So I think there's a story of it, there's an issue of it thinking of a risk. So I mean, a lot of this is quite, in a way, quite kind of basic, stocked up. But important, right?

Yoann - 0:21:09 And to your point, you mentioned about the segmentations, you mentioned about the pricing and who is going to pay and willingness to pay for solutions you might have. You mentioned about risk. Who might be or who should be responsible to think about these considerations as early as possible? Is this the responsibility of the engineers that will initially come up with the initial concept? Is this the responsibility of the clinicians to even before you go to a clinical trial, you know, trying to demonstrate the efficacy of a treatment or interventions, or who should be responsible for that, or is maybe none of them, I don't know.

Surya - 0:21:53 Well, I think it depends on the organization, so if you are a small company, then everyone has to think about the commercial aspects in some sense. Everyone has to be switched on. If it's a bigger company, then you can afford to the people who are scientists.

Yoann - 0:22:15 Okay. But what about NUS, for example, if you think about an academic research institute?

Surya - 0:22:21 I mean, I think it's a good idea. So I mean, NUS has people who specialize in entrepreneurship. And who can, there's people that teach entrepreneurship. So, you know, I don't want to burden everyone with having to be an expert in everything. But I think it's... I think if people are on a pathway where there is an expectation that they will produce usable technology, it's good for them to have some sort of training in entrepreneurship. A researcher might not take these considerations of market segmentations, about willingness to pay and so on, that early in the process.

Yoann - 0:24:08 How do we explain that? Is it a lack of awareness, knowledge, not having access to the right tools, not having access to the right expertise? Because sometimes you don't know who might help you, or so if you recognize you don't have the expertise. So from your experience, yeah, what's the rationales, how do we explain that, some of these gaps?
Surya - 0:24:11 So I think from the point of view of researchers, so there's one story with researchers and another story with clinicians. So I think with researchers, the story is that during their PhD, because they've come through a PhD, and during the PhD you have been trained that you are a scientist. This is your identity. Your identity is as a scientist. And your objective as a scientist is that you have to publish. So you have to do things which are cool and which the community is going to like. And there's a book by Wilson Bureaucracy, so I'm sorry for the slight digression, Why Do Government Organizations Do What They Do? Something like that. And he has this discussion about the State Department. So why does the State Department? So the State Department apparently, like I said, can't keep any secrets at all. And so the puzzle is, why is this the case? The reason is, is because if you look at the people in the State Department, they are career diplomats. And while they're trained, you have to keep the conversation going at all times. So that's how we select them. We select people who like parties, who like having little meetups, who like trading, like gossip, information. We then tell them, you know, this is your job, your job is to prevent another war. So you have to keep the lines of communication open. And then you take these people and then you say, okay, actually there's things that you can't talk about and things you mustn't talk about. And so what they do is they start to find ways to get around these barriers that you put in place.
And I think we do quite a similar thing with PhD scientists. We say, you know, your job is this and this is your identity and, you know, forget about the market, concentrate on your systematic literature review and identify from that what is the gap. And then they do that and then we say actually yeah that's not all we wanted after all so i i think we do that with i mean i think with clinicians the story is a bit different i think clinicians are trained in a different way i mean for one thing they're very busy, but they are trained to focus on the patient. So they're told your job is to know the patient, understand the patient, listen to the patient, respond to the patient. So they also have their own training and that's what we do in the School of Public Health and NPH.

We spend all our time trying to take clinicians and say actually it's not about the patient, it's about the population and it's about you know the reason that these people are coming to you with you know all sorts of respiratory diseases and elevated blood pressure and diabetes and everything it's because you know they haven't been smoking and taking any exercise for the last 30 years and maybe if he had done something like that earlier on then you know, you wouldn't have to put them on statins and give them inhalers and things like that so I think that's, I think it's a bias of professional training. Sorry, long answer.

Yoann - 0:28:30 No, no, no, but again, it's highly relevant, so definitely really insightful. And to these scientists and clinicians that are about to embark on a new project or that are involved in a tech development validations, and they don't have access to someone like you, or they don't know, what are some of the tools or some of the recommendations you might have for them to minimize the risk that might be involved in the process, or for them to maybe consider slightly more some of these considerations that are going to influence the HTA and the economic benefits of the solutions? Any tools or any recommendations that you would suggest to them?

Surya - 0:29:20 I mean, I think one of the things that's quite effective is if you can get a success story. So if you can get a technology which has been effectively commercialized, which is local. So I mean one of the problems in Singapore is that the market is very small because it's a very small country. So that's one of the things that you have to be thinking about. How are you actually, where are you going to grow and where are you going to develop? In what markets are you going to develop this? So, you know, if you get someone to write a case study or talk through, you know, that development journey and highlight, I think, highlight what can sometimes happen with business cases is that business cases are told as the story of a success. So, you know, we did this and it was fantastic. And then we went on from trial to trial. And I think it's nice to try to write up pieces which have that kind of back and forth, you know, we tried this, it failed, we decided we were going to, you know, to market in the UK and it didn't work and we wasted a whole lot of time. So I think having some sort of case library is quite useful because it's the story of most teaching. You can't teach people, you can make people want, the challenge is to make people want to learn. So, you know, once people want to learn, then they will learn themselves. Yeah. Yeah. And I think, I think, kind of highlighting that there is a path to success, but you have to think through and plan and be prepared to change course if things don't work. I think having some way of communicating that is a good idea.

Yoann - 0:31:54 And you know, so you mentioned about having a kind of a business case and some of its case studies. I've also seen a couple of simplified HTA, mini-HTA. Is this something that you think could be relevant for, again, our scientists and clinicians to be exposed to earlier and without having, obviously, the expertise that you have, but a simplified version as, I don't know.

Surya - 0:32:27 Well, we have some conflict of interest here because, you know, my colleague Billy Wang does HTA and has, you know, a business which is trying to promote early stage HTA. So I'm glad you mentioned it. I think that's a nice idea and I think it is in a way more than the outcome of the early stage HTA, it is about the learning journey. So just encouraging people to, because a lot of what happens with these early stage HTAs is that they are, I mean, actually, because the uncertainties around everything is so big, that, you know, it's really hard to say whether the technology will work or not. You know, but that itself is an insight because that shows you, well, you know, you do have to start thinking about how you're going to buy down some of these uncertainties. Yeah, and a lot of the time the focus is on the technical uncertainties, but the commercial uncertainties, and the technical uncertainties are in a way the things that you can do something about, but the commercial uncertainties are also important as well. So the early stage HTA should incorporate both of these types of uncertainties. And I think as you said, it's a way beyond the output of a process is a way to get the early entrepreneurs, whoever they might be,

clinicians, scientists, but to think about some of these considerations, right? So to get them exposed.

Yoann - 0:34:40 You know, from conversations that are, and this is my last question, Surya, but from some of the conversations that I had with clinicians and researchers, they have, they tend to have a limited understanding or awareness, I should say, about these considerations of cost and cost effectiveness and so on. But I realize that we kind of speak a different language, you know. Your understanding of what is the HTA, what is the cost effectiveness, you know, solutions, they have obviously different interpretations or understanding, but they do consider some of the factors that will be important when you do your HTA assessment, such as a lot of them will consider what is going to be the change of the impact from a workflow standpoint of me having my solutions at a new age, for example, and how many more nurses are in terms of staffing and so on, how this might influence, basically, the adoption of a technology. So it's not about looking at the cost directly, but indirectly we know that the healthcare resources utilizations is one of the driving factors behind the cost effectiveness of a technological solutions. So my question to you and from your experience and the interactions that you have with the different teams, have you seen factors that are indirectly, or maybe without them knowing, but are highly considered towards that economic kind of impact? Or, and considerably, have you seen factors that are not at all considered, but should be considered, because you know that these factors are going to impact the HTA, basically?

Surya - 0:36:23 So, I have a number of thoughts. I mean I think it's good if you didn't come out with a technology which is cost-saving, you know, for society are not always cost-saving for the organization. So, you know, in particular, because organizations, healthcare organizations, tend to build by consultations. So if you make a consultation more efficient by let's say AI note-taking of the consultation then that does indeed save the organization money or by telemedicine video based consultation. That increased from Scottish NHS point of view, we were very happy with that because that did actually increase the productivity of our primary care workforce. But you know one of the problems is that if you dispense with a consultation entirely then that means that for organizations which do make some consultations then you lose a billing opportunity. I think that's one of the reasons why we substituted video or face-to-face quite readily, but it's quite difficult to get to the next step where we substitute AI for human interaction, interaction with a consultation, interaction with a consultant, even if that interaction is the same or better quality. I think that requires a fundamental rethinking about changes to the financial incentives and the reimbursement system. So it will differ in different places depending on the financing arrangements. But I think that's something that is important to bear in mind. Yeah, I also think that, I mean, it's nice to have a cost reduction, you know, rationale, but a lot of the time, especially for doctors, what is really pinch and grabbing is health improvement rationale. So yeah, so if you can improve adherence to medication, then that's not a positive story because you can relatively straightforwardly model through what that would mean in terms of slowing down disease progression and preventing adverse events. If you can evidence those health benefits, if you can evidence statistically significant health improvement, then you can extrapolate that forward. And particularly in the working age population, if you can slow down disease progression, then that means that you can maintain earning capacity for longer. So we're doing a lot of work with National Programme on Precision Medicine, and things which are really attractive from an economic point of view are things like in which you can if you can delay progression of kidney disease so that you push renal replacement therapy to after the age of retirement then you know I think that becomes quite a compelling story. So that's not possible with everything only. I mean, actually, I think one of the things that's kind of underappreciated about digital mental health solutions is that a lot of this is morbidity which affects the working age population and if everybody could be optimally functional at work and not worried about their their kids, their relationship, this bad thing that happened to them 30 years ago, then we probably own much more product.

Yoann - Productivity.

Surya - Yeah.

Yoann - Okay. And so yeah, we did, you know, we did cover all the topics, questions that I had that I wanted to discuss with you, extremely insightful, so thanks a lot, Surya, for that. But you know, on that topic of how clinicians, researchers, engineers, researchers, would consider some of the factors or would not consider some of the factors that might influence the cost-effectiveness of the digital health solutions. Is there anything else that you would want to add that we did not discuss or any specific observations that you would want to share or I don't know, anything else?

Surya - 0:42:25 I think cost-effectiveness is only part of this, part of the story of having a business plan. So, because particularly with digital health technologies, just because with, again, doing the kind of medicines comparison, with medicines, how you sell is often relatively straightforward. So there are, in many countries, you know, HTA agencies which do appraisals of medicines and take a value-based approach and look at the costs and look at the QALYs and, you know, will it set the high price if there is a case that this medicine is delivering a big benefit over comparator. I think it's harder to, you know, often there isn't the, even if you make the same argument and present the same evidence for digital health technology, often there isn't the person there to receive that message and to... and the system to respond and purchase. So I think having, as well as having HTA and having cost-effectiveness analysis, I think it is a good idea to understand the regulatory landscape reimbursement landscape in the different markets in which we're operating. And yeah, I mean, bringing a technology to market is, I'm sure you know this, I mean, so I'm just kind of underscoring it really, but bringing a technology to market is more than just technical exercise and demonstrating cost although having an argument why your technology is cost-effective is obviously a good thing. Who harmed you? Correct. So, yeah, so that was my thought.

Interview Transcript with Santana (P11)

Raw Data Prior to Atlas.ti Coding

For context, Santana requested the interview questions in advance. The transcript therefore contains initial bullet point responses from Santana addressing these questions, followed by the actual interview dialogue.

Santana - Answers to the questions:

1. Could you please describe your role and involvement in the development of DTx or digital health solutions more broadly? Who are the key collaborators you typically work with in this process?
   - As CEO of a DTx company, I was responsible for the overall success of a DTx working together with clinical and technical experts as well as commercial functions
   - As a consultant, I work with CEOs of DTx companies as well as other functions of digital solutions companies

2. How would you define the economic impact of DTx?
   - Impact on costs and benefits of healthcare provision
   - A societal perspective could be taken, which takes into account not only costs and effects on health systems, but also the broader economy => challenge of defining the right endpoints
   - There is a need to translate DTx value elements, such as improved access to high quality care, into methodological frameworks, that capture these effects for health eco evaluations

3. Who is responsible for ensuring digital health solutions deliver economic value, and what role can both tech. and clinical researchers play in this process?
   - Manufacturer, Insurer, Patients, Provider, Policiy Makers
   - Clinical researchers: Optimise trials for DTx and adapt methods (e.g. choice of control group)
   - Tech researchers: Optimise software to maximise engagement; work towards common standards to ensure interoperability

4. From a HTA perspective, considering the potential economic impact of DTx, what BEST PRACTICES have you observed in tech. development and validation by both tech. and clinical researchers?
   - Focus on officially relevant aspects of reimbursement decision makers during RnD, e.g. benefit categories and how they are measured

5. From a HTA perspective, considering the potential economic impact of DTx, what GAPS have you observed in tech. development and validation by both tech. and clinical researchers? What aspects, costs or factors should be considered earlier in the process?
   - Clinicians: integration into the daily workflow of a physician
     - Clinical researchers often are not practicians anymore
     - Tech: not caring about about the final effects of the products
   - Being to much concerned with own field of action and not seeing the bigger picture

6. When a team approaches you for a HTA of a new technology, what do you wish they had done beforehand?
   - High quality evidence about costs and effects relevant to the decision-making body
   - A good understanding of the patient pathway and the standard of care / epidemiology

7. What steps could researchers take earlier to better consider the future economic impact of the technology they're developing?
    - Align with HTA agencies decision making criteria
    - Include HCPs and patients into R'n'D

8. How can researchers and stakeholders involved in DTx development incorporate cost considerations and economic value factors earlier in the process? What tools or knowledge would facilitate this?
    - Costs of standard of care + hypothesis about how new product affects this
    - Knowledge about actual workflows and incentives in practices

9. What challenges do researchers face when integrating economic considerations into the early stages of DTx development and clinical validation?
    - Uncertainty
    - Finding a common language amongst all stakeholders about costs and benefits

Santana - Interview - 0:20:58 Okay, I'll just kind of like maybe walk you through my answers and I'll send you afterwards so that you have the context of it there. And thanks a lot. So question two was how would you define the economic impact of DTX?

My first thought was, you know, it's for me so specific to DTX on that level. Yes, the economic impact for me would be the question for any new health technology, you know. And so that very broad, I guess the first there is, you know, the impact on costs and benefits on healthcare provision. So that would be a healthcare systems point or two. review as well that some evaluations consider it, the societal perspective. That would be another way of looking at the economic impact, so not only at the you know cost and benefits to the healthcare system, but of a broader economy. But I think there you have the challenge of defining the right endpoints.

So in terms of benefits, when you say quality adjusted life years, I guess that it's kind of, it's broader than a sheer medical end point, of course, but still it's maybe not what we as a society aim for, right? And it might be different for different societies, right? For some, they have a happiness index already as kind of like a principle guiding their policies, and you know most of us or most Western countries I guess for them is really GDP. So not so much actually looking at the benefits, so there is no operationalization. So and then there is the in-between I guess yeah where we say okay we're actually taking the health economic approach, costs and you know benefits measured by qualities and then costs maybe we kind of add something like presentism or absenteeism, so the impact on the labor market.

But to my opinion, that's kind of like a bit hybrid already. Because you not only have the system, but you not only associate the perspective as well, which my old professor, he's now actually evaluated how far you should consider environmental impacts as well. I mean, you can make it really, really bad.
So that's from a high level. And then the DTX specific pitch for me is, how can we find methods to kind of translate some of the DTX effects that standard drugs don't have into costs or benefits. So for me, always a good example is, you know, access. So how can we, for example, find a good method of attributing this increased access to, you know, costs and or benefits? And I think for me that's, and that's, you know, you're the question, but that's part of it for me anyway. So, so that's all. That was a lot of talking.

Yoann - 0:24:03 No, no, no, it's perfect. And again, thanks a lot for taking the time to put your thought together and already answering the question. I really appreciate it, Santana.

Santana - 0:24:14 Pleasure, pleasure, really. For me, I'm passionate about this, so it's fun. Okay, so then question three was about, you know, who's responsible for ensuring that economic value? And I think in general, you know, all the stakeholders, all this have some part in it, right?

There's the manufacturers, of course, when, you know, designing the product, there's insurers when thinking about, you know, policies to, you know communicating the existence of those products to their policyholders and you know to the broader societies. Obviously, patients you know they have a responsibility as well because it's not a drug I mean you can't just pop it you have to use it for providers obviously. So for me at the end of the day you know every stakeholder has some responsibility but you were specifically asking them about tech and clinical researchers and you see what I mean. Here I was thinking about clinical trials, especially. And there for me the answer was that we still have some methodological uncertainties around how we design trials for DTX. So for me a good example again is always the control group. So is waiting list or is it a sham? What's a good sham? How concrete can it be without having an effect? So I think there we still don't have good methods to ensure that we actually measuring only the effect and we don't under or overestimate it.
I mean, we'll always, but I guess, you know, that there has to be some research being done on, you know, to understand what the effects of different choices are. I think that's for me what, yeah, when I thought about the clinical researchers.

And when I thought about tech, I remembered my time at MSense when I was working with the tech team. And there for me, it was two things, and actually it's a third thing, which is not here. So the first is make it easy for patients to use the product, so really think about how to optimize it for patient engagement, kind of like gamification, all these things. That's the first thing, and then the second thing is I feel like tech researchers could play a more active part in working towards harmonization of technological standards and we have the snow in the city and the fire, and the way the snow in the city is not so much the tech, but you know what I mean, you have these frameworks already, and I feel like tech research could actually contribute more, because at least in Germany I feel that the discussion is in silos a bit, and tech researchers seem to be not much included. Yes, yeah, that was that for question three.

Yoann - Yeah, I think that these questions, I mean, your answer to these questions, I think it reflects the complexity of the ecosystems and how the different stakeholders from the patients to the clinicians to the tech provider, we all have a role to play and to contribute and to influence the economic value of the DTx, right?

Santana - So it's a ecosystems kind of driven approach that is required. So I think you did capture that really well, yeah. Because even if you have a product that in theory, you know, delivers economic value, it has to be actually delivered, you know? So it has to be prescribed, patients have to use it, so, and there I think, like you say, it's an ecosystem, like all players have to contribute to that, but yeah, that's the facts of it, of course. Yeah, so for question four, I guess that's, I wouldn't say narcissist, but that's what I did with MSAPS.

So the tech team, I really, kind of from the beginning, made them aware of what are reversement decision makers, HTAG, what are they looking for? What's the kind of metrics that they will jump the product by? So that the tech team actually really understood it's not about building a product, it's about building a product, yes, but about building a product that then is appreciated by the HTA body, so I think, yeah, so I think that was one best practice that I for myself implemented in the company is that we frequently talked about this.

When we talked about product development, the frequent asked question was, so how does that impact actual medical benefit? So how does that impact even like a specific category that we know the decision maker will consider in the decision making process? So I think that's something that's really useful in aligning everybody to the final goal, which is not only having a product, but having a product reimbursed in the market that is used by all these stakeholders that we talked about.

Yoann- And do you see this like, we see this is a best practice, but do you see this happening more often these days where some of these considerations are taken into considerations early on

in the tech development process or it's unfortunately just in a few institute, few organizations and we are not yet there.

Santana - So I can only speak for the German market in that respect. And there I would say yes. So I think the new companies, new startups, from the beginning, they think about what does VFRM actually want from us. So yeah, so I think in Germany I would say, and I know some of these startups, they then work with agencies to support them through the application process and I know a bit how they do it. And so I think that for Germany, I can say yes. So I think for the DIGA market, there has been a learning about how to approach this.

Yoann - Which is maybe, and Germany was the first market to have this DIGA and fast track processes and so on. But I think it maybe it kind of increased the level of awareness, right? When in most countries you don't even know or it's a bit like you kind of struggle to understand what might be some of the requirements. And obviously it's really difficult to take such requirements to considerations, right?

Santana - So, and this is again coming back to question four, three actually, right? It's also the responsibility of the decision-making body to actually clearly communicate what do they want, what do they accept. So, HelloVeta, I think, was the first company who applied under the PECAN and they got rejected. So, I talked to them, you know, in Amsterdam, actually, at the Health Europe, and they were super confident, you know, they were like, okay, you know, it seems like we've done what we were supposed to do. And so, and I think that maybe is related to that as well, that maybe it wasn't that clear what they actually had to provide. And I don't know, but it could be one of the reasons.

Yoann - 0:31:50 Yeah, and I saw also, and I was really surprised, and it's also back to the scalability and how do you bring one solution in a market, let's say like from Germany to France, and it's not so straightforward. And obviously their examples kind of demonstrate the complexity of just like going in a new market with more or less the same clinical trials and the same kind of evidence, right? So, yeah.
Santana - 0:32:11 Yeah, yeah, yeah, exactly. And then there's, yeah, that's a good point too. Yeah, exactly. So gaps, and I kind of mentioned it earlier, I think from a clinician point of view, and that's what I meant I was thinking about you know set up of clinicians that are actually not clinicians anymore but that work in offices basically and there my experience is just that sometimes they don't have actually the kind of practical implementations in their head you know they're they are physicians yeah in that sense so they know about you know the human body and all these things but they don't know about the processes you know in an outpatient practice and so they don't really yeah consider that yeah which you would think you would think okay it's physician they know our physician things in practice but maybe not be good well maybe they started medicine but then became researchers and I'm more concerned with but that's just maybe a very specific perspective of mine. I don't know if it's representative.

And then for tech, it's kind of like the opposite of what I said earlier. I think often it's the case that tech teams don't care so much about the final effect in terms of what the product actually does for society, but more they have their product backlog, and their scrum team, and they kind of like work through their work packages. And yeah, so I think, yeah, that's what I meant there. I think this question, I didn't quite understand.

Yoann - 0:33:51 So for Six, what I had in mind is that basically what I realized, as you mentioned earlier, I think we all speak kind of a different language, right? So what economic value might mean to you versus myself or clinicians might be quite, quite different. And what I realized through the conversations is that when you talk to the clinicians, they don't really consider the economic value of any solutions. But then, but when you go a bit deeper and you realize that they do indirectly, like what might be the additional manpower, or healthcare resources utilization, how it's going to change the workflow, you know? And all of this productivity and efficiency are some

factors that are going to influence the economic value of your digital therapeutics, right? So they do take into consideration some of the factors, but not from their perspective. They all kind of, it's just like back to, we all speak a different language, but at the end of the day, indirectly, they do consider some of these aspects. So here, what I heard often is about productivity, is about workflow, improvement, healthcare resources, utilizations, and that's what they are referring to when we are talking about economic value, basically.

Santana - 0:35:12 Got it. Yeah. Okay. Yeah. Okay. So it's about how you're trained as well, I guess, right? What kind of frameworks and concepts you associate with these phenomena that you observe. Correct. And then, yeah, yeah. So all good on that. So, yeah. Maybe I'll jump to seven. Yeah.
Okay. Well, I mean, this is, if I'm in the wish land, yeah, if I can wish, I would hope that they had high-quality evidence about cost and effects that are actually relevant for the decision-maker by the making body. That would be the ideal scenario. But I'm not sure if that's kind of a…

Yoann - Yes, I guess it's like, what would be the kind of good enough that you would expect? I'll give you an example. In one of the conversations that I had, someone was saying, at least I would want these teams, researchers, clinicians, to come up with a well-defined list of costs. You might not have done your HTA because you're not an expert. You might not know what is a cost effectiveness, but having a minimum understanding of all the different costs that will impact the implementations or the cost that might be required in terms of deployment, in terms of implementations, maybe additional headcounts. At least having this understanding is kind of a bare minimum that you should have when you come to see an HTA expert, basically. But this is just one of the examples that was mentioned, basically.

Santana - 0:36:48 Yeah, I got it. Yeah. Yeah, so it's about a minimum kind of information. Yeah. Yeah, so maybe I would add also like a good understanding of the actual patient pathway. And I think that's the most basic because without that you can't even think about the other ones. So I think that's important. Without that, yeah, I mean, that's just ludicrous, that because then you don't talk about the…Yeah, and I think this is the, yes, is one of the most basics, but the most important, and an example that I get often on that one is also in terms of like, just like, traditional market research, understanding the size of the opportunity, you know, your total market that you can address, what is kind of a market share you might get and penetrations and so on. And I think this is what's kind of like, it's more, I don't know, it's more on the business side of things, but I think having such segmentations and market research, it's also important.

I mean you know what's the care but also like the pros and cons of different decisions there yeah yeah that would be the basis yeah yeah what's up for visit to yeah okay so this is kind of basically repeating what I did so I think it's really about you know aligning early on with the HTA agency's decision-making bodies about the decision-making criteria, that is with respect to the reimbursement generally, but then also include, and that is kind of like also the insights from the rapid review, really include patients and HCPs in the product development systematically. Because, yeah, even if in theory you can deliver this economic value, it doesn't help if providers for some reason don't prescribe it and the patients don't use it. So yeah, so that's what I thought about here. Yeah, so this is kind of related to seven here. So it's a cause of the standard of care, but also good hypotheses about how the new product affects this. And yeah, knowledge about the actual workflow, the patient pathway. Yeah. And yeah, so uncertainty is the only one that came to mind instantly. But another one that just popped up during our discussion is this different perspective of different stakeholders, like finding a coming language amongst all stakeholders about Boston's benefits.

Yoann - 0:39:55 I wanted to ask you, you know, there have been a couple of publications on what they call a mini, mini HTA that could be considered early on in the overall kind of life cycle of the digital tablets. What's your view on that? Is this something that as a framework, as a tool that could be considered early on by the researchers, or you still need to have the expertise to be able

to conduct such like streamlined versions of a full HTA or relevant, not so relevant, why not, too early on, I don't know.

Santana - 0:40:31 I think it might be, and I'll just stop, I'll send it to you, I think it might be a bit too early for real HTA in the sense that you probably wouldn't know the actual effects at this point of the new product right so you couldn't really think about all the consequences but what you really could do is have a proper understanding of the standard of care right and then think in hypotheses about you know if the product had this effect or that feature how that would then influence the yeah the cost and effect so I think for me yeah it would be more about the understanding the current status, because the full HTA would be about also the consequences of introducing the new product. So there I think you lack the data. So I think a bit what I wrote in the, yeah, the hypothesis about new product effects, but yeah, and a good understanding of the current standard of care would be like step one, pre-clinical validations. Then you go to the clinical validations, and this is when the mini HTA slash full HTA come into the picture, right? That's how you will see on a kind of a time horizon on.

Yoann - 0:42:00 Now that's great. That is super helpful and insightful. So thanks a lot, Santana and Val. If you obviously don't mind to share the email, your Word document, that would be great. I will do it now, so don't forget it. And yeah, so basically we went through all the questions, so it helps to refine and also to confirm some of the kind of insights and findings that we have been kind of working on basically. So that's really helpful. And also to have your perspective as you do work with a few of these stakeholders, right? So you get basically, you understand the full spectrum of kind of requirement from the development all the way to the implementations and from more like a reimbursement standpoint. So that's really helpful, yeah.

Santana - 0:42:49 And for me, it's really helpful to understand the other geographies as well, because I'm quite limited to Germany, so it's really great to kind of through this work with you and the other experts actually get like a global picture on this.

Interview Transcript with Christoph (P12)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:01:45 Basically, about a year ago, we did a systematic review of all economic value assessment that have been published on digital health solutions, digital therapeutics. And I think about 18 of them, 18 publications met our criteria of economic assessment of digital tablets because we wanted to understand, are they cost effective or not cost effective? Because you know, that's the cost considerations and the potential additional cost of the cost savings to a system will be important or is important and will be more and more important in some of the decision making reimbursement and so on. And what we did during the systematic review is to identify a couple of factors and costs that we know are going to impact basically the economic value that a DTX might generate, right? Generate for the healthcare provider, healthcare systems or patients. And I think, and then our last paper, and then unfortunately we were not able to contribute to the last one. But the last paper, what we did is to ask about 80 individual experts, stakeholders, to what extent each of the factors that we know that are going to impact the economic value, how important are these factors to you? And how do you do you consider them? And how do you consider them throughout basically the tech development, the tech validation, so the clinical trial and the implementations. And why we did that is like, I give you a really specific example, like patient adherence to the interventions, right? We know that it's going to be a critical factor that would drive the potential clinical outcomes, right? But also the financial impact, because obviously if patients are not following whatever prescriptions, not compliant, not adherent to some of the recommendations, then no outcomes, clinical, and no financial benefits basically, right? So now that we know that patient adherence is critical, has a researcher or has a stakeholders that will be involved in the DTX development validations and implementations, how will you consider this in your day-to-day decision making process, right? Will you invest more? Will you develop specific features to address potentially this or to ensure that your patients are going to adhere to your solutions or how do you address basically these factors because we know, again, that these factors might impact the economic value that a DTX might generate. So in this paper now, we are asking, these are qualitative interviews, asking a couple of experts to try to understand how some of these costs and factors are considered or not considered, and trying to define, validate some of the assumptions that we have, but also define what could be some best practices, right? If we know that some factors should be considered earlier, or later in the process, how do we incentivize someone that could be you, that could be me, that could be a policy makers, but to consider certain elements at the right time and not too late. Today, the tech development process is kind of a sequential process. There is the tech development and engineers will be on their own, then you have the clinicians and they would look at the safety and efficacy and that's it. And then it comes to the implementations. And then this is when you realize three, four years down the road that some of the decisions that you have made two or three years earlier have a huge impact on the cost and the economic value basically of your solution. So that's what we are trying to understand better, I guess, and that's why I wanted to have, you know, you have been involved in many initiatives, especially with Savonix, but we wanted to have basically your experience on some of these questions.

Christoph 05:51 Yeah, well, just to, yeah, thanks for that, that's really helpful, because that sets the parameters a bit clearer for me now. So, I mean, I suppose the caveat for me is that I did it in [company name] certainly. I've redesigned a new therapeutic more recently that I haven't yet taken into investors or anything. That's something that I may well be doing very soon. And I've sort of thought about this quite a bit. And I think the experience is, you were right, I mean I think there's lots to think about there. And it does determine with the people. But anyway, how do you want to conduct this? Let's sort of, I'm happy to jump in any way.

Yoann - And so two things I would want to say, Christoph, before we start. One is whatever you're going to share with me is obviously strictly confidential, just between you and I. And I would not want to know if it's during your time at Savonix or is this new therapeutic kind of

intervention. I mean, you could share with me, it doesn't matter, but it's not important, basically, to the conversations, it's more about your experience. So if you don't feel comfortable to answer some of the questions, again, there is no obligation to answer some of these questions. Sounds good?

Christoph - 07:05 Yeah, I'm happy to say when and where it makes sense, even use examples of things that I've learned along the way. And to be honest, I mean it was a journey. I'm still on a learning curve with all this. I mean, [company name] was a massive learning curve. But as an example of doing it for the first time and trying to build therapeutics for the first time that were of a decent scale, I think that one is a big one. So that'll probably form most of what I'm answering, what I'm aware of, from my experience.

Yoann - 07:36 Why don't we start with this as maybe the first question, if you don't mind to share with me, what has been your experience when it comes to DTX specific involvement that you had in some sort of DTX development, commercializations as one, and two, what have been some of your key learnings? Maybe that would be also quite quite relevant

Christoph -08:02 Sure, sure. So Well, I don't know if you do this but my experience with the whole in my field And of course, I'm gonna restrict a lot a lot of this to see it is because that's all I know I mean, I'm sort of a little bit more probably in other areas But I'm much more about the neuroscience side. But I was really back in the early 2000s, I was the CSO for a company in London which built really early digital, they went through therapeutics and that's another caveat there is that I've worked more in the digital diagnosis that the therapeutics had. But I was working with a company, I really designed their digital solution to be used in clinical trials. But that one didn't have the same sort of parameters of what [company name] later had, which is a sort of a user-driven experience where you're actually sort of self-managing. And so those were my two sort of pillars of experience. One where it's very much driven by a doctor or a researcher and the other one where it's very much driven by the individual. So there's sort of two poles of experience. And so you asked me I think you said here what were the sort of responsibilities. I'm happy to just answer that question and I can go into the key learning. But the responsibilities sort of certainly involved the product design in both of my experiences there, which is the sort of starting with, okay, how do we choose or use or look to what's out there in the therapeutic side that you may have acquired through your own experimentation or through knowledge or just understanding of the literature where things are going and choosing the right therapeutic from there. That's kind of an important thing in itself because if you're on top of your subject, you know what you're doing, then you're going to choose therapeutics which are really at the cutting edge. I think that's important first. It's got to be something that works and that people are seeing that works and has the validation initially behind it, whether you did it or someone else did it.
And then you design the product around that, and then of course you have to then sort of either, if you haven't already validated it in an experimental sense or in a population study or something, then you then have to apply it in a digital study. So you have to see if it actually works in the digital context. So that would be the other role I've had, and then there's the sort of the commercial side, which is, and that came in a little later for me where you've taken an idea, you've validated it to some extent and you've done a certain amount of product design and development and then you take it back to people using it and then you say, okay, how has this worked for you? Are you finding this useful or not? And what's missing, what's not? That should be through the whole product design process from the very beginning, but in reality, my experience at least, the early stage of the, it starts with that number one idea, which is this will work as a therapeutic, it's been shown to work and it can be adapted to digital. That's really the first part I think of my role has been. And then you start the process of seeing how you can integrate it with others.

Yoann - 11:36 And I have a lot of questions on what you said, but we want to focus on some of the key learnings as you went through this journey, or journeys.

Christoph - 11:48 Yeah, yeah, yeah, sure. There's so many, I mean, I think, I mean, I can put them into categories almost, you know, there's the sort of investment side, which is the key learning, then there's the actual validation side, which in many ways is the easier part, and then there's the implementation side, which is its own category. So which one are you using? Would you like me to focus more on?

Yoann -12:17 So I think the three categories might be relevant to our topic, but maybe on the first one, the investment and implementations. So what we are trying to, maybe one of the questions I should, I think throughout the conversations we'll come to some of these learnings, or kind of takeaways. But, so maybe if I'm a bit more specific in the questions, you mentioned on the product design, you know, designing some of the features and so on, and getting some inputs from the patients. Did you get, you of the team, but did you get inputs from different stakeholders other than the patients? What kind of type of groups and individuals that were involved, or that influence, kind of directly and indirectly, the development and the design of the solutions?

Christoph - 13:12
Yeah, I mean, I think there were, I mean in my experience, I think one of the things that really helps you validate an idea is that I'm starting with an idea of whether it's worth pursuing something, you know, as a therapeutic. Is actually talking to other researchers and knowing what other people are doing in your field. I think that really matters as a scientist. You've got to know that this is something that other people can see is an emerging trend or something that other people can see is going to be on the horizon as a way to manage health care. And I think a lot of people, clinician scientists are kind of, if you explain what you're trying to do or they explain to you what they're doing, you can see the logic and go, you know that just makes sense. That theory should work and it's solving a problem. So there's that stakeholder, which is your colleagues, your standard sort of group of people.

And then I think the other sorts of people you need to know. It depends on the problem, but for example, the sort of stakeholders that I've dealt with are universities and how much they're prepared to, say for example, release their IP. That's a big sticking point. Whether or not you're at a university who you've been working for or you've got some need of their IP, whether they're prepared to share it, what their conditions are, some are more restricted than others. [University Name] for example can be very difficult to deal with on IP. So if you've got an idea for a therapeutic, you want to be able to build a validation of that therapeutic, you have to be able to have some agreement first and they have to come to it. So, you know, I don't know if that answers your question.

Yoann - 14:54 Maybe just to confirm, you mentioned about having these conversations with researchers toward the kind of program of the process. By researchers, could you elaborate what you mean? Because the more like engineers kind of driven researchers, the more clinicians or clinically driven researchers? Because sometimes, just to ensure who might be behind this kind of terminology of researcher.

Christoph - 15:23 Sorry, yes, so I mean clinical and clinical researchers, because obviously your solution is going to be a health solution. They would look at it and say, okay, this is something which is needed. It makes sense. I have had these conversations where I've taken an idea for therapeutic, I'm thinking one I had a year or so ago with a leading researcher in the field and I said, what do you think of this, having never seen something like this before? And he said, it is what's needed, it's a great idea, but then because that's just the beginning of it, knowing there's a need for it. It's the implementation which is the sticky bit.

Yoann - 16:06 Exactly. But it's that you need to start somewhere, right? And maybe a kind of a follow-up, but a bit more specific question. So we discussed a bit about the project design and some of the input that you had from the different stakeholders. In some of these kind of interactions that you have and discussion that you had with some of the stakeholders, are the cost elements, did this come into the pictures or through the conversations at some points about,

okay, we need to think about the design of the product and obviously addressing a clinical gap or need. It has to make sense, the safety and efficacy. But are these kind of cost considerations and elements came into the picture at some point or led to harm?

Christoph - 16:55 Yeah, well, to do that, I don't know. I mean, I think when you talk to investors, they're money people, they will automatically be thinking those ways, don't they? And I have had conversations with investors who sort of look at it and say, well, what's the cost of development implementation, or development validation and implementation and what's the ROI on my investment from that, that's one part. But in terms of health system utilization, I think the cost bit is, it's almost not a difficult conversation to have because digital is generally going to be cheaper, isn't it? I mean people buy even solutions are much paying people to do something is far more extensive in its costs than having a digital solution do it for you. So that's not a conversation I've had a lot of, not in terms of the sort of what's the cost of developing something like this. Well, it's generally okay, it might cost $2 million to build it, make it work and make people use it. But $2 million in the sort of in the scheme of a significant health problem is nothing.
So I think the reason I'm being negative there is because I honestly don't think, I think people are ashamed digital is going to be cheaper than the problem you're trying to solve or the costs of solving that problem, existing costs.

Yoann
And would it be fair to say, from what you said, that in a way, these conversations about trying to define what's the additional cost of having a DTX and what are the development costs and so on, in a way are kind of maybe pointless to have because if you do the things right, in theory, you should be cheaper or less, kind of less inexpensive than whatever is the standard of care. But the conversations with investor, Investor which is more about the ROI for them Or for the organization. This is this kind of maybe critical conversations to have is it is it fair to say that?

Christoph - 18:58
Yeah, because you'll never get it off the ground without that first I mean, that's that I've had that conversation exact conversation with a potential investor here over something I I went to just There's a billionaire here, very, very wealthy guy who has an investment arm in digital health. And they launched a fund here, sort of like 200 million or something. And I went to them and I met the chief science guy. He's a scientist. The guy who leads this fund is a scientist. And I spoke to him and I said, look, this is the idea.
And his sort of discussion of this was, well, it's a great idea, but I'm pretty sure that this will be taken care of by some other health provider or someone else will pay for it. Why shouldn't the private sector pay for this? And so he was thinking in terms of, well, who eventually is going to pay for this? And I think that conversation that they get to pretty quickly, who's going to pay for this? Is it going to be the government? Is it going to be a payer? Is it going to be the individual? I think that's their critical question. And very often they'll look at it and say, well, you know, if it's going to be the government, then they'll probably fund the cost of development. And there might be any returns on it. It'll just be something they use. In say, a socialised health care system like here in Australia. So, you know, they might give you a couple of million dollars to build it, they'll use it, it'll never be commercialized. That happens a lot. I think it's socialized healthcare.

Yoann - 20:31 Yeah, maybe unfortunately. I think I totally agree with you, but I think that's maybe the critical questions, who is going to pay for the solutions at some point. And from your experience, have you seen that the teams, the DTX teams, whatever stakeholders, they will start asking themselves these questions. Is this more in the early stages of a tech development? Is like, okay, you go to the clinical validations and you're back to the development board, the drawing board, and then later you go to the deployment. From your experience, where have you seen, when have you seen that this question has come up?

Christoph - 21:09 Yeah, I have seen it. I mean, I think you see that the pitch deck stage, you know, when you're pitching for a, as a company you're pitching for an investor or a client to use whatever you're doing, they want to see something that says that this is going to save them

money in some fashion, even if it's just roundabout figures that are kind of maybe not grounded in a lot of reality, that may be grounded in something reasonable. I mean, you know [Person Name] very well, she's very good at that kind of thing, which is sort of putting together a financial rationale for using it. I think that stage happens for me at the pitch deck stage either for investment or when you're starting out early or subsequently once you're in the early development stages and you're looking for big clients that might end up using that solution. I think they're the two times I've seen it used for sure.

Yoann - 22:05 And so would it be fair to say that basically the earlier the better, that you are one, having these conversations with potential investors, so having some sort of like kind of pitching sessions, but also two, asking as a team, asking yourself who is going to pay for the solutions. You might not need investment early on for whatever reasons, grant and so on, but it's still a relevant question to ask yourself and the organizations as early as possible. Would it be fair to say that?

Christoph - 22:36 Yeah, I think it is fair to say that. I mean, as early as possible I think is important because why do it if it's not gonna be, it's not gonna be cost effective or it's not gonna be viable, usable by the people. And I think, I mean, I'll give you an example, this is not in the therapeutic space, but one area where we had a, I mean it was a real sort of question mark over the whole [Project Name] project, which was what's the existing process, what's used right now to test cognition in people and of course it's a piece of paper that every GP has, they can pull out, it costs nothing and they can do it in five minutes. There's no software to download, there's nothing to do. So trying to do a job better, it may be better to use a digital solution to diagnose mild cognitive impairment and to diagnose it definitively but it's not a better human solution. Like using a piece of paper from your filing cabinet is easier than using an app. And so that's sort of that's where I think you need to ask yourself, well, what's the cost of an MMSC? So we actually did this project, well, we did this on a slide, where we actually tried to break down the real cost of an MMSC versus the use of [DTx name]. And the MMSC actually did come out more expensive when you consider the cost of the doctor, the cost of the training and all that. When you put it all into the equation, actually, it is cheaper to use a digital solution. It's not easier, but it's definitely cheaper. So we got one part of that equation right.

Yoann - 24:09 So, I love your examples. So as you said, you got one part of the equation right, but is this good enough to convince, from the conversation that you had, the patients that, okay, it might not be easier, but it's maybe cheaper in a way, because the cost that you consider about their time in Soho, and sometimes it's maybe cost that they don't really realize or maybe not consider, so maybe the first kind of decision criteria for them, to them is the convenience, I guess.

Christoph - 24:41 I don't know. Yeah, and this is it. I mean, if I understand what you're saying, the question, I do think that a whole human factor, to get it right is all of the above. It's not one or the other. It can't just be cost-effective. It's got to be easy to use. The patient has to adhere to it, etc. I think there's a huge intricate art in getting digital therapeutics to be used and I think that's why we're not seeing them yet being used in widespread. I don't know very many examples where they've been used in a widespread sense.

I found out in my space just last week that [Company name] which is a Australian-German collaboration, they built a therapeutic for dementia obviously what I know and it's just being implemented now at the German healthcare system. So that's an actual example where they've actually managed to get it to the users. But the science on that goes back a very, very long time. Like 10, 12, 15 maybe years. So it's taken a long time to get from idea to actual implementation and use. So anyway, that's why I don't think we've seen that much of it in reality in the health system.

Yoann - 26:0 I agree. So just to kind of summarize what you just said about maybe one of the reasons why we are not fully addressing all these kind of requirements about usability, about

relevance, simplicity, cost considerations. It's kind of a value proposition that is like we are not fully kind of meeting the requirements yet, right? Is that the right way I would phrase it?

Christoph -
I'd say all those things are super important, but I mean I'm thinking of a therapeutic that a guy I know in the US built and it seemed like a really valid idea, really well validated, starting to be implemented and now he's taken a job with [Company Name] because the company wrapped up. I think this is the same problem we had at [Company Name] which is, yes, you can get it all right, but if your investors don't have the horizon to stay with you on that journey, which is very long and costly, then you can fail on that score pretty badly, I think. So that went to be maybe even more important than getting all those other bits right. You know what I mean? To some extent, up until you're a viable company returning investment to the investors, you can still fail, even when you get it all right. No, exactly.

Yoann And you know when we did this kind of survey, we asked these different experts in our last paper about how important are some of the factors and would they consider some of these factors throughout the life cycles of the DTX, you know, these factors that we know that are going to impact the economic value of the DTX later on, we realized that a lot of these factors were not considered or not as, let's say, a top priority, right? The top priority, when you look at the development stage, is to have a state-of-the-art kind of technology. But it's the engineer or engineering kind of driven kind of process instead of the hard technology. And then when it comes to the clinical validations, it's the safety and efficacy, kind of clinician driven. And unfortunately, some of these factors about usability, about adherence, about manpower, you know, you mentioned about the healthcare systems, kind of the usage of manpower, utilizations and so on, are not that considered or not much. How do you explain that?

Christoph -28:55 Yeah, you're right. That's exactly my experience. I think it comes in far too late, that whole question of who's going to use it, is it usable, is it scalable, is it something that people want to use. All that stuff comes in far too late, I think. But then you mentioned something that just caught my mind and it was I was about the engineering the live and the engineering driven part of this I see that a lot and where someone says hey, this is fantastic new technology. It's it's VR or it's voice recognition or it's it's you know, you can use your phone to sort of measure movement or something and People say oh, this is this is the technology this is driving support this great ability to do these things. And actually that is interlinked with the investors because investors in particular are very interested to see cutting edge stuff. This is new because the technology is new.
What they fail to see is that really the science behind that's being implemented through the technology is not that new necessarily or it's not that groundbreaking. But actually the science, sometimes simpler solutions can achieve more without all the you know the bells and whistles of Technologies so but it but you won't you won't Excite an interest investment on the basis of something that's already been done or that could be that's been done sort of I Don't know. It doesn't have that ring of technology that makes people excited. If you want to ask it again?

Yoann 30:27 No, no, no, it's all good, no worries, Christoph. So maybe on some of the key learnings, so you mentioned earlier about on the investment side or investment category, then on the clinical validations and implementations, would any of these learnings be related to the cost considerations, economic value of digital health solutions by any chance?

Christoph - 30:57 Well yes, I mean I think, yeah from the outset I mean you look at a problem, so I'm thinking probably the best way to think about it is what you put in a pitch deck and it literally is about, okay this is the worldwide cost if you want to get to a scale solution this is the worldwide cost of this problem and the costs are broken into the interpersonal, the costs to a family or the cost of the health care, cost to the taxpayer, you know, whatever it might be that you're looking at. So you're making a sort of a prima facie argument that this costs too much money to society first and foremost or a society or part of a society. So that's your first rationale really. That then drives the reason to do this. And again, I come back to this point, the digital, it's promise is always

gonna be that it's cheaper than what you're doing already. You know, the way you're doing things. Or it's reach is greater, or it's ability to do the job better, and therefore becomes a cost saver in the long run. And so, yes, we did consider these things. I think we often thought about, so you know, if you're going to implement something like this, it's not just about sort of, in our case, it wasn't just about detecting dementia earlier. It was about effecting change in behavior that could lead to reduced other health problems like stroke or other. So there's a sort of multiple effect of looking at the cost of a single problem but then there's all this sort of ancillary savings that you can get from addressing a problem.

Yoann - 32:31 I see.

Christoph - 32:32 So we would think about those things and we would mention them, and then try and drill down to more specific use cases where they exist and where you can make an argument for that. Because then together, when you look at that, you can see multiple value adds or values of your product. It's not just simply in doctor visits, for example. It's in the wider cost to a family's income or the loss of productivity of a member of society.
So yes, you can build all of that into your discussion from the very lowest to the highest to make that point that this is a valuable proposition, you know, that this is worth doing. I don't know if that gets it.

Yoann - 33:23 Yeah, that definitely makes sense. And maybe to give you a, to be specific, give you specific examples, like, and again, coming back to what you mentioned earlier about the manpower utilizations. We know we are kind of stretched, we don't have enough nurses, we don't have enough GPs, specialists, and so on in many countries, right? So, how, and so obviously this would impact the manpower utilizations, would impact the overall economic value or whatever cost savings of a potential digital solutions, right? So, how do we, how could we incentivize, let's say clinicians, researcher clinicians, to consider during the safety and efficacy kind of type of clinical trial where we are trying to generate evidence, how at this stage of a life cycle of a DTX, how could we incentivize clinicians to consider the potential manpower utilizations of potential solutions? I'm taking this as a factor, but there are many factors that will obviously influence and impact the economic value. But I just take this one because I think this is also what clinicians, they understand, right, in terms of manpower to the patients. If you need like five more nurses to run your program, then it's kind of going to be a no-go, right? So how do we incentivize clinicians to think about these specific aspects?

Christoph - 34:45 I think that's, if I understand the question, I think there's some ways that, I'm thinking of some, I've just been talking to some guys in the US with a digital tool for assessing autism and their value proposition is essentially you get to see more patients in a day because you're taking the labor out of labor-intensive things and I think that's really the key driver for a lot of the clinicians which is and in my case too as a clinician so I'm seeing patients now and I'm using more and more and more technology to assess these patients remotely and they're doing a lot of the assessment without me being there. So in the past, just as a simple example, in the past I would sit with them and run through a questionnaire. Now I'm using digital email-based questionnaires which they fill in in their own time, it's analyzed on the system and it comes back to me with some conclusions. That saves me enormous amounts of time. In the case of this bunch in the US I'm talking to, they have a remote, they're using an algorithm which is based off of some key data points that come from a video analysis which is done just by the patient in their own home through some standardized questionnaires and through a rating scale done by the clinician whilst they watch the video. But you bring this together, it's a lot of time. It's like taking a, because autism assessments are very time intensive and so you know, instead of the clinician having to spend two or three hours doing this, they could get it done in 20 minutes or 30 minutes and still be equally or more accurate. So for the clinician, anything that involves time-saving and better efficacy or better diagnosis are the things that they're going to be driven by. I don't think the clinicians are necessarily going to be driven by how much money they'll make if they're in private practice they might. I mean that's certainly a factor. If I can see a man working with a psychiatrist who sees 20 patients a day at the moment. I don't know how he does that I honestly don't know

how he does that but he's very driven by money and so for him anything that saves time is very attractive because it makes him more money So these are the sorts of things that I think drive clinicians that I I see, you know with technology.

Yeah, I mean, I think it's all about understanding what's the agenda and kind of of the different stakeholders, right? And how your solutions might address the agenda or requirements of the specific stakeholders. And to your point about clinicians, for some, it might be about, you know, ability to see more patients. So I want to see more complex patients and the patients that are kind of, you know, you're just coming with mild symptoms that could be managed at home or whatever, then yeah, it's kind of a triage of the patient that should come and see you or not.

Yoann - So yeah, I totally understand.

Christoph - 37:49 Just on another note, an example. So here in Australia at the moment, and I think everywhere in the world, there's just been an explosion in autism and ADHD diagnosis. And the pressure that it places on the clinicians here does affect them. I mean they're burning out. I mean some of the guys I'm working with even in private practice are working long hours to try and help as many people as they can. They're driven by optimism. I mean I've seen families at the moment who have been waiting two years for an appointment. That's not unusual. And so there are clinicians who are feeling here, feeling not just tired, stressed out and you know, overworked but they're also feeling guilty that this problem exists and has not been dealt with by the health system. So there's an example where governments have a completely different agenda which is to, you know, is obviously to address a health care need that is pressing. But it flows right onto the individual clinician who's dealing with that problem on the cold face. So, you know, that illustrates your point perfectly. And unfortunately, this is Australia, right? We're not looking at kind of a tier three countries, developing countries where, I'm not saying it will be okay, but it's what you might expect when the rest of the infrastructure and so on are not, you don't have a number of specialists.

Yoann - But, so this is a side question, Christoph, but quickly, why do we see these explosions in terms of autism, autism, ADHD, a number of cases, because we know how to diagnose them, maybe now versus before, you have all this social media and screens, times and so on, but I don't know, how do you explain all this additional number of cases?

Christoph -39:36 I'm not really sure. I think that COVID has had something to do with it. It may be that people are more acutely aware of what their kids are like, seeing a lot more of them close at hand. There's certainly, I don't know, in the West at least a new awareness of ADHD in all sectors of society. I mean we're seeing just doubling of, there's been a doubling of prescriptions for ADHD medications here in two years, three years. It's just gone through the roof. So there's almost a word of mouth thing going on as well. In the UK, I've seen this sort of word of mouth effect which is, oh my cousin had this and since he's been taking medication, his thinking has improved and he now feels better. And because there's a solution as well I think. So it might just be an effect of sort of entering the mainstream. In Australia particularly the ASD side of things with the autism spectrum disorder has been driven a lot by the fact that we now have I think called the National Disability Insurance Scheme which is a four billion dollar fund which is basically if you make the diagnosis it opens up a large amount of funding for your child to be managed. So that is driving people who may have question marks over their own, who've just sort of possibly just dealt with it before or not, thought there was anything for them. Now there's actually a route towards assessment and treatment that wasn't open to them before. So that's part of what's happening here. But certainly, you know, there's other factors as well that maybe, who knows, I've been reading a paper about accumulated abysmal plastics and genotype and that there seems to be sort of this, I mean these are Western constructs and Western diseases and you know it may have a lot to do with our industrialization. Yeah, so, you know, I don't know the answer is not there but it put a definitely a kind of additional stress on the systems and the Individuals behind what the clinicians and the entire health care kind of professional. So yeah, what really unfortunate?

Yoann - maybe, last question Christoph if you don't mind And as clinicians, you know, when we looked at the clinical validations of the DTX, it'a all about the safety and efficacy. Could I ask you to elaborate a bit more on, from a clinician perspective, what are your top priorities when it comes to the clinical validations? What are you trying to demonstrate and the type of evidence that you would want to generate if you, tomorrow, you might clinically validate a DTX, basically.

Christoph -42:32 Well, I mean, I see in the back of my mind has always been, is this publishable? Can we get it disseminated? Will it make the cut in terms of the quality of the effect that you're looking for? And that in digital, I know you're talking about therapeutics, in diagnostics, it's all about sensitivity and specificity. So those are the things you want in your diagnostic. And then there may be some considerations, certainly in [Company Name] we had some considerations over trying to get that sensitivity and specificity using the fewest number of measures and the least amount of patient time. Because we could see that through our own data that the longer this assessment went on, the more people didn't perform the task well and the data started to get more rubbishy, junky as you went on. I'd say that probably applies to therapeutics as well. In my space anyway, the CNS space, the principles of therapeutics are about repetition for example. You do see efficacy with repetition of cognitive tasks, for example. That's fantastic, but you have to do a lot of repetition to get efficacy. So that doesn't consider the human element of this, which is, is a person going to sit down every single day and do this task, a repetitive, boring thing that they've done before? How do you make it interesting? And that's where gamification has to come into the equation because it has to appear to be fun and you have to have some stickiness, some user experience that's enjoyable, but it also has to have that therapeutic effect. And the company which totally nailed this, in my opinion, is [Company Name] in the US. You know, yeah, I mean [Company Name], we work with those guys up there and that's how you do it. You take an existing problem like gaming, which ADHD kids need to do a lot of, and that's what they get their stimulation from, and you turn it into a therapeutic.

And that then gives you repetition, then you get your benefits of the actual digital therapeutic. So, yeah, so that's in a user-administered, user-driven example. What I think, and I'll tell you this is my largest, biggest learning from the whole time at [Company Name], which is that the biggest problem in any digital device that you've got, whether it's a therapeutic or a diagnostic, is this adherence issue and compliance to it. And I believe that, I could be wrong, but I think most of them are going to fail without the involvement of doctors. I really honestly believe that there has to be a figure that you trust that drives the behavior, that helps you to do what you're expected to do to improve your health. There has to be someone you're either accountable to or aligned with in some fashion that gives you that motivation to continue on with the treatment. So it's the same principles if you see a physiotherapist. Doing your exercise, people are terrible at that. Doing them in front of a physiotherapist, people always do it.

Yoann 45:54 I totally agree with you. And two years ago when I was in London in a DTX conference, one of the DTX CEO mentioned more or less the same thing. He said, you know, and I think, you know, DTX is still kind of emerging, it's kind of new. And he was like, we as DTX entrepreneurs and developers, we are all about trying to get more and more users in your database, right? You want like new patients, new patients. But he was like, that's wrong. because we know that within 30 days, anyway, most of these patients will disappear, will not be adherent, will not be compliant. So it was like, let's forget about patient acquisitions.

It's important, but we should all shift towards how do we retain the few patients that we have on the app? Because that's how you could basically prove not only the efficacy, but the effectiveness of the solutions, and it's not about growing the database, but it's just, it's more the quality and just ensuring that the, right? Whatever is gamifications, the nudges and so on, whatever mechanisms you have, but it's like how do we retain these patients and if it's a subscriptions kind of models, then how do we get them to renew the prescriptions every month, right? And I think that's really the issue, I guess, that most of the DTX have not addressed yet, I mean, it's more or less the same thing for any drugs pharma, right? I mean, we know patients are like, for whatever it's

insulin, cancer drugs, and so on, not that compliant. But I think when it comes to digital health solutions, DTX, there are additional mechanisms, including having the physicians involved, but that would help to ensure a slightly better engagements and adherence of the patients to the prescriptions that we see all the interventions yeah.

Christoph - 47:48 I agree with everything you said and you know there are these people who I think there's a class of people who you know digitize who are the sort of people that try and beat their score on a Garmin or try and beat their whatever. They're health conscious, health minded people who will always track their own progress, track their, and will do what is in their own interest. But I would say they're a very small proportion of the general health population. I think that they're, that kind of patient that does exactly what they're told and sticks to it and checks and complies. I think they're, I don't know, I don't know what percentage, but I don't think it's very many, I don't think it's the bulk.

Yoann - 48:32 I agree, I totally agree with you. Great, I don't want to take too much of your time, Christoph, but is anything else that we have not discussed on this topic of, let's say, cost effectiveness of digital therapeutics and how should we, could we consider as early as possible some of these cost considerations in the life cycles of the DTX, you know, throughout the product development, validations and implementation. Anything else that we have not discussed that you would want to mention? So, any questions, any feedback?

Christoph - 49:02 Maybe just, well, I mean, probably are, but I mean, just off the top of my head, I think one thing that's probably not thought about is if you're doing a physician or whatever clinician implemented approach or at least a clinician guided or something they're involved in the process is how it works in their workflow. So involving it, so understanding the workflow of the clinician that's going to be either recommending this or implementing it to the patient or understanding what the results mean to the patient, I think that understanding the workflow. So you know a 15, the average GP has five minutes. If this helps them because they have a lack of knowledge in this area, then what they need to look, what they use from this, whether it's the results of efficacy, it needs to be something that works for them in their workflow. I think that's really important because you know they don't want to be messing around with a whole bunch of different programs and solutions to be able to get to something. They've got a few minutes, they just need to see, bang, this patient has done what we set out to do with this therapeutic and that it worked or it didn't work and I know what my next steps are. I either need to do this or do that or do something else but I have a clear understanding in a very short while what the results are, what they've done and what's next. So I think that's important, the workflow element because yeah I mean yeah that's one of my big takeaways. You're hearing me say this because I've gravitated further and further away from this idea of self-managed health care. I believe it's the hybrid is the solution for the future, where the patient and the doctor are working collaboratively and the technology is greasing the wheels of their, or making that happen.

Yoann - 50:58 I totally agree, and I think it's kind of a topic we wanted to explore also with the institute, is like how the patient-doctor-physician relationship is going to evolve, or should evolve, with digital health solutions. Because I think too many of the digital health solutions are looking at addressing patient needs without taking the physician's considerations, requirements, whatever it's workflow, is it tech integration, and so on, into considerations. But at the end of the day, I think, and that's my view, but I think it's exactly what you just mentioned, I think digital health solutions are there to optimize, optimize the physician, but optimize this relationship, right, building maybe a stronger relationship between the patients and the physicians And not trying to replace Any kind of physician interventions basically right so Greasing the wheel as you said I think is exactly what I think in the next like five or ten years

Christoph - 51:53 What digital health solution should should him for basically? Yeah, I agree. That's been my takeaway from [Company Name], which is you're never going to motivate people with a little, I mean even my Apple Watch, the congratulations, you've met your goal today. It's

like, well it wasn't my goal, I wasn't that committed to it, I'm glad it happened, but I'm not a, I'm not a, I don't have OCD, I'm not that kind of person. Yeah, definitely.

Yoann - Great, but so thanks so much again Christoph for your time on a public holiday. Great, but so thanks so much again Christoph for your time on a public holiday.

Interview Transcript with Cheah (P13)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:12:21 So maybe to start with, Cheah, is to get the broader context, if you don't mind to share with me your role, and maybe the many hats that you have under the NUHS kind of cluster.

Cheah - 0:12:49 So, I consider myself a bit of a jack of all trades. So first and foremost, you know me, I'm a clinician. I practice in the public setting, and this is a high volume, high throughput setting in ophthalmology, which is a discipline about eye care. And that is my main, I would say, my predominant job, so to speak. At the same time, in academic institutions, we do other things. So that includes research, research in the form of clinical results, clinical studies, but also in the form of novel treatments or innovation, and including novel models of care, getting just not just devices, but also new ways to implement treatments or therapeutics that have not been tried before. At the same time, as we are embedded in the NUHS system, which is part of the NUS system as well, I also interact with faculty from within the National University of Singapore, engineers, even scientists, to work on solutions using clinical questions that they come up with. And last but not least, I think I actually work a little bit with industry, so on an at home basis for consulting questions that they have relevant to the areas, medical specialties that I do, but also on digital therapy, not digital therapy, but new therapies and new treatments, as well as mobile solutions and devices. Yeah, so that's in a nutshell what I do.

Yoann - 0:14:18 Yeah. I see. And maybe to understand it better on why in a way you have these different multiple hats, right? As I said, maybe, and that's not negative, but not as just clinicians in a way. Is this driven by just your kind of personality on who you are and you'd like to know, to be involved in kind of different projects and exploring and learning? Is it aligned more because at the end of the day, we all have kind of KPIs and has a KPIs also in terms of potential licensing or potential like tech development, improvement and so on is also part of the KPIs of clinicians? What are some of the motivations?

Cheah - 0:14:56 Right. This is going to sound a bit corny, but I think the real underlying motivator really is the curiosity. I think because I find that there are always questions that weren't answered, and sometimes the answers I can find through peer-reviewed literature So, peer review literature, don't always apply to our context or don't always match what I see in real life. So that drives the curiosity in me to try to any day or seek out what happens within Singapore, within the area where I practice. And of course, there are always, when we are practicing, as a clinician, we are always thinking about new ways or better ways to do certain things.

Secondarily, you know, things like P&T, KPIs, I think realistically innovation or patents, IP, is a very small part of our portfolio. In a sense, evaluating by merit of your year end bonus, et cetera. So I don't think it's a good to have, right? But it's not a primary driver because if I really want to do that, and really financial output is really the goal, I think actually being a people-led organization would actually give me more, to be very honest.

Yoann - 0:16:14 And do you think that, because at the end of the day, I know to your point about, I guess there are many ways that we could improve the healthcare delivery, new ways, processes, and technologies, and so on. The importance of such KPIs that are maybe related to the innovation part, and not just about the job delivery, but what else could be done in terms of improving the experience of the patients and so on. Do you think that these are some of the KPIs that should have maybe a higher, more weightage in terms of driving a bit more, because you have the right personality in a way for what you do, but for some, you know, KPIs kind of drive behavior. So do you think that these are some of the KPIs that should have maybe a higher weightage as an institution?

Cheah - 0:17:01 Absolutely, I fully believe in the fact that incentives drive behavior. And I think that there's no question that if we recognize this aspect of the intellectual contributions more, more people will veer towards this path. And there's no doubt about that. The challenge or the caveat we have is that this also in a way warps the personalities which go into this field. Because I think I still, in a way, I'm being a bit naive, I feel that a person who does this kind of thing should inherently be genuinely curious and genuinely keen to do this and not just because there's a financial return at the end of this. Yeah. Yeah, so I think this part I'll be a bit careful, but certainly I feel that in terms of recognizing KPIs and the year-end assessments, more perhaps could be done for innovation-related work compared to the traditional publications and citations, etc.

Yoann - 0:18:01 I see. And, you know, so you are involved in quite a few kind of projects, let's say, more on the tech development side. What are your kind of top and key priorities when you think about some of these technologies that you have been working on and you are afraid to choose one of them specifically, but what might be your, when you think about a new project, a new technology, what are your top one, top two priorities?

Cheah - 0:18:27 I think the main litmus test I always ask is whether this is going to be a meaningful problem. That is usually the first thing. It's not about the solution, but about whether the problem is something that is worth solving. And the second thing is, does the solution justify its costs? And I said that does the anticipated solution necessarily reduce some element of current effort for either the healthcare provider or the patient or one of the stakeholders in that cycle of care. It is because we can create things for the sake of having new things, but sometimes in the process of creating a solution, it adds a lot more costs. And in terms of implementation or actually executing it, it makes the whole exercise more costly and if it doesn't significantly improve the healthcare outcomes. Then it's going to be a barrier eventually when people try to implement because it's incremental change and there are two sides. It's a cheaper solution. If it's better outcomes, everybody will get it. But if it's a more expensive solution with marginally better outcomes, then there's deliberation. A lot of times there will be resistance to change.

Yoann - 0:19:34 Okay, and I would come back to this kind of cost consideration, but maybe before, one question before is, when you think about the potential impact of your, any of the projects that you are working on, more on the digital health side maybe, how do you think about the impact, or how would you define the impact of such solutions, maybe more, less from a clinical standpoint, but more from an economic standpoint? You mentioned about the cost, you mentioned about the efficiency, but it would be great to get your perspective on that.

Cheah - 0:20:06 So I think in terms of impact, there could be, like you said, on the individual level, how it is for the person, but also on the population level, how it affects the entire system, or the way the existing workflows for the chronic disease process that we're treating. So I think there are a few ways to look at this, perhaps on a population level, cost is I think one, right? Cost effectiveness, the actual time incurred, the resources incurred on both the provider level, the patient, the recipient level, and of course on the entire, we may even measure things like healthcare outcomes, quality of stay, like did they suggest that IPS is a problem? So I think that is actually beyond my realm because it's usually what the School of Public Health or the health economics actually do for us. But I think on my level, what I look at is how this implements the actual workflow of patient care. And just on a very ballpark level, whether it actually makes sense for this new model versus the existing traditional model.

Yoann - 0:21:14 And this is, to have such understanding in a way, you know you mentioned about ballpark, kind of you know, whatever investment and impact and cost and so on. This is something that you do on your own, like with Excel file, or is this something that you kind of have conversations with different experts, like more like health economics, economics kind of individuals within the network, the cluster, or is more like, the more like common sense of like understanding all the cost and what might be some.

Cheah - 0:21:44 There was a different levels. I think the initial smell test, so to speak, where we are just hearing about solution, of course, you can be on your individual level, whether you think this makes sense based on our own experience being as part of the system. Then if we are, if we pass that smell test, so to speak, and we are going to design something or plan something that is more tangible then obviously I'm going to get the experts in because I cannot rely just on my intuition. We need something quantifiable and that can withstand peer review as well as switching. And that is where we collaborate with our partners from Source Report. Also I think the BISI Institute, we have collaborators, we have conversations. Usually what we do is that we design a study with a clear end point, clear goal, a visual grammar component. That's what we do in our center.

Yoann - 0:22:36 I see. And when you design your clinical trials, so looking at more of a kind of, obviously, the clinical impact and outcomes, do you also consider and have a couple of end points that might be more related directly or indirectly to some of these economic considerations in terms of productivity, workflow, kind of improvement and so on. Is this also part of some of the endpoints that are kind of measured or?

Cheah - 0:23:04 Absolutely, in fact, at least in one of the studies that we are doing, it is actually our primary endpoint, which is that it is the cost effectiveness of this model of care beyond, you know, the secondary endpoints are actually the efficacy and the safety, because we've already done that in previous studies. This is actually really about implementation and getting some pseudo real world evidence or data of how this, when implemented, drives the cost or really lowers the cost for our patients as well as the providers.

Yoann - 0:23:36 And how have you been exposed to, because I mean, typically clinicians, they don't kind of, they have a limited exposure in a way of all this cost effectiveness and so on. So how did you get exposed to all these kind of considerations?

Cheah - 0:23:48 I don't consider myself really an expert in this area at all. I have some knowledge, partly during training, there are specific components of our examinations that cover things like cost effectiveness, very basic examples of whether to adopt a new technology, whether when we assess a new technology, how do we ensure that it's not just efficacy and safety that we're looking at, but it's also an overall cost, what I call incremental costs for this new technology. So that's the basis during our specialty training. And of course, in our institution itself, we have mentors and we have collaborators who have worked with our mentors. And they come in, I join in the meeting, they listen to the way they discuss some of their plans, and that's how I maybe learn from my seniors and stand on their shoulders.

Yoann - 0:24:45 And so this was part of your training, part of the curriculum. I mean, the basics, right? Obviously, we're not going to ask you to be an HTA expert, but at least the basics of having some of these considerations was part of the training.

Cheah - 0:24:59 Okay. Actually, what it has is that, this is just in my specialty, we've got the College of Ophthalmologists. So, the Royal College of Ophthalmologists, which is based in the UK, publishes guidelines on health technology assessments, specifically on new iDevices. We got NICE a lot about devices as well as implants. So they have guidelines on how they calculate and justify adopting new technologies for the UK system. So when we were studying for those exams, we actually I was a bit nerdy so I actually downloaded all the guidelines and looked at the ICERS and what they mentioned. It's not strictly a requirement per se but it really helped me appreciate how they make the decision. So this is a policy level, it's not a clinician level, it's a policy level, but it's really interesting for me to read, to see how they calculated this, decide to adopt this test technology over another technology, and what's the justification. And so that kind of rubs off on me when I now look at things, and I kind of just follow some of these concepts.

Yoann - And is this done across specialty or a Common practice?

Cheah - I would believe that there are similar forms in most disciplines, right? Because most of us are still taking the UK exams and the UK has a lot of colleges with different specialties and I think they're all obliged to publish guidelines for UK, actually not for us, but because we are training for them and we get to be exposed to some of these guidelines as part of our training.

Yoann - 0:26:31 And you mentioned also that you are conducting a trial as we speak and your primary hand point is more on the cost efficacy or effectiveness of the solutions. And obviously you have done a couple of studies before that one, and so are there any learnings from doing these studies, looking at the data and the results from maybe a cost perspective, that things that you wish you could have done differently, maybe six months ago, a year or two years ago now, but you see, you know, the data coming in terms of the cost effectiveness and so on, is like, any learning basically that, you know, from doing that studies and looking at now the cost aspects?

Cheah - 0:27:17 Okay, I have to caveat that this cost effectiveness study has not begun recruitment yet. We have gotten the approval and we've done the proposals, right? So I don't have prospective data that I can analyze yet. But we have got initial proof of concept studies for individual devices to show they are safe. But I would say that a lot of times planning can only get us so far. So there would definitely be ways that we can plan things better. A lot of this would be logistics on the ground, you know, what happens and it can be simple things like whether that place that you're doing the providing the service has a lift landing or not, you know, that itself can or whether you put a banner downstairs because you're on level three. And I think these are just very, very, sounds very mundane, I mean, but honestly, these are the things that potentially could impact the patient's, the participant's perception of this, and also in the sense that their rates and their responses to the whole experience. And you know, on my desk specifically, because I know that this is kind of disruptive from a technology standpoint in terms of the use case, not in the more traditional kind of tertiary hospitals, but more kind of in the community, kind of GP primary care level.

Yoann - 0:28:35 You don't mind to share with me on how some of these cost considerations were considered or play a role quite early on in the concept? Because I guess with what you just shared, your background and so on,

Cheah - 0:28:45 I guess this was kind of part of the priorities from day one.

Yoann - So I don't know if you want to share a bit more about how this play a role in designing the concepts of some of the activities that you might have done.

Cheah - So for a lot of times when we come up with so-called disruptive technologies, it's sometimes about creating a new category. But it doesn't mean that we have to start everything from scratch because it is disrupting a whole category of solutions or treatments. So, if we use the concept of value-based pricing, we can look at how the current or newer solution provides

additional value for the users as well as for the recipients. And then we can use that to price our solution. Therefore, a lot of my current considerations in product design and based on work-based implementation is, in a way, benchmarked against traditional models of care. And the other thing that we also look at is the user-friendliness or the ease of use for our solution. Because we know that every additional step is a barrier. So we really spend a lot of time and I think start with a lot of effort to simplify the process as much as possible so that it's almost a dummy proof-of-one-step process and assembly and collection. And we really wanted to make sure that that part is not the real limiting factor. Also, that is beyond just the cost, but it's also the actual process.

Yoann - 0:30:08 I see. And did you have, like, on that project specifically, did you have, like, kind of a price tag in mind, like, if the device costs more like $2, $5, you know, to manufacture at scale, it's basically, it's a deal breaker, basically. Is this something, like, some of the considerations that you have been working with, or was really more about the experience and by providing the right experience, you knew that the cost kind of will follow?

Cheah - 0:30:34 Yes, so cost itself goes hand in hand with business model. Therefore, this part, I have some ideas, or rather, put some thought in how I envision this to roll out. But a business model usually is very dependent on the industry player or which commercial entity decides to take it forward.
So different ways we can look at this. So one way is to look at selling the hardware as is, right? And packaging everything else within it. We sell the device. Other considerations would be to actually do this as providing the hardware for free. Instead, we have a sub-prime model, so it's something that's fixed. Then the consideration for the device becomes different because by lowering the cost of the device, ensuring a minimum standard, it actually helps to drive down your or increase your market, market margins. So I think these are some things that we consider at a time where we're deliberating this. The bottom line is that there are certain key elements, certain key pieces of technology that cannot be compromised. So items like specific lenses, we definitely need them to be of a particular quality, and specific. Thankfully for us, that's actually the only expensive item. Like, it sources everything else, I think, as far as we keep within a range of consistency, it's reasonable, right? And of course, the materials, it needs to withstand a certain amount of handling. And we haven't reached a stage where we're looking at ISO certifications, IEC documentation yet, because that's what the commercial vendor would eventually be doing when they're producing at scale. But this is something that we have actually thought about at a point of design that we told staff, don't go and make something too fancy that is very difficult to mass produce, but do something that's reasonable. Yeah, so that's some of the tool I put in.

Yoann - 0:32:15 Okay, I see. And in the NUHS in our cluster, how this maybe this economic impact of new innovations might be considered or not considered? Are we more innovation driven but obviously more from a clinical perspective and looking at the clinical impact and you just need to kind of break even and that's good? Or do you see and do you feel that there is more and more some sort of like importance that are given to the cost considerations that okay the patient safety and the outcomes of the disease are top priority, but now these cost considerations are more and more important over time, or how are they considered or viewed?

Cheah - 0:33:00 So there are two entities that play a big role, NUS, and then of course the NUH, the research office of the RTPI. So I think most of the time, there are principles or policies that are aligned, which from my understanding is that they are not looking to maximize profits, but they are looking at widespread adoption and to make sure that the technology benefits the people or the end users. That's at least the official line. In terms of real looking at the margins, profitability, whether a solution potentially have a good market share, sizable return. I think that is the point where the research office will deliberate whether to actually file for IP for that or not. That is at that stage, whether they see a viability of this as a product that can eventually commercialize into a market. But when they are actually already an IP that is already launched, right? I am not very sure myself how they do the thinking on population, but I think profitability is not the key. So,

getting it out, either the power licensing or the startup is probably the priority after they have found it.

Yoann - 0:34:13 Yeah, definitely. And you know, as clinicians, as researchers, what might be your wish list or how could we, what do you wish you might have in terms of tools, in terms of expertise, in terms of frameworks, whatever to help you consider some of this clinical, but also obviously on the cost economic kind of considerations as you're heading the process?

Cheah - 0:34:40 I think I'm going to be a bit biased because I've got a little bit more experience with the bio-design process at Framework, but I personally feel that I actually benefited greatly from taking part in the biodesign Singapore biodesign program. I saw that you were wearing a biodesign shirt.

Yoann - 0:34:57 Yeah, you know exactly, that's why I was like smiling. It's like I have mine today or so, yeah.

Cheah - 0:35:02 So, well, I think that really is a much broader perspective to what we are doing, because before I joined the program as a clinician, all I cared about was as a problem for me, I wanted to solve the problem for myself and my patients. But a lot of times, the solution solves the problem, but it doesn't end up somewhere because considerations of regulatory reimbursement with the actual greater landscape are not in our minds where we are facing that problem. A lot of times, even just looking at the problem itself, whether it's a problem of solving the market side, etc. But I think having that broad process of thinking framework will be very useful for clinicians. The second for clinicians would be perhaps a safe space, a sandbox so to speak, for them to in a way do simple prototyping with help. I think that is provided that someone could already evaluate the idea and make sure that it is something that is viable. During the biodesign process, where I found myself the most lacking is the expertise of personal experience with hands-on prototyping. Because unlike the postdocs, not postdocs, unlike the medical MDs in the US who all have a basic science degree, some people even have PhDs, prior to entering medical school, we are primarily trained as undergraduate physicians. ability to do a bit of this troubleshooting and all through our own learning bootstrap. So no formal training for most of us.

And on the other hand, the scientists, engineers don't speak medicine, don't really talk about clinical problems. So it can be a bit difficult to have a conversation or even have a collaboration. So a closer linkage between these two entities would be useful. That's how I see it. Yeah, I think from our end, a lot of times also, this is challenging, but for clinicians, really it's where do you find the time? Because a lot of times, you really just spend your head in the sand, you know, doing the work because there's always been done that the sad truth is that service of clinical obligations takes priority and the volume of work to be done over time. So if you're always operating at that capacity, 90 to 100 percent, at the end of the day, we are flat and there's really no bandwidth for us to take on this. So it takes someone who's crazy, who doesn't have too much things going on, who want to spend their own time, invest in this, to take things on. Otherwise, we'll be like, finish my day. Let me go back to the grind because that's all my energy for that day. Whereas if we have protected, not so much protected time, but if there is reserve for them to think about things, by being deliberately a little bit less occupied, then there is a potential for them to have that way to think, to make things change and potentially, actually significantly change how things are done.

Yoann - 0:37:58 I think you, so I totally agree with, and I think you kind of answered my, the last questions that I wanted to ask you, which was about some of the challenges, some of the challenges, sorry, that you might anticipate or you might see in our clinicians, researchers to consider some of these business model kind of related kind of considerations, including some of the cost and economic considerations. You mentioned about the lack of bandwidth and time as one. Do you see any other challenges that if tomorrow we, let's say, NUH, would more kind of a top-down approach asking you us to consider also, okay, innovation is great, but there is also be

some kind of cost considerations, cost effectiveness considerations. Yeah, what might be some of the challenges that our clinicians might might kind of foresee?

Cheah - I think aside from time, the other thing that clinicians, or the other problem that faces us, clinicians innovators or clinicians in general, is effort. People may not care enough about doing this because I derive enough satisfaction with my clinical work, I'm proficient with what I do, right, and doctors are generally not risk takers. So we may not see the need to make things different because it's safer to follow guidelines. That's what we're trained to do throughout our training. It's easier to follow whatever is done in research papers than to try to pioneer your own path and face scrutiny, criticism and doubts. And I think that is it. Unfortunately, I'll kill you, but because the dogma in medicine is always to rely on evidence and to do the safer path. So I think that is the second thing that may face clinicians, which is apathy. And all of them, they may have time, but I don't care anymore.

Yoann - 0:39:53 Yeah, I agree. Unfortunately, yeah. And maybe just to close the loop and to come back to my first questions, I was discussing just a few days ago with someone that has more or less your profile in terms of the clinician background, but also more on the entrepreneurial kind of things. And I mentioned to this person, but I was like, you're almost like an entrepreneur. And that person, the clinician's like, oh no, no, no, I'm not an entrepreneur. I'm a clinician, at best, I'm an innovator. And I thought this kind of interesting that this person didn't want to be recognized in a way as an entrepreneur because he or she was an innovator. And I just wonder if like, how do you consider yourself as, obviously as clinicians, but you consider yourself as an entrepreneur, intrapreneur, as an innovator, part of the system, so or just as Cheah and that's it?

Cheah - 0:40:45 Well, it's, yeah, it's really hard to put. Nowadays, to be frank, I find innovation to be a bit of a buzzword these days. Everyone is an innovator and that's not wrong because innovation is about, you know, trying to find new ways to do things better. So it doesn't mean that you have to come up with new devices, new AI or whatever to call an innovator, in a way. Entrepreneur, on the other hand, is perhaps a little bit a bit beyond just that, right? It involves, to me, in my perspective, you know, as an entrepreneur, it involves professional banking. You have to go places to sell your idea, pitch to get investment. I think that element of entrepreneur is probably not in me at this point, right? I'm not at this point going to investors, pitching ideas, maybe in the future, possibly. But at this point, I think if I end up doing that one day, meaning end up looking at how I'm going to this investor, NGO, otherwise, getting my fund raised and looking at how I'm going to recruit such that this startup or this company that I'm doing is planning. I will consider myself an entrepreneur if I'm at that stage. But if what I'm trying to get my solution, my technology out there, then I think innovator may be a more appropriate term, appropriate bracket for me to be identified. I think that's really no right or wrong.

Yoann - 0:42:11 Okay, okay. Great, thanks, thanks a lot. So I went through the questions I wanted to discuss with you. I just wonder if there's anything we have not discussed that we should discuss, or any questions you might have, or anything else on that topic of, you know, the kind of economic considerations of digital health solutions throughout the life cycle of such solutions, basically from development validation to implementation. Anything else?

Cheah - 0:42:37 Yeah. I just, you know, of course you have a lot more experience in the digital health space than I do. And one of the questions that we always face whenever I either attend or go for pitch-in is, how do you cross that chasm to profitability? Because a lot of digital health solutions do not on its own generate enough revenue eventually to make it sustainable. Yeah. Right, and I think that we see, do we always necessarily have to rely on some kind of centralized government funding for this kind of initiative? So, could you, or do you foresee this becoming self-sustaining, becoming actually an entity of its own? And is this a question that you get from our systems, from more like external, kind of the more traditional investors, VC and pre-seed investors, or is it doing pitching?

It's a sentiment I've got when I spoke to a few other clinicians. When, so there are some clinicians, innovators who have been developing new therapeutics in the form of pharmaceutical therapeutics or devices. And quite a number of times, in fact, when I was there and someone else was talking about, you know, developing an app or some kind of digital solution, the initial reaction is always, how do you make money? Or how do you make sure it's profitable? Right, and there is always seems to be the question that comes back at whoever is trying to come up with a digital therapeutic solution. I was just wondering if you have thoughts.

Yoann - 0:44:10 So, you know, you're totally right. And I think that's really the challenge. It's about getting the momentum, the traction, getting the base of users, the hand users, the patients that will use the solution. That's the first priority. And there are a lot of different considerations when it comes to the monetization, reimbursement and so on, how do you price a digital, like an app. You know, it's an app, so as a patient, it's an app, so I'm not willing to spend more than one or two dollars, because it's what I'm used to, on more traditional wellness type of apps, right? And then quickly, the questions of scalability also, and that's, unfortunately, it's almost none of the solutions out there except a few, maybe a handful of solutions, kind of managed to address that questions of adoptions and of scalability. But the third one, which is about the profitability, which I know, obviously, they are all interrelated. It's still a really a challenge because there is no, in most countries, there is no kind of reimbursement pathways.
In the few that you have, it's not that meaningful. The existing reimbursement that you have, if you are like, let's say, in the UK, in Germany, or in France, is not that meaningful, or not to the extent that this software as a medical device would want to get basically reimbursed. So it's really a challenge. And a study was just published, I think just a few days, few weeks ago done in with the DIGA in Germany, you know the software as a medical device in Germany, so digital therapeutics and basically one of the top one, top two considerations but also bias for physician to prescribe a digital therapeutics is the question of cost and in a way you might kind of argue as a physician, that's not your issue, basically, right? You might want just to think about the clinical impact, the cost considerations, but also the experience of their patients using the solutions, the digital solutions, was basically the top two considerations. And I found this really interesting because it goes beyond just the clinical impact, right? And to your point about innovations being a buzzword, I think all these digitalization of healthcare in general has been for some time, but I think we are kind of, I don't know if we are about to hit the rule, we have already done it, but a lot of companies are going bankrupt, as you might have seen on the news, because unfortunately, it can't just be a buzzword anymore. And they can't get any ROI. And I know some companies that are just not going to the software as a medical device route. They're just like, I'm just going to position my solution as a wellness solution, you know? So I don't have to go through any clinical trial. I don't have, and in a way, it's quite interesting because like three, four years ago, when I had these considerations with the pure digital therapeutics, you know, the kind of manufacturers was like, no, that's no go, this is a medical device. Right, it's a software as a medical device. So you get to two or three years clinical trial.
If you think about some of the solutions in the US, like Akili, Akili Interactive, they have been working on the solution for the past like 10 years, right? Not every single startup can afford to spend 10 years on developing and validating a solution. And so, yeah, three, four years ago was like some would go the wellness route to avoid all these like additional orders. And it was kind of really a taboo. And just about a year ago, I was in a digital tabloids conference. And because every single of them were struggling to get tractions, to get reimbursement and so on, then this came to the topic on the table. It's like, okay, maybe we should try to explore different path to market, different business models. And I'm not sure if it's right or not, to be honest, because at the end of the day, it's still a medical device. So to your point, we need to get the evidence on the safety and the efficacy, effectiveness. But at the same time, I don't know. So I don't know if it's right or wrong, but definitely, some of these organizations are trying to be a bit more resourceful and creative, and they're exploring the different path, basically. I totally get you.

Cheah - 0:48:46 It's interesting, and I'm not sure what is going to be the trend. It's interesting to follow the market like the US or some of the European markets and to see what will be done here in Asia-Pacific. I look forward for Singapore to have a bit more official guidelines on that.

While we are in this topic, cost-effectiveness-based studies in Singapore are actually a relatively new area. And what I realized is that as we are studying certain diseases, that we are always just extrapolating evidence from the West. And we don't even have fundamental basic costs to kind of knowledge of certain diseases locally. And that actually makes it difficult for us to benchmark because every health system is different. So I feel that maybe like, yes, I, as Sosu-Yiu called it, public health, or even wisdom, you know, having that framework done for particular disease areas, will help a lot, and that is a whole area that we can just attach at this point, at least academically.

Interview Transcript with Chevannah (P14)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:00:34 Hello, good morning. How are you?

Chevannah - Very well, thank you. How are you? Good, excellent.

Yoann - We are, in the next couple of like maybe two or three weeks, we are going to submit a paper. I don't know if you remember the paper number two. And we basically, what we did is like we asked over like 60, 62 individuals to define the factors that are important to, that might impact the economic value of a digital therapeutics. And so we identified 59, 59 factors that would impact the economic value of a digital therapeutics. And then we asked the same 62 stakeholders, basically, to what extent do you consider these 59 factors in your day-to-day job, right? Because if you are researchers, if you are clinicians, if you are like a more like policymakers and so on, obviously you all have a different agenda. And we identified a couple of gaps and that's why we are doing this new paper and thanks again for accepting to be interviewed for that one. But I'm hoping to basically send the paper to for publications in the next few weeks, have a pre-print. And then I had a note to myself to follow up. I forgot her name. I was supposed to follow up also internally in view of maybe potentially presenting that paper in November, right?

Chevannah - 0:11:02 Yeah. I have kind of a mixed-up message because I don't think that can help much. In terms of the questions, I don't have any answers on that.

Yoann - 0:11:26 Which is fine. I think what I wanted to discuss with you, and you let me know if some of the questions are not relevant or out of context and so on, or not applicable, but is really your role, basically it's two questions. Your role with individuals that are developing and validating and implementing digital health solutions. So not only digital tablets, but digital health solutions. So kind of your role and how do you help them and you know your throughout this kind of life cycle of any solution. So this was kind of mainly the first questions and the second question is to understand in these different kind of interactions that you are having with the different teams and they might be academic or you mentioned about GE and so on, is like how these considerations of economic value might be considered or not considered at which stage? Because some of the teams, they just look at, okay, we are going to have the best tech ever, we are going to have, looking at clinical trial, so do they consider the economic impact at some point, or is not really of considerations, or is not valued? So it's really to understand from your perspective and in a different ecosystems on how some of these economic considerations might be important or less important and taken into consideration by the different teams. Or it's just like, let's look at the clinical impact and that's it. And we are going later on to figure out, because it's a DGA, it's not a DGA and so on, some of the economic considerations. So it's really these two questions about your interactions with these teams. And then two, then we can talk about are these economic value factors being considered or not, basically.

Chevannah - 0:13:18 I do think I have this end-to-end kind of value proposition for digital solutions and then building, first of all, in the very early stages, ideation, conceptualization, strategy building, and then going in the product market feed, and then at the end, go to market strategy. So the build part normally is done by IT team and also I'm helping startups and companies to not only to fit the product into the market but also to find the right partner from the clinical side. So, understanding the complexity of the health systems, specifically based on geography, is crucial. As you just right now mentioned, the social economic impact. on the economic and social factors in different countries.

Let's say Spain, one of the European countries, and then Spain was interesting enough when I was visiting France, who I know, digital health, to figure out that they have mostly, they don't have

widely available public insurance, health insurance system. Most of the Spanish citizens insured over the private medical insurances.

So, and that's why the hospitals which are present, presented in Spain, most of them are private ones. and they are really incentivized by delivering best care to population. So this incentivization leads to applying the innovative solutions. And that's why I found most of the Spanish hospitals, interesting enough, they are looking for chief innovation officer, chief digital officers to build this. They are first of all digitized. They have a fragmented IT infrastructure, but still they are connected through and interoperability gives another opportunity to invest more in digital solutions. The population becomes also very interested in applying these solutions. Pharmacies, I was stepping in any pharmacy and was asking, they use electronic prescription for a while. And so in contrast to Germany, where we just now building this IT infrastructure, we don't have extra funding for, we have a different incentives to digitize hospitals and care, basically, we're not talking about only hospitals because it's a primary care, secondary care, but a totally different health care system because most of the population out of 83 million, 79 something like that or that number insured by statutory health insurances. And that is a kind of must. You have to be insured applying for the job. So that's why my understanding, my perspective, the largest investors in German health ecosystem are health insurances, digitalization, digitization running across the care. This is a huge contrast to, let's say, Spanish ecosystem. And then if we will look on U.S. market, it's absolutely different because most of population in the U.S. is not insured, and only those who are insured, they have access, first of all, access to care. Secondly, it depends on these access to care. They have, yeah, the opportunity to use any digital solutions. And so it's totally different incentives based on the healthcare systems. And I think the healthcare system structure is basically is driving all these processes of digitalization. Yeah, and then when we define, going back to my role, when we define the right partners, then helping to evaluate maybe the results and paper trials and so on. So it's a kind of like more... I just read recently a very nice book, Generalist, by David H. Stain about this specialization... and generalists, especially those who are just focusing on something, and generalists who can see both long-term and short-term things. So I think I'm kind of both. I'm kind of a generalist who can see long-term applications and also look specifically on short-term priorities, where we start, where we look, what does it fit, how and what we can do that.

Yoann - 0:20:09 I see. And do you see in all these interactions, do you see the need more and more for these digital health solutions to have like a business case and to demonstrate the economic value of their solutions? Do you see this coming and emerging or not yet?

Chevannah - 0:20:28 I think it's now, there is no discussion, do we need more or less? I think we are kind of already in the flow that it's the same like with AI. conditions where we don't have any other choices. Do not use this. The value of digitalization is already approved and showing by many success stories and applied and basically the way how it can be used, deployed, is different and the cost involved. The example will come, for example, the technology calls ambient intelligence. And ambient intelligence is basically IT, variables and sensors which physically can be connected and applied for acquiring the health information. intelligence has a lot of potentials specifically with the applications of AI in the secondary and primary care. So the example is very simple. Instead of using, I'm working in a hospital for example, and I have several, I have one system where I have to collect the whole information on the patient, where I can just exchange information, see immediately the results of examinations and those kind of things. additional information which I have to physically type. So, since a couple of years there is a new law in German hospitals they are supposed to have two portals, one for the patient communication, one for the communication with the healthcare professional in the hospital. So, in that case, the developers are coming and telling, okay, we have this, we have this, we have this solution, so you just need to click this, click that, and so it's just overwhelming healthcare professional because they don't have time to click on many solutions. Instead of that, having one portal which can apply everything, and this is where ambient intelligence can be highly applied. So those kind... this is kind for me... the Kant law, Immanuel Kant said once that quantity brings to new quality. That

new quality develops a next quantity. So the next quantity leads to another quality. So we reached specific quality of digital solutions specifically and particularly after the COVID. And now, consumerization and it's not possible to stop or return. Even those digitally less literate population, they are adjusting the solutions and they are looking into these solutions like booking the appointments with the doctors or electronic prescriptions or other solutions, so there is no way back, only way forward, dependent on the new coming challenges and needs. These processes, the new processes of digitalization are leading to the new needs and challenges within the healthcare system. system with the new complexity of new regulations, not previous regulations, but regulations on AI application and cyber security and other things and privacy. And this new challenges, this is only one, but the other challenges they're leading to develop the system for them, for them, for them.
Yoann - 0:25:39 I see.

Chevannah - And you know for any DIGA, so they have to demonstrate the clinical efficacy of the solutions within 12 months. I think some categories are related to the patient experience, some sort of improvement of the experience of the patients.

Yoann - Do you know how the economic considerations are taken into consideration for DIGA or is mostly about the clinical impact for now or the experience that we have, the impact on the experience?

Chevannah - I would think the second one, the latter one. So at the moment is still I think there is not much, if I'm looking at the German market and I'm looking on the French market there's not much solutions DTx which can be assessed fully and I think it's more currently on the clinical experience improvement within the patient journey path. So how is it prove the patient experience and patient journey? rather than the long-term outcomes the economic outcomes. I don't think that we have a comprehensive system which already assessing this long-term, mid-term outcomes. It's not known to me. I haven't seen. Maybe it's an ongoing process and Megan probably knows or Jessica Schuller is currently part of one of the company where they're trying to build some digital solutions and previously working in this alliance. But from that perspective, I haven't seen.

Yoann - But you know, I remember Megan, she's at DIME now, right? She's with Digital... Medicine Society. I have no idea what is this. But I think she stays in the advisory board of this alliance. I think they, I'm not sure, but I think they hire it as somebody and then it's still, and it would be a non-for-profit organization and she, I think she works for another non-for-profit organization.

Chevannah - 0:28:37 Yeah, the team, so they were acquired by Eversana. Yes. I've never heard about this company before, to be honest. It looks like a US-based, but globally active company, which is providing consultancy on commercialization for pharma and medtech and pricing strategy. It looked like they had a gap in the reach and other things and lots of solutions and products which Hellware International had was probably a great fit into this gap. It looks like this is my interpretation. But the whole people, the Hellware team, they are now working officially for Eversana. And they have a part of the company now, the Hellware International. They preserved the name, but it's just based in Italy.
The international other locations moved to Eversana. So Alberto is definitely, he became the president of this life sciences healthcare sector. And other guys who were in his team, including Luigi, Alberto, and Christine, and everybody else is with him.

Yoann - 0:30:16 Okay, I see. Now it's good to know, like, you know, because the interaction, basically for me, is like once in a year right when we have a conference So it's either typically is either I go to the DTX London or I go to the frontier Health and so it's good good to know what everyone is kind of Doing and so on but back to the study, you know I think that's that's mainly the two questions that I wanted to confirm with you and to get a more like the your perspective

and from the European side. But I think, I don't know if there's anything else, and you have seen some of the questions, but I don't know if there's anything else that you would want to mention, you know, that we have not discussed, or anything on that topic of economic value of digital health solutions. I don't know if there's anything else you would want to share, or any questions.

Chevannah - 0:31:12 I looked at the questions, absolutely. What could be discussed, economic value of DTX? I think probably, this is what I mentioned, we need kind of like, maybe market-based infrastructure. So to maybe to, no, this is probably different. What I wanted to mention, and I think this is now working with different heads and now working with the IT teams, I think the establishing standards, specifically standards for data exchange is absolutely essential.

And once we will have the standards for data exchange, and I'm talking about essential standardization, semantic and also the infrastructure standards. Once we will have, then we will have, we can see how scalable this solution, and once it's scalable, how in setting these solutions, and what drives application of these solutions, what drives the building of a new solutions what drives market in Yeah in terms of the deployment of this solution The standards I mentioned semantic I mentioned the IT infrastructures, but also standards for data exchange currently I'm working with the project we've selling gene therapies. And we're talking about how we can track and trace the product once the patient meets the doctor and the doctor prescribed this treatment. and the doctor prescribed this treatment.

Interview Transcript with Camirah (P15)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:00:00 So first of all, thanks for your time, accepting to participate in this study. I think it's quite important to have your view, as you have been involved in a few different aspects from a tech development, but also interacting with the community, the different stakeholders from clinicians and so on. And so yeah, I was kind of looking forward to have this conversation with you to get your input. One thing that I've not mentioned is that obviously there is no right and wrong kind of answers. It's just your perspective, right? So yeah. So maybe to start with, if you don't mind, could you help me understand the process you went through from development, and you call validations of your solution that you've been working on for a couple of months now. So just the high-level kind of steps of the process, and also some of the stakeholders that can help you one way or the other, kind of directly or indirectly.

Camirah - 0:01:05 So, thanks for the question and conversation. So, to start off, usually when I do studies on tech development for a clinical use case, I would start off with a niche assessment with the patients. So the patients are always the core of my research studies. I don't really deal with processes so much but really on the patient outcomes. So usually I will start with some form of qualitative studies like what we are doing now to find out what are the main barriers and facilitators to someone improving their health status, be it using non-digital or digital solutions. So, for example, for my apps, we started off with an observational study to find out what's the current rate of current uptake of weight loss programs in patients and then we realised that it's mainly because of the low help-seeking behaviour of the people in Singapore. So then we tried to find out why and we went to do some needs assessment with the patients and then found out that it's because it's very cumbersome to come to the hospital, cumbersome to go to the health service programs to receive intervention. That's why we thought of using digital solutions because it transcends geospatial and time. So we also tried to find out what's the adoption of apps in patients and specifically weight loss apps. So from there we also tried to find out what are the essential elements of features that they wanted to have in the app in terms of weight loss. And from there we developed the kind of requirements we wanted for the app. So then at this point we will get clinician buy-ins. So in my case we had the weight management doctors, dieticians, physiotherapists, researchers and stuff like that. I think one thing that we did not have, and it's a pity, was having administrators in the hospital.

Yoann Like the hospital administrators.

Camirah - 0:03:23 Correct, correct. Hospital administrators. Because if we really want to roll this out as a clinical service, then for sure we need their buy-in also, but we did not do that. We were too focused on the clinical service delivery team. So we developed that and then went through a couple of trials. One was a pre-test, post-test study first, so somewhat like a feasibility study. Then after that, now a randomized controlled trial to see whether it really works. At this point, we still have not done cost-benefit analysis. So it may be a money-losing intervention, we don't know, but we may be throwing money into the ocean. So this is one downside. And then, what was the next question?

Yoann - 0:04:11 So the one question was the different steps of the process which I think you already answered, and some of the stakeholders that were involved or not involved. So basically, your point is that maybe from a kind of economic perspective, perspective. Maybe I should not answer this question for you, but how many months was this process for now?

Camirah - 0:04:34 Around three years already.

Yoann - And so, is it fair to say that when you had the initial phase of the tech development, you mentioned about the user centricity and patient needs and so on, what were your key priorities at the time? Phase 1 of the development and the requirements was purely about patients' needs and how you are going to address them?

Camirah - 0:04:59 Yes, mainly the patient needs. And then we also monitored their adherence and engagement to using the app besides their needs. Because sometimes whatever the patient tells you may be different from what is really observed. So, luckily, our engagement rate is not bad so far, but I think it's because of some form of self-selection bias.
So, recently we tried doing some form of costing analysis. But, having difficulties in doing that because you know this kind of formulas sometimes we are not too sure whether that's like the gold, there's no gold standard per se. And then we are not sure whether we are holistic enough in presenting the costings of this project to the higher ups of management. So that's something we are still struggling with.

Yoann - 0:05:56 with anyone on how some of these cost considerations should be taken into consideration? One way or the other, from clinicians or from any stakeholders, any conversations on the economic impact of some of the costs?

Camirah - 0:06:14 Actually, with clinicians, not so much, but I've been talking to the DC team and the AI.
Yeah, the AI. Our business is DC. Yeah. So also because of this implementation part of the study, we went to DC, I think, because Nick Cervales is my mentor. So, and we specifically looked at this because we foresee implementation as a barrier. And then also sought his advice on how to do the cost-benefit analysis. He's given some pointers there. So that's what you see.

Yoann - 0:06:59 And maybe if I take a step back, you said now you're part of the clinical validations, I mean in this phase of the clinical validations. What are you trying to validate? What are your key priorities in which implementation would be?

Camirah - 0:07:17 Our implementation is one, our end point is to weight loss and any reservation of sub-clinical preservation site, impact group of horrors and group of threats. So that's one, and because recently we found that it's okay more or less having some good positive outcomes in terms of the end point, the weight loss. So we are trying to bring it to the next level which is to implement it in a primary care setting. So this is where we have to do a lot of considerations on the administrators by designing a way of treating. So now we include them into the conversation, the administrators.

Yoann - 0:08:00 Primary care right?

Camirah - 0:08:01 Yes, but primary care is still under our NUHS.

Yoann - 0:08:05 So polyclinics?

Camirah - 0:08:06 Yes, polyclinics. So we've spoken to them. We are also trying to form a workgroup within NUHS to see the feasibility of having this as a hospital-wide program.

Yoann - 0:08:20 And you mentioned that you had these conversations with Nick about some sort of cost analysis. Why did you have this conversation? What was the need or what kind of triggered this need for having these conversations?

Camirah - 0:08:36 Because it's a requirement of one of the grant applications.

Yoann And it's actually very good, I think. More and more, I find that these grant application forms require you to justify the economics of your invention.

Camirah Yeah, especially NHIC, they will always ask you to justify.

Yoann - 0:09:00 Independently of the maturity of your solutions? Or is it because of the specific grant or...

Camirah - 0:09:06 Yeah, I think it's because of the specifics. POC or POV kind of run calls, they require you to state the economics. But I think usually, because we are not so well versed in it, we just give the macro kind of...

Yoann - The high level picture, right?
Camirah - Very high level, which sometimes may not be attainable.

Yoann - And so you said that Nick, and it's not about Nick at all, right, but so you had this conversation with Nick, so he gave you some kind of high level kind of pointers and guidance on what you might want to consider, or what might be good enough for the grant, basically?

Camirah - 0:09:43 So, besides economics, it's the implementation part, like how do we assess or evaluate the fidelity or the adoption of this kind of program, how do we do stakeholder engagement, how to analyze their responses, how to overcome barriers and facilitators when you look at the big picture. And he also recommended some frameworks to look at. And these frameworks would trigger you to consider about those structural and process-related factors. And these are usually things that a traditional researcher won't think about.

Yoann - Do you remember by any chance some of its framework?

Camirah - 0:10:27 Oh yeah, so SHIPA is one of them, CFIR, VA is another one, more specifically COMBi, that's more behavioral kind of the... So these are the three more popular ones.

Yoann - 0:10:43 And so, in some of its framework, so it's more towards the implementation science, right? Right. And so the cost, economic considerations, would be one of the dimensions of some of this. Right?

Camirah - 0:10:55 Yes.

Yoann - 0:10:57 You've answered quite a lot of questions already. How would you define the, sorry it's a bit back and forth, but how would you define the impact of your solutions, kind of at scale? How would you define impact for your solutions?

Camirah - 0:11:17 So traditionally I would define it as the decrease in prevalence of a certain disease, but recently more and more I think it's important to also put in the economics part, like how much cost savings or cost value addedness do we provide to the healthcare system.

Yoann - Why is there such new or emerging considerations for the economic considerations?

Camirah - Mainly because of the grants. Because I think funding bodies nowadays, more and more, they want to justify why should they invest money. So to justify that, we always have to tell them how much economic benefits would our solution provide. which are hard to find.

Yoann - 0:12:00 You mentioned earlier about a traditional researcher. Maybe I should have asked this question earlier. Do you consider yourself as a researcher? How would you define

your role as part of the cluster? My role? Because it's more on the research side, more on the implementation side, a bit like clinicians, hybrid, between the translational...

Camirah - 0:12:24 I think I'm more of a hybrid, because it's difficult to kind of split up, because while I'm the researcher, I'm also the person carrying out the intervention and doing all the administrative work. So researcher slash entrepreneur. I'm not only money. So maybe innovator.

Yoann - 0:12:54 I was thinking about entrepreneur because of what you have done for the last 3 years with these specific solutions. You are basically taking the role of a CEO, right? I mean, going through different steps, leading the tech development and so on. But innovator, yeah.

Camirah - 0:13:11 Entrepreneur, I would expect someone to start a startup, but I think we are not daring enough to take that step.

Yoann - 0:13:20 Not yet, right?

Camirah - 0:13:21 Yeah, maybe never.

Yoann - 0:13:23 Is this part of your road map or personal aspirations? This is not for the context of your study, by the way.

Camirah - 0:13:31 Yes, but I think maybe after I get tenure, because now a lot of the work that I'm interested in, in terms of innovation, has to take a backseat because I'm on tenure. I only have 5 years to prove myself, otherwise NUS will kick me out of NUS.

Yoann - 0:13:46 So, I'm not so familiar with all of this, but it's basically at the end of 5 years, you get 10 years kind of renewal, right? Like for life. Oh, you have 5 years to... yeah.

Camirah - 0:13:58 Yeah, I have 5 years to prove that NUS should hire me for life.

Yoann - 0:14:01 As a full-time, long-term, for-life contract?

Camirah - 0:14:03 Yeah, yeah. Okay. So only after I get that, then I can focus on my own innovation work.

Yoann - 0:14:10 And would the commercialization or implementation of such solutions help you?

Camirah - 0:14:16 Yes, yes, it will.

Yoann - 0:14:19 So really on the translational kind of projects?

Camirah - 0:14:24 Which is why nowadays we are also talking to start-up partners who want to license our solution.

Yoann - 0:14:33 In this kind of cost analysis, more conversations I guess at this stage, but what kind of cost have you considered so far?

Camirah - 0:14:44 In terms of?

Yoann - 0:14:46 about the cost analysis of the cost impact of your solutions to the healthcare systems and to the patients. I don't know if you had any conversations with Nick or anyone about some of the specific costs that you think is going to make it or break it.

Camirah - 0:15:02 I think two main ones. One is managing the digital solution system. Another one is the manpower running the program. These are the two main ones that will cripple the project if not managed well.

Yoann - 0:15:19 Could you elaborate on the first one? I'm not sure I'm...

Camirah - 0:15:21 Oh, so like for the app, because we are constantly collecting data... Oh, it's the maintenance... Yeah, the maintenance and the upgrading, the patches and all these things.

Yoann - 0:15:33 So it's more the cost related to the solutions, right? To keep up the solutions, whatever, that are privacy and so on. That's right. And then the second one is about the headcount, right? The resources that will be required, but more from the manpower.

Camirah - 0:15:47 Yeah, so the clinical, patient-facing end. Because the tech solution is not supposed to replace the human being, it's supposed to augment the work that we do, so that you can see more pictures. And because this is a new service, we need new manpower.

Yoann - 0:16:07 Beyond Nick as a potential expert that you have access to, do you have access or do you know who you can talk to when it comes to all these costs, considerations, health technology assessment? Do you know who you might have a conversation with or who you could engage? Within your network, within the new edge?
Camirah - 0:16:30 I think for the tech assessment wise, I know some people informally may be able to help the informatics people. But also I know there are also companies that help to assess the tech. So that's for the tech and financial part. What's the other one you mentioned?

Yoann - 0:16:54 On the economic aspects, do you know who might help you on the cost? You mentioned about the cost analysis.

Camirah - 0:17:00 Yeah, that I don't know. Yeah, not sure.

Yoann - 0:17:04 So for the grant, you submitted some high-level forecast? How confident are you with this forecast?

Camirah - 0:17:14 0.1, maybe 0.1. I think it's too high level already. We try our best, but because the figures that we extracted are national figures, but the target population is actually only a sub-population and they are at the rate. For example, I use the prevalence of obesity in Singapore, but even within NUS, our prevalence of obesity is different.

Yoann - 0:17:38 Right.

Camirah - 0:17:39 Yeah, so definitely the economics will be slightly different.

Yoann - 0:17:44 I will mention three specific factors of cost, and you tell me if you have considered these factors or not. And I think you mentioned already some. So the first one is on the health care resource use, so manpower and so on. So I guess this is your top two factors, right, that you already considered. In terms of the adherence rate of your customers, patients to the app, it's also something that you already considered, right? And also, the cost of the DTX of the solutions, which is basically the maintenance, so all this has been considered. To what extent have these three costs have been considered, just like kind of high level for now? Or you had like, because you mentioned, for example, on the adherence rate, attrition, and so on, did you do like additional kind of research to try to understand what could be some of the benchmarks and to compare your services? Or how far have you been to try to understand some of this?

Camirah - 0:18:46 Unfortunately, no.

Yoann - 0:18:47 Not yet, OK.

Camirah - 0:18:48 Yeah, yeah, not yet.

Yoann - 0:18:50 Could you share, if you have any examples of stakeholders, input, feedback that you had over the last three years that really helped you one way or the other to kind of guide the development? It could be negative or positive comments, but any stakeholders that particularly helped you one way or the other over the last three years? I mean, kind of influential as we say.

Camirah - 0:19:14 I think the most influential would still be the doctors' comments because usually they are the kind of team leaders for any kind of health care services. So they would have an understanding of what are the roles and responsibilities of the different allied health members and the doctors within the team. And then they would also be able to provide some information on how administrators think of the solution. And then I will modify from there. So for example, recently we've been working on moving this project to primary care. So previously it was always focused on tertiary care and community, but now we are focusing on primary care. So mainly because, I mean partially, it's after a discussion with the clinician, we thought that a new model of care is needed. And then we discussed a little bit more about the different stakeholders' participation and things like that. So I would say the doctors provide very good feedback.

Yoann - 0:20:19 Which goes beyond the clinical aspects, right? It's towards the implementation, the stakeholders, the buying.

Camirah - 0:20:26 Yeah, yeah.

Yoann - 0:20:27 It's quite influential in your case, right?

Camirah - 0:20:29 Yes, yes. Especially the uptake and adherence of the patients. They will be very familiar with that.

Yoann - 0:20:37 So what's your plan with the hospital administrators? You were saying that maybe they are the only stakeholder group that you have not engaged directly with yet. What's your plan with them?

Camirah - 0:20:48 So now we are having conversations with them. So before we do that, we have to prepare a lot of statistics to show them how the current situation is like and how the solution helps to improve the situation. So then they would provide more inputs on the other parties working on similar things. Then bring everyone together and brainstorm again.

Yoann - 0:21:14 Would you say that having these conversations with them is almost kind of trying to convince some investors to come in? Like you're trying to pitch your solutions to them? Like some sort of investor meeting?

Camirah - 0:21:25 Yeah, yeah, yeah. In a business way. Yeah, you're right, because they are also the ones to pay money.

Yoann - 0:21:33 Yeah, so you want... I think their buying means that you can go ahead of what's the implementations, right?

Camirah - 0:21:39 All right, all right.

Yoann - 0:21:41 But did they, in the initial conversation that you had with them, did they mention these cost considerations or economic impact in some of the conversations about, you know, your solutions is great, the clinical safety, efficacy, obviously, but to your point earlier about the resources and so on, is this something that kind of came up in some of the conversations?

Camirah - 0:22:01 I think maybe we haven't gone so deep into that yet. Because now we are still trying to form up the model of care for the specifics. Then only we can start to calculate all the costs.

Yoann - 0:22:15 And now that you know what you know, after three years, is there anything that you would have done differently towards the cost kind of considerations, having the hospitals and administrators engage, is there anything that you would have done differently now, that you know that you know? From a process standpoint, if you look at the last three years.

Camirah - 0:22:40 I think yes, I think I would have chosen the test site, the place where I conduct the research. I would have gone into primary care straight away. I've not done any research there yet, so I have to study all over again. You need to reconfirm and validate. the impact of the cost considerations will be more or less important at primary care level versus tertiary care.

Yoann - Is there any difference that you might expect?

Camirah - I think if any difference, slight differences, because for the longest period of time, poly, primary care is spending a lot of money on this. So then, I'm not too familiar but I can see that they are now more concerned about primary care.
Yoann - 0:23:53 Are you aware of any specific framework or methodologies that are out there to try to assess the economic impact of your solutions? So the last three years, the entire process, the lifecycle process, when do you think that some of these cost considerations should be taken into consideration, some of these cost elements? So you had the phase one on the tech development.

Camirah - 0:24:22 Is this too early?

Yoann - 0:24:24 Because maybe you don't have the solutions yet. I don't know. During the clinical validation, so should this clinical validation just purely be about safety and efficacy? And the cost considerations become kind of a third phase of implementation. So when do you think that as an innovator, when do you think some of these cost elements should be taken into consideration?

Camirah - 0:25:01 I think it depends. Because for maybe, let's say something that you know would never be reimbursed by the government, The kind of economics thinking must come in right from the beginning, I feel. Because if it's like a purely consumer-driven price on that product, right, then if it's too expensive, I mean, if it adds up the research costs and everything, requires the product to be that expensive, then obviously no customer will buy and use this money and close shop. But if it's a product that is so important that the government would definitely subsidise, like for example, this few wonder drugs that just came out, right? SGLT2 has been heavily subsidised now that there's a supply to it, you can just, you send to the buyer. So that kind of product, I think, you don't have to think about economic, so early.

Yoann - 0:26:02 In case of potential reimbursement, right?

Camirah - 0:26:03 Yeah, correct. The government's bringing it.

Yoann - 0:26:06 Good. Anything that you would want to share when it comes to tech development, your digital health solutions, and the cost considerations, the economic impact, anything that we have not discussed that you would want to share, or any questions you might have?

Camirah - 0:26:23 I think one thing that strikes many tech developers in the academic or clinical setting is that a lot of these techs are developed very silently. For example, I'm developing this tech now, someone else may be doing that but I don't know, and then we replicate and end up with the same product. And then you don't know what to do with the replicated product. So, because I think different from commercial, for like clinical and academic setting, our end goal is not so much about making money, it's about like the clinical end point, the customer's benefits, and so we don't want to be like reinventing the wheel, and rather collaborate with each other. But now the problem is we don't even know what each other are doing.

Yoann - 0:27:18 Yeah, so it's like... But you know, to your point about maybe your goals of the systems, our systems, is maybe not about making money, as you said. So do you think that this kind of might influence someone like yourself as an innovator, as a researcher, on how some of these cost considerations might be considered, or cost payments are considered. Especially if you are in the private market.

Camirah - 0:27:42 For sure we won't be so concerned about the cost. That's probably why a lot of us don't know how to convert. We're usually driven by it. A lot of us don't know how to do it. I mean compared with startup founders, the first thing they would do is to calculate the market size, terms and sum and all these things, but we really don't know the... So I think that's a huge difference.

Yoann - 0:28:06 Good point. Anything else you want to mention? Good point. Anything else you want to mention? Should I stop the recording? Awesome.

Interview Transcript with Priscillah (P16)

Raw Data Prior to Atlas.ti Coding

Priscillah - 0:02:30 On a soumis un papier il y a deux jours. Nos projets avancent. C'est le principal. J'ai vu que ta collègue est partie.

Yoann - Oui, Agatha est partie. Elle revient à Singapour, mais pour d'autres raisons, dans une semaine. Mais elle a rejoint Roche en Suisse. C'était une qui nous a aidé à écrire le livre il y a maintenant une petite année. Donc, oui, c'est les cycles que tu trouves dans toutes entreprises publiques ou privées après quelques années. Donc, voilà, on est passé nous aussi au niveau de l'Institut dans un cycle où on a pas mal de personnes qui sont parties et que du coup, là on revient sur une phase montante où on a 3, 4 personnes nouvelles qui ont rejoint. Donc c'est intéressant aussi d'avoir ces phases au niveau du centre.

Priscillah - La même chose ici, en fait, j'aurais voulu que ça soit un cycle de quelques années. Moi, j'ai une équipe très particulière de talents non traditionnels qu'on amène dans le domaine de la santé, alors que jamais apparemment ce profil a travaillé. Tout d'abord, les attirer, les convaincre de venir. Je finis par convaincre les très jeunes. Et les très jeunes, étant donné que le système de santé ici, les salaires sont bas. C'est tout un truc. L'incubateur que je débarraie, tous les trucs non traditionnels. Les ressources humaines, ici avec un système public dont tous les postes sont pré-négociés avec le gouvernement, les ressources humaines m'ont donné un seul instrument pour engager tous mes postes.

Et ça n'a rien à voir avec le genre et leur niveau salarial. Je suis dans mon quatrième cycle de recrutement. Et je t'avoue que je commence à être épuisée parce que là, on existe depuis un peu plus que 4 ans. Tous les ans. Tous les ans. J'ai deux ou trois personnes qui quittent. J'ai deux personnes de gros postes pour moi. La majestueuse des opérations, elle est partie. C'était vraiment mon bras droit. Je viens de trouver d'autres personnes, mais là, c'est problématique parce qu'il faut tout répondre exactement. C'est une façon de faire, de travailler qui n'est vraiment pas fonctionnelle dans le domaine de la santé.

Yoann Malheureusement, oui. Je crois qu'au plus jeunes sont les talents, au plus c'est peut-être compliqué de les garder aussi parce qu'ils ont beaucoup de… les aspects financiers, mais ils ont tellement l'envie de finalement découvrir beaucoup de choses ou se retrouvent relativement frustrés avec des choses qu'ils retrouveront dans d'autres environnements, d'autres entreprises, que des fois, c'est vrai qu'ils ont besoin d'expérience aussi pour… comme on dit, « the grass is not greener on the other side ».

Priscillah C'est aussi générationnel. Je sais que chaque génération dit ça. Mais je trouve que c'est la génération que nous avons élevée. Et il s'attend à voir tout tout de suite. Alors qu'ils ne sont pas prêts à mettre le travail, les heures. Ma génération, moi, je n'ai jamais posé de question. Je commence qu'un, je finis qu'un. Combien de journées je travaille dans la maison? Ce qui m'intéresse, c'est le travail. La première question, c'est le moyen de travail. C'est quoi? Combien de journées par semaine je peux travailler à la maison. Puis à un moment donné, je leur ai dit, écoutez, je comprends aussi la practicalité, puis oui, parfois c'est vachement plus facile de travailler à la maison, mais je veux aussi qu'on comprend que travailler à la maison, ce n'est pas une journée de congés, c'est un jour de travail. Parce que j'ai l'impression qu'on confond les deux parfois. Tout ça pour dire que gérer cette génération, je trouve ça un défi. Je suis entièrement d'accord avec toi. Ça me vient chercher. Exactement. Talent management, people management, c'est toujours un peu compliqué, on va dire.

Yoann - 0:07:04 Exactement. En tout cas, je te remercie beaucoup de ton temps et d'avoir accepté de participer. Je vais tenter d'être bref. Donc on a demandé à 62 experts dont 3 de partager avec nous comment un certain nombre de facteurs étaient importants au vu de ces

stakeholders, de ces experts, mais aussi comment ces facteurs sont considérés au quotidien. Et en fait on a réalisé qu'il y a un certain nombre de facteurs qui vont influencer la valeur économique d'une application digitale de santé qui ne sont pas forcément pris en considération à la conception, à l'initiation par les chercheurs, les clinicians.

Et en fait, c'est une approche très séquentielle où lorsque tu arrives à ton go-to market ou l'implémentation où il y a quelqu'un qui va venir te demander est-ce que tu as fait une étude économique et c'est là où tu vas te poser la question, ah oui, c'est quoi mon cost-benefit, cost-analysis, mon economic impact, etc. C'est des considérations qu'on a trouvées qui arrivent assez tard et donc je voulais avoir ta perspective là-dessus de voir avec les chercheurs avec lesquels tu travailles, avec les clinicians, les physicians, les acteurs en fait avec lesquels tu travailles, théorie ou pas, ces facteurs qui vont venir influencer l'economic value d'un DTX ou de Digital Health Solutions. En fait, ce que tu vois, est-ce que peut-être au travers de ton centre, tu essayes d'adresser aussi.

Priscillah - 0:09:02 Exactement. C'est exactement ça. Donc, la conception même du centre était pour répondre aux problématiques avec le DTx, y compris celle. Les enjeux principaux qu'on a trouvé, Yoann, c'est tout d'abord est-ce qu'ils ont bien saisi le besoin? Et je ne parle pas de surface parce qu'au niveau de surface, il suffit de vivre une expérience et de détecter une problématique. C'est souvent ça le point de départ d'un entrepreneur. C'est toujours une expérience perso qui les fait réfléchir sur un besoin. C'est si étendu pour comprendre comment ça rentrerait dans le flux de travail d'une équipe clinique, que ce soit médicale ou dans l'entièreté des conditions de soin, là, il faut avoir accès. Il faut pouvoir accéder aux gens, aux lieux, aux datas pour vraiment saisir quel est l'enjeu, puis comment les gens qui ont le domaine de la santé, ils sont très résistants aux changements. Donc, d'une part, on fait l'entrepreneur comprendre les fines pointes d'un enjeu qu'il cherche à adresser avec sa solution. Puis de l'autre part, on sensibilise l'explicien les équipes administratives. Et donc, il y a un gestion changement qui commence à se passer dès le départ. Ça, c'est un aspect. Deuxième problématique qu'on trouve, surtout ici au Québec, on est un très petit marché. Et donc, les accélérateurs et incubateurs traditionnels que je l'appelle parce qu'ils ont plutôt le développement des boîtes, développement d'entreprises, beaucoup plus que développement de la solution. Et même quand ils donnent un certain soutien pour des développements de solution, c'est à la traditionnelle. Donc, ils vont peut-être leur trouver quelques KOL, mais je trouve avec digital, ça prend plus que ça. Ça prend l'étape 1 que je viens de décrire. Et donc, étant donné qu'on est un petit marché et que l'on porte sur ces développements d'entreprise, y compris le développement de modélisation d'affaires, ils vont les orienter vers le marché américain. Alors, c'est un marché complètement différent de l'autre. Nous avons alors inclus l'aspect création de valeur de départ. Dans la conception même d'un produit, d'une solution, on commence à réfléchir tout de suite sur la valeur créée. Qu'est-ce que tu cherches, comment tu fais, ce que tu cherches à adresser, comment l'argent bouge, quelle est la valeur créée que tu cherches à créer avec ta solution, comment l'argent bouge dans le système et comment toi tu te positionnerais avec ton modèle d'affaires pour que ça soit achetable ici, mais pour que ça soit rentable pour toi. Et troisième aspect qui est très important, c'est l'aspect de ne pas tomber dans le piège de créer quelque chose sur mesure, mais de garder ses chapeaux entrepreneurial et ses chapeaux commercialisation. Quand tu l'as mis en contact avec les cliniciens, les cliniciens sont très compétents dans leur propre réalité alors que la réalité d'un place à l'autre, elle peut changer. La problématique pourrait être la même, mais la façon de la percevoir, d'adresser pourrait être différente. Et donc, dans ce sens, on cherche à faire des validations multicentriques, donc de garder le contact avec l'entièreté des réseaux pour qu'ils soient en mesure de valider le propos et de garder ce chapeau commercialisation afin de créer quelque chose qui sera applicable d'un seul centre de vol d'attachement, mais que ce soit applicable de point de vue clinique ailleurs. Et c'est en civilisation de l'entreprise que la modélisation d'affaires et l'étude économique, elles changent d'un marché à l'autre. Il faut regarder parce que j'ai l'impression souvent que pour que vous placiez dans un autre marché comme le marché américain, ça va paraître vachement bizarre si l'endroit où vous avez été développé ne vous a pas adopté. Donc, pour vous, ça a tout un sens. C'est y étendu pour faire le

même travail dans les autres marchés parce qu'avec le modèle économique du système santé, et votre modélisation d'affaires par rapport à ces marchés-là. Donc voilà, un très haut niveau.

Yoann - Une approche compréhensive.

Priscillah - Exactement. Donc cette première phase, la phase qu'on appelle la phase d'éco-développement de co-création, il n'y a pas de chercheur. Généralement, il n'y a pas de chercheur impliqué. Je vais vous expliquer pourquoi dans deux secondes. C'est un processus qui est très participatif, dont l'entreprise vient évidemment avec sa solution, tu as l'équipe clinico-administrative dont la solution soit en équipe. Mon équipe a l'expertise en gestion de projets d'innovation et en co-création. Ça, c'est le préfix que je te dis, c'est tout nouveau. Donc, moi, j'ai une cellule de spécialiste en recherche et conception de l'expérience d'utilisateur et de design, UIWix. Et donc, ce n'est pas eux qui vont designer quoi que ce soit, ils vont designer le processus d'échange entre deux parties prenantes pour s'assurer que ceux-ci posent des bonnes questions parce que j'ai vu tellement de solutions qui ont collaboré avec le milieu et qui ont sorti avec des trucs que personne ne voulait adopter par après. J'ai vu une entreprise ici qui a précédé la création de notre incubateur. Mais étant donné que c'est un médecin d'ici qui a eu l'idée et qui a développé la solution, on les a soutenus. Moi, je soutiens les entreprises autour du cycle de l'innovation. Donc, je les soutiens jusqu'à l'adoption et même au-delà parfois parce qu'on trouve même quand quelque chose est adopté, il y a quelque chose à apprendre après. Le cycle doit continuer.

Donc, on continue à les accompagner et à chercher le feedback des utilisateurs qu'on remet par rapport à l'entreprise pour qu'elles soient en mesure de peaufiner sa solution. Et lui, étant donné qu'il a co-développé en théorie sans nous, il a co-développé en théorie, j'ai dit que je vais vous aider avec l'adoption. Donc, on a trouvé l'argent. J'ai trouvé le moyen d'approvisionnement parce que ça ici avec l'approvisionnement, la loi sur l'approvisionnement public, c'est compliqué. J'ai eu un coup de fil de la part de… C'est une solution qu'on cherchait à adopter dans notre centre de médecine familiale. Et j'ai reçu un coup de fil du directeur qui me dit « mais qu'est-ce que tu fais? Je ne veux pas laisser ça. » Puis j'étais comme « mais comment? Qu'est-ce que tu veux dire? Tu ne veux pas laisser ça? Tu as participé dans toutes ces études. Les résultats sont extraordinaires. » Il dit « c'est nice, t'en rêves, mais je ne veux pas ça. » Je dis « comment ça se fait? » Il me dit « ça s'intègre avec rien, ça me compliquera la vie. » La vie est déjà trop compliquée. Mes médecins ont 15 applications qu'ils doivent gérer, rien à connecter avec rien. Je ne peux pas rajouter un autre truc. Ça ne va pas la tête. Et là, je me suis rendu compte, malgré la collaboration, les trois, ils n'ont pas posé de bonnes questions. C'est intéressant. L'équipe est là pour s'assurer que les bonnes questions sont posées. Et dans ce sens-là, on est en mesure d'amener d'autres acteurs, non seulement des équipes cliniques, mais aussi le TI, la santé numérique, les archives médicales, la direction de qualité et mesures de valeur. Tous ceux qui ont un mot à dire sont interpellés et impliqués dans le processus. qui va avoir établi les liens à travers l'établissement et qui va les mobiliser au fur et à mesure.

Yoann D'accord. Et lorsqu'il s'agit de cette création de valeur et notamment sur la valeur économique, est-ce que ton équipe, vous utilisez des outils ou des checklists, des frameworks, des best practices qui peuvent être publiés ou des recommandations, des fois ça peut être des recommandations du gouvernement en disant voilà pour une solution qu'elle soit remboursée, elle doit remplir un certain nombre de critères donc on va walk backwards, tu vois, pour essayer de comprendre la valeur économique qui va devoir être démontrée. Des fois, il y a un processus qui est plus entre guillemets ad hoc dans le sens où c'est beaucoup de brainstorming, de brainstorming sur la partie du business models, donc c'est bien plus large que la valeur économique. Mais voilà, je voulais savoir si tu avais des… par exemple aussi, juste pour terminer, il y a un centre de chercheurs plus sur la partie économique, donc HTA, experts, qui propose de faire des mini HTA. Donc, tu as le full HTA qui arrive généralement à l'implémentation, mais de faire un mini HTA halfway through pour justement valider des considérations économiques. Voilà, je voulais savoir si au niveau de votre centre vous aviez des

best practices, des outils spécifiques qui peuvent vous aider à évaluer cette valeur économique potentielle à chaque étape du projet.

Priscillah - 0:18:37 C'est quelque chose qui est en voie de développement présentement parce que le système est en transition d'un modèle de financement vers un autre. Donc là on s'en va vers un modèle qui s'appelle FAP, le financement axé sur le patient. Donc, c'est le principe des bases d'un système de financement basé sur la valeur. Et donc, nous avons créé au sein de notre direction des qualités une cellule qui des experts, en fait des gens qu'on a entraînés dans le Value-Based Healthcare, qui est en train de développer le cadre pour l'ensemble de l'organisation, puis de regarder l'organisation des données aussi et la qualité de ces données-là pour qu'on soit en mesure d'aider les scènes de passer à... parce que là présentement c'est par la volumétrie, généralement, et là on s'en va plutôt vers un modèle qui va être basé sur la valeur, qui change la donne complètement. Donc pour l'Institut national d'excellence en santé et services sociaux, qui d'ailleurs fait des études d'évaluation pour chaque geste médical ou chaque traitement. avoir des données probantes pour que, étant donné que le système, c'est un des derniers dans le monde qui finance les taux. Donc, tous tes services sont couverts par le gouvernement et tous tes traitements que tu reçois au sein du système sont couverts également. Donc, tu payes seulement ce qui t'a prescrit et que tu dois aller à la pharmacie chercher. Et même avec ça, il y a un programme gouvernemental pour ceux qui n'ont pas des assurances privées, il y a des assurances gouvernementales qui te couvrent en partie. Et la dentisterie. Et certains gens, le psycho, le physio. Mais c'est si étendu que tu peux. Les listes sont longues. Mais tu peux accéder au même service dans le système santé. Tout est couvert. Pour qu'ils te financent quoi que ce soit, il faut avoir des données probantes qui démontrent la valeur des habilités, l'acceptabilité et la valeur économique. Est-ce que ça va la peine? Donc moi, il y a deux ans, j'ai eu un lymphome et j'étais traité dans ce système. Donc tout mon traitement était couvert par le gouvernement parce que je l'ai reçu au sein de l'hôpital. Et je peux te dire que le traitement que j'ai reçu, donc j'avais le traitement actif et après ça j'avais deux ans de traitement préventif, si tu veux, donc pour empêcher le récidive. Et ça, ça a été le résultat d'une étude longitudinale sur dix ans qui a démontré que, bon, les patients qui recevaient ce traitement-là, il y avait 50% plus de chances après 10 ans de toujours démarrer à l'admission, ce qui fait en sorte que le gouvernement ait décidé de le financer, alors que c'était 60 000 par infusion. Et moi, j'en ai reçu 15. Donc, tu peux t'imaginer. D'accord. Et Inès est en train de… en fait, on communique avec eux assez régulièrement. Ils sont en train de réfléchir sur l'aspect évaluation de valeur économique pour les solutions. C'est si étant dit, je ne vois toujours pas de code de remboursement pour de thérapie digitale. C'est ça, c'est ma prochaine question, mais donc oui, c'est ce que j'imaginais aussi, c'est qu'en réflexion, mais pour l'instant, il n'y a pas encore de... Pour des dispositifs, on vient d'approuver, par exemple, gestion des diabètes avec un capteur, puis un pont de désolé, ça, ça vient d'être approuvé. Je ne sais pas si la plateforme, parce qu'au départ, il n'y avait pas beaucoup de plateformes qui ont été homologuées. L'homologation, on le comprend sur la première étape, pour tout ce qui est traitement et diagnostic. Le Santé Canada, qui est l'équivalent canadien de l'OFDI, par exemple, détermine qu'il y a beaucoup d'urgencement avec l'OFDI. C'est très similaire. Mais on a notre propre processus. Il faut être homologué. Il faut que Santé Canada te le dise. Ton dispositif est dans quel classement? Est-ce que tu as besoin d'avoir homologation? Généralement, tout ce qui est wellness, normalement, ce soit, c'est considéré comme un dispositif médical même si c'est un logiciel. Et là, il faut passer par l'homologation Sample Canada.
Donc, ça, c'est l'étape 1. Après ça, est-ce que ça va être financé par le gouvernement ou pas? Au Québec, c'est question du Québec et de son propre processus. Dans le reste du Canada, il y a quelque chose qui s'appelle CADPH et au Québec, tu as LINES. Au Canada, LINES à Québec et ils ne sont pas agencés entre les deux. Donc, c'est très difficile pour les entreprises ici parce que tu as un processus au Québec puis un autre processus pour le reste du Canada.

Yoann
Et du coup, et ce sera ma dernière question, mais imagine que tu as une solution digitale développé au Québec et tu vas à l'implémentation et imaginons qu'il y a un code de remboursement pour cette solution digitale, est-ce que cette même solution digitale pour aller au

marché voisin qui est le Canada devrait passer par un... On est vraiment sur quasiment deux pays, pas pays, province etc. mais des régulations ou un cadre réglementaire qui est tellement différent que ce sont considérés comme deux marchés différents où il y a quand même des sacres des ponts et des passerelles qui font que tu vois par exemple il y a une entreprise récemment qui était en Allemagne avec toutes les études cliniques etc qui a essayé d'aller en France et la France leur a dit non, leur a dit c'est not good enough pour notre marché et après tu peux débattre c'est marché européen les allemands sont pas si différents que les français etc mais il y a des problèmes de requirements réglementaires, de residence et du coup voilà je me demandais à quel point la complexité d'une entreprise digitale d'aller du Québec vers le Canada en fait.

Priscillah - En fait je te dirais que c'est encore plus complexe que ça et j'essaie vraiment activement de combattre ça, c'est d'un établissement à l'autre. Ils vont se demander de générer, de prendre leur cour, parce que nous on fait des choses différemment. C'est pour ça que moi, j'essaie maintenant d'avoir cette influence multicentrique et d'impliquer les autres centres pour qu'ils ne bénéficient pas de ça. Pour ce qui est de l'homologation, c'est la compétence du fédéral. C'est le fédéral qui homologue ton produit et ton homologation est bonne pour tous les territoires canadiens. Pour ce qui est de la remboursement, tu as deux systèmes. L'INES au Québec, CADIS au Canada, c'est si étendu pour chaque province et chaque établissement même, comme je viens de te dire, il veut avoir leur propre province. On souffre ici, mais comme d'ailleurs je l'ai vu dans les autres pays, d'autres pilotes. Et je me suis rendu compte aussi, c'est parce qu'on n'a pas de réserve d'argent pour acheter ce type de produit. Et donc, souvent, on se sert de projet pilote pour le faire entrer dans le système. Puis on s'est dit, après ça, on va deviner comment on va financer. Souvent, ça ne marche pas. Et donc, ça fait de pertes d'énergie et de ressources pour deux côtés parce que tu n'as pas de financement. Donc, moi, avec cette approche de suivre l'entreprise de départ, de l'idée jusqu'à l'adoption, bien évidemment aussi d'aller au-delà de cette problématique, d'essayer de regarder la valeur économique dès le départ et aider les équipes cliniques à déterminer où est-ce qu'ils vont trouver de l'argent. Parfois, la solution va créer de la valeur réelle, traduisable en budget. Je te donne un exemple. En mesure où je viens d'amener un robot dans les laboratoires, avant, c'était une personne qui se promenait d'une place à l'autre, qui transportait des trucs. Là, c'est un robot qui se promène. On a pu couper la personne et utiliser l'argent qui était déjà octroyé pour ses rôles et l'utiliser pour l'achat de la technologie. Mais ce n'est pas une approche populaire. Ça rend des gens nerveux. Au niveau adoption aussi, c'est compliqué. Comparé à tout ce qui est intelligence artificielle, les gens se méfient énormément parce qu'ils se sentent remplacés. Puis on se dit les mêmes choses. Oui, si disons, les compétences vont être remplacées parce que c'est vraiment plus fiable, empathique aussi. Oui, finalement, oui, finalement. Les gens qui sont plus empathiques, plus intelligents pour un but émotionnel que de médecins. Et donc, oui, jusqu'à un certain point, on s'en va. Là, la génération de patients ainsi que de médecins, les médecins ne sont formés que pour la santé. Pour dire santé, ça veut mettre le mot sur quelqu'un. Le patient, il est éduqué que pour se faire soigner, il faut voir quelqu'un, il faut qu'il s'est touché, qu'il t'examine. Mais les nouvelles générations qui se sont formées via des technologies sans jamais rencontrer personne, elles n'ont pas le même apport. Donc, d'ici 15 ans, je vois une tendance de changement et que les professions seront remplacées. Tout ça pour te dire que c'est très compliqué.

C'est très compliqué et voici le raisonnement derrière la création de notre programme qui cherche de les accompagner jusqu'à présent parce que sans avoir les gens qui ont les deux chapeaux, qui ont les deux têtes, si tu veux, la tête santé ainsi que la tête entrepreneuriale et qui sont là pour pousser le système de A à Z, il y a beaucoup de départs, mais pas beaucoup d'arrivées. Mon directeur d'ETI m'a dit l'autre jour que dans le système il a trouvé 15... il a trouvé 1 500 applications qui flottaient sans avoir... sans être attaché à quoi que ce soit, qui a eu l'année dernière 150 projets qui ont démarré sans abouti. Donc tu vois que... sans cet effort... Ça écolle toutes les conversations que j'ai pu avoir avec les experts sur Vodesu. Donc, quelque part, je ne sais pas si c'est bien, mais en tout cas, il y a un alignement. Dernière petite question tactique et malheureusement, j'ai deux chapeaux. J'ai le chapeau qui est plutôt orienté vers l'intérieur et j'ai

le chapeau qui est orienté vers l'extérieur. Chapeau orienté vers l'intérieur, chapeau orienté vers l'extérieur. Donc, j'ai deux chapeaux. J'ai un chapeau qui est orienté vers l'extérieur. Chapeau orienté vers l'intérieur, c'est vraiment préparer l'organisation pour le neuf. Qu'est-ce que ça va dire? Ça va dire sensibilisation, connecter, partager des connaissances, des outils, des ressources, la mobilisation, la communication stratégique, interne, externe, positionnement, partenariat, relation avec le gouvernement, relation avec l'écosystème. Tout ça, c'est mon chapeau. Là, j'ai un autre plus petit, un gros chapeau, qui est l'incubateur. Orot, c'est vraiment le véhicule pour travailler avec les entreprises. Donc ça, c'est vraiment l'accompagnement des entreprises. C'est une vraie incubation, mais c'est une incubation qui est focusée sur la solution même. Il y a ses chapeaux, valeur économique parce qu'on veut s'assurer que les solutions sont intégrées. On accompagne. On est vraiment très rare parmi les incubateurs. On n'est pas juste là pour créer des technologies et aller « merci, au revoir ». Si on s'engage projet, c'est parce qu'on veut vraiment l'adopter. Et le pont entre les deux programmes, si tu veux, c'est que l'équipe qui me soutient, elle soutient les deux types d'entreprise.

Yoann - Écoute, je te remercie énormément. Comme toujours, ce fut une discussion brève, mais comme toujours, très intéressant, très inside foot d'échanger avec toi. Je te remercie beaucoup. Encore une fois, tout ce que… Non, il n'y a pas de souci. En tout cas, je te remercie pour ce temps

Interview Transcript with Priyah (P17)

Raw Data Prior to Atlas.ti Coding

Yoann - 0:11:25 Excellent. So maybe to start, if you don't mind to share with me the role that you have within the institute and how do you collaborate with the different stakeholders and at which stage of the solutions development do you basically come into the picture and do help these clinicians and researchers maybe?

Priyah - 0:11:48 Yeah, so it's a bit gray because I wear two hats, right? So I'm in Center for Innovation in Healthcare, CIH. And CIH has one role, but we are also part of the PCI team. And I lead the team to do the PCI part. So maybe I can share on both roles that I play and how I'm trying to bring both together. So for CIH, as you know, we started in 2018. And at the beginning, what we were trying to do is really to build an ecosystem of partners. And we were trying to define our own value proposition. And our value proposition is really that we are in a healthcare system. assets are our healthcare professionals, our patients, our clinical data, right?

And innovators that come to us can leverage the assets that we have, right? So as you can see, these are very clinical focus, but we understand that for innovations there are so many different components that we need and usually what we require as complementary expertise will be regulators, the business side of things and also the technology side of things, right? So which is why at the beginning what we did was to form a network of partners in those three other areas, right? And including funders as well as investors.

So that was our goal, what should they give me, to build this ecosystem such that when innovators come to us, we not only can help in the clinical side of things, but if we can't, we refer them or connect them to partners can help. Because all these components need to fall in place together in order to progress to the next stage of the innovation journey. Yeah. And so ecosystem is one. Second is that we build up services. Right.

So because we are good at the clinical side, which is why we do a clinical trial unit, but a very mini one because so at the beginning when we before we even decided to build such a unit I went to many different partners outside like SCRI, you may be aware of, the Singapore Clinical Research Institute where they actually run trials as well. There's also an IMU unit in NUH, Investigational Medicine Unit, that runs clinical trials. So I wanted to tap on either one of them when our innovators come so that we can run clinical trials together. But I realised there's bandwidth issue and also agility issue. The turnaround time is really slow and if we are engaging startups, they can't afford to wait, right? So we said, okay, it's fine. We will build up a unit in CIH that is small, but is able to fulfill the needs. So we have CRC clinical research coordinators who can write up, no, they don't write. They will look at the protocol, advise what are the appropriate revisions to make because that has to be submitted to the DSRP, our ethics board. And also advise on the... and our project manager's advice on the other documentations that are needed for the trial to proceed. So, essentially, we have the know-how of how to run a clinical trial within our clinical institutions. So, that was one of the goals of setting up such a unique and also our way to be able to provide better value to innovators. So that's one.

And many times when the innovators come to us, we are like, okay, what do you need? And they are actually in all varying stages of innovations, right? From ideation, prototyping, to the regulatory stage, and also after they are commercialized and they want to come back to the market. And many times when they come, the fact that we are from a healthcare system, they want clinical insights. And we also realize that we are not the right people to provide very valuable ones.

I mean, we can provide on the surface kind, providing, okay, the context of what it is and all those. But what is really needed are the target clinical users for your clinical innovation, right? So

what we wanted to do was to match them, create a platform where we can match the innovations, the innovators that come to our own clinicians, nurses, allied health, whichever that is relevant to provide clinical insights. And for us, the other hand is also for us to learn what are the innovations out there so that we don't become irrelevant. So we thought that it would be a win-win situation. But that came with challenges, right? I keep asking people, do you want to meet? Do you want to do trials? So we are slowly morphing this model.
So, I mean, I won't elaborate for now, but we can go into this. Yeah, so the matching was one which if eventually there is interest to collaborate, usually it will be the form of a trial, then we will activate our clinical trial service part. But many times our PIs, those who are already very well resourced, they can actually do it on their own. So we provide value where we can. If not, we let them go out on their own.
If they need, they come back to us again. That's good. one part on how we try to provide value to external innovators. Internal innovators, as you know, there's also like a wide spectrum of them, right? So a large part of it is also talent development, like how do we mentor these young talents such that, because it's not just going to be one innovation, it's going to be an entire portfolio in their whole life, right? So even if their innovations are not great, we still want to encourage them to be on this journey and the soft skills that they learn can actually be quickly applied to the next innovation that they embark on. And we have seen a couple of cases and it's really quite heartening, right? That they actually learn from before and they move quite fast after that. It's an accelerated part of the journey. And we will again assess which part of the journey they are at. Like for example, if it's prototyping stage, then we will say, okay, we refer you to engineering partners. Then when you are ready to test on humans and we come back in again. So that's the CIH part of goals that we were trying to do. Then along the way, along the years, we were suddenly asked to do this practice changing innovations program, which I think you are more familiar with. And at that time, I guess it was because we were asked to come in one year after the PCI goal, the target was set by the BOF, right? So, I mean, I try to go back and understand why this was created in the first place, right? And I think it was really because of the ROI in a sense, right? We have, I mean, NUHS, NUS and NUH hospitals have been around for so long. And then there's been so much money put into the research R&D portion. And there's so many pilot trials and clinical trials ongoing, but which ones are really the ones, right? How many of them actually make it to become an innovation that we can use for our patients today. So you can see that there's really very little or less than 10 of them.
So I think that's the reason why our board was saying, okay, I think we need to dedicate more resources to try to move our innovations towards that part where we can eventually use our innovations to practice change. So then that's where we came up with an entire program, framework, methodology, advisory board to select, evaluate, come up with work plans and to really accelerate this journey. So it's quite stringent.

I mean, you have seen the selection process and all those. So that part, the PCI programme is really focused on deployment and adoption of our homegrown innovations into our clinics. And it can be anywhere within NUHS. It can be in the hospital, it can be in the polyclinic, community, depending on where it is most relevant and where it can make the most impact.

Yoann - 0:22:32 I see. That's, thanks a lot, is really comprehensive and it also helps me to know to take a step back in terms of the different roles that you have between CIH and PCI, you mentioned about the ROI of some of these kind of innovations. And you also mentioned about the kind of the end goal, which is really about the adoptions, basically, the deployment and the adoptions of these technologies. Would it be fair to say that from a new HS perspective, the ROI of one of the solutions is about implementations and deployment and adoptions is how an ROI might be defined from an UHS perspective of some of the solutions. Because more or less, we all have kind of slightly different kind of concepts or definitions of ROI. So that's what I'm trying to see maybe from an UHS perspective how such ROI might be defined.

Priyah - 0:23:38 Yeah, so for each of the PCIs, we define the clinical outcomes that we want. It's not really economic value, but it's more of a clinical impact, which may eventually lead on to economic value, right? Because the focus here is not about commercialization, but it's about the

clinical impact that we can bring to our patients and population. It is quantifiable for each of them and we actually have to conduct studies to prove that it is what it is. We articulate these outcomes right at the beginning when we select them. The clinical outcomes can be, I can give some examples, for example, gastropia, it can be to increase the percentage of early detection of percentage increase of detection of early gastric cancer. So what is the baseline now versus when you introduce this particular test kit, how detect and there is a larger aspirational goal at the end, which is even longer term, like a 10-year kind of thing. How can you eventually treat them better and better survival rates for these street cancer patients? So that's one. For example, there are some that Let me see.

So gastro fear is a gastric cancer test. Okay, the AI, AI radiology imaging type, it is to have a percentage increase in the, or reduction in time for reading these scans. So it increases productivity of our radiologists. So that can be one, which essentially after that, you can translate to economic value. Not economic value, but the money that our institution can save. Then there are also digital innovations, right? I don't know, have you heard about CHEM? It's like a WhatsApp chatbot.
Actually you can see it is in the public domain. We have a couple of these kinds of innovations. So one of it is like a chatbot that reaches out to the community. So for that, we also look at the clinical outcomes. Like for example, if you claim that you are looking at blood pressure, the readings of the blood pressure. So if you get on this WhatsApp chat or that, ask you to measure your BP every day, and also gives you some tips and reminders, right, of how you can improve your lifestyle, how you can eat healthy and all those. There are a lot of confounding factors but we still try to put in a clinical outcome that is measurable at the end. So how can this, the introduction or the intervention using this chatbot helps to reduce the blood pressure readings for the population. I mean for this kind of chatbots, there are so many different use cases that you can use for. But for the PCI program, what we want to do is to narrow down a use case, you measure it, make sure that it is something that is proof that something is actually working. They can be expanding this to many, many use cases at the end. But what we are trying to do for this program is really to also help them think about what is the end outcome that you want to achieve. Anybody can create a chatbot, right? But then what is it that you are trying to do at the end? You know, you can put in a lot of fancy stuff, fancy whatever, but are you achieving what you want at the end? And are you even clear about what you want to do at the end. So that's one. Then there are also some big data analytics software that can be used to analyze our backend data because we have so much patient data that is unharnessed. So at the GCTO side, they have, you know GCTO right? Dr. Niam said right? Oh yeah, they are in their office now. Yeah, so yeah, he will be able to explain much better than me. But they have a few of these digital projects that are also under the PCR program. So we also focus on the use case, right? What is it that you want to measure, right? Like for example, if you want to measure calcium levels for patients that went for the blood test, then what is it? What is the effect? Are you trying to detect patients with hypercalcemia?

Then how does this work into the clinical workflow with the various departments? So for each of the different PCIs that we have, we got to first articulate what is the impact and outcomes that they are going to achieve and then work backwards. For example, now you have a standard of care already, then what is the standard of care that you are trying to change? With your intervention, how does this impact the clinical workflow? And then what are the barriers that are impacting? And we are preventing the progress right now, then we will really, you know, be, throw our hands on and help them overcome this progress. These are the barriers, but keeping in mind the end outcome that they want to achieve. Because these CIs, they have a lot of, you know, start projects and one platform can do many, many things. So we try to, you know, keep them on the ground.

Yoann - 0:30:02 I see. And you mentioned that the way you're looking at some of these innovations, the impact is obviously more from a clinical side. But you also mentioned about efficiency, productivity, which kind of, as you said, indirectly, they are related to the economic impact in a way that some of the solutions might have. And I'm just wondering on how such

maybe economic value of the economic impact might be taken into consideration through the process of the conversations you might have or through the process of development validations with the clinicians. Does this matter or does not matter much? Obviously, you need to demonstrate the clinical outcomes, right? That's a given. But I'm wondering, for example, if you have two solutions that one might be quite expensive to implement for because you need like additional headcount or you need additional kind of investment and so on versus you have another one that might be lighter in terms of the initial upfront investment. So yeah, I'm wondering on how the economic impact might be taken into consideration or is really about just let's demonstrate the clinical outcome first and then we would kind of worry about the financial kind of considerations as we deploy at scale, basically in kind of a sequential process.

Priyah - 0:31:25 Yeah, so we do take into account the financial consideration. So I haven't come across a case where we are comparing two apples, right, but then one is cheaper than the other, right? Because they are all so different. But for example, if I take the example of cell therapy, there was always this consideration because it's really expensive. So one treatment can be $400,000 if you consider the entire treatment regime. And it didn't take off for a few years because of the financial sustainability. Essentially, the stakeholders were very worried that how are you going to sustain this, right? We cannot be going into debt, right?
For us, we are not profit-driven, but we do need to recover our costs, especially for our subsidized patients, right? So for innovations like this, we do help them come up with a business plan, like a sustainability plan. Not like those commercial kind where you have income statement, balance sheet, this kind. But rather helping them think through, okay, at least you must be clear what is the cost of providing this treatment? Because there are some therapies that are so complicated and multi steps, right? Which along the way, the different touch points will all occur costs. Like for cell therapy, the cost will be okay.
Chemotherapy, the consumer bus, right, that is used. If it's inpatient, then inpatient cost. And then when you come back for visits, outpatient, and then if you need to extract your cells, right, and then eventually go to the entire cell production and all those that is done in our other labs, then these are all costs to factor in. So for the longest time, they didn't have a concrete figure about the cost. They're like, okay, you really need to list down every single thing. Okay, it can be in a package, right? Because there are bundled payments and all those. It can be that, but you minimally need to list down the different items that are involved in the entire treatment regime.

Then from there, we can work through, okay, whether you are, there's manpower, additional manpower cost and all those, and do you need to put a markup to it for other areas, right, where you need to cost recover? And then from there, how do you actually recover these costs? Like, for example, when you be asking the patient to pay for everything, and very often, because it's such a large sum, it's very difficult for patients. So there are different avenues that we consider when we thought about, when we went through with the clinicians, like what do you, how do the patients currently pay? So one way is through philanthropy funding, and then the other way is through, so one way is philanthropy funding, the other way is crowd sourcing, crowd funding. So you see like GiveAsia and all those, right?
So they, to make sure that the payment comes in, then there are different parts in the entire human regime that is actually subsidized currently already. So without doing all these things, there was no clear concept, right? Like how you going to sustain this?

So we actually wrote a proposal and then broke down the different parts and then went back to our CFO to say, hey, you know, actually this can be sustainable, right? And it can be cost-recovered. So this is really the hard numbers, the financial part. The other part is on the more intangible stuff, right?
Like the HTA component of things, value-based driven kind of outcomes. So we are working with our colleagues, you may know, Shikha and Prof Dermot. Yeah, so it's, their unit is called value-driven outcome unit. So they are able to pull out the patients that have gone through this test, right? And what are the specific costing and all those. And eventually they can use this data to analyze in whichever way they want. Initially, we wanted a HTA study for each of our PCIs. But it really cost money and a lot of time to prove. So now what we are doing is to fall back on our own

value-driven outcome unit to help us analyse all this. There is also study run for like quality kind of study to also tie in this component of the non-financial part of things.

Yoann - 0:37:22 So would it be fair to say that for most of the PCIs or innovations you do this, you define with them the sustainability plan as one and then for some of them this is where you go to that unit on the value driven outcomes kind of unit on the more like HTA type when it's required, but it's not systematic for all PCI. It's kind of two steps process, right? The sustainability plan, and then it goes to the value driven outcomes unit, right? Correct.

Priyah - 0:37:55 So for like devices, if it's a capital purchase, it's also about the cost, right? And whether the price is acceptable to our public. So we also realise that innovations don't come cheap, right? And some of the startups really don't have the economy of scale yet. So their per piece innovation is expensive and is not acceptable to our public (meaning public clinics. So some of these we say, okay, why don't you try the private clinics first?

Because I mean, people over there have bigger pockets, right? To purchase. Then when you reach the economy of scale, right, then you come back to us. I mean, that may be a model. So initially, when we were thinking of adoption and deployment, we kept thinking, you know, you should deploy in our hospital, in our clinics, but some of these really don't make sense. I see. Here, right? And it's about eventually PCI's goal is not just NUHS, but it's also either nationally or globally. And some of them may be more suited for developing countries, right, rather than here. Yeah, so we don't force, but rather we help them articulate the impact. But then, after the impact, then when we map out the different workflows and then consider the financial part of things, then we, okay. Because a large part of it, in order to scale, you, the dream of every innovator is to get subsidies and subvention from MOH. So for us, it's also, this is what we want to achieve at the end. When it is on the subsidised list, it's going to scale very quickly and we can do the whole of government approach, go on to a healthier SG and all these things. But in order for us to reach there, we really need to make it mainstream and the evidence must be there. There must be a full-blown HTA study for ACE and MOH to consider it.

Yoann - Okay. And you know, on the sustainability plan, one of the things we can have realized is that these kind of product tech development kind of life cycle, you know, from the development, then you go to the validation, the clinical validations and the deployment. Is this what you see or so that maybe some of these cost considerations are considered maybe too late or they could have been considered earlier by some of the innovators and researchers or?

Priyah - 0:40:51 Yeah. Yeah. Because at the beginning of the journey, yes, if I agree with you, because at the beginning of the journey, everybody is just thinking about what solution to address whatever I'm at me, right. Then, um, they will go on, for example, if it's a technology kind of innovation, then they will go on to build. And they build and build and then especially if it starts out from a research research lab, right, then they will build components that you can't actually source if you want it at scale from manufacturers. And very often times it's over spec, right. So what we try to bring in is that if I'm able to match them with clinicians, but sometimes clinicians also don't know what they want, but you know, that's another conversation. But it's more of like a business strategic direction that the innovators need to take into account. And I completely agree with you. It needs to be something that is thought earlier on, which is why at the beginning, I mentioned we are good at the clinical, right? But the other parts are the technology regulator and the business side of things. So the business side of things is very much, has very much to do with the financial and cost of doing this.

So for example, some of the devices I said, okay, the price point is really too high. So when you go back to a drawing board again to tweak certain things, there are certain things that you can pick up to reduce the cost. Because at the end of the day, if your market is the public healthcare system, the cost really cannot be high. And you cannot bank on subsidies. The good thing here is that in order to use it in public healthcare, you do not need to be subsidised, unlike some other

countries that need to go the very long way before you can come in. So we are flexible in that way. But then again, because of subsidised patients and all those things. So yeah, it is something that I think has been developed.

Yoann - 0:43:15 And maybe the last question I would have is, you know, the role that you play with these innovators, you know, in terms of like, in terms of guidance, facilitations, and bringing this maybe sustainability considerations into the picture, right? Do you see this unique to NUH and NUHS, or do you see most of the hospitals having such kind of unit or teams or expertise in-house to help the different NUHs? Or from maybe a kind of a set-up and structure standpoint, most of the hospitals will tend to have such unit, or is something specifically that kind of maybe a best practice that NUH might have?

Priyah - 0:43:59 So, if you're talking about PCI, I think it's something very unique to us. Although the other clusters have been trying to talk about adoption and also deployment, but from our interaction, we sense that their definition is different from ours. But actually, NHG has reached out to us, the CHI group, to say that, you know, can we learn more about PCI? And they actually want to start a unit like ours. Yeah, so actually I have written, our team has written a manuscript on PCI. It has been submitted. Yeah, and we are waiting for the editor to get back to us. So when it's ready, I will be more than happy to share it.

Yoann - 0:44:49 Yeah, it would be kind of a playbook, right? Or like kind of a whiff.

Priyah - 0:44:54 Yeah, because our CE is trying to come up with this health system manual, right, where all the important initiatives are documented, published. And it's like a playbook, right, for our health care system and for others to learn from. So, yeah, it's going to be quite comprehensive. And it's nice to see that our work is being recognized.

Yoann - 0:45:26 Recognized. Exactly, exactly. Great, please do keep me posted. I would love to read it once it's officially out and published. So, definitely. So, you know, I went through questions that I had for you, but I don't know if there's anything else you would want to share, anything that we have not discussed that we should in terms of, you know, this kind of economic value considerations of any digital health solutions, anything else in terms of experience, feedback, or questions you might have. I don't know if there's anything else we have not discussed on that topic.

Priyah - 0:46:02 Yeah, so the, I guess the cause of digital innovations always lies within the infrastructure, right, especially for healthcare digital innovations and you know that it has to go through a lot different approvals and that eventually for it to make better sense and for it to provide greater value, it always needs to be integrated into the NGMR. And to integrate into the NGMR requires cost, right? A lot of cost and approval about NHS is that we have GCTO, we have our Endeavor AI platform which is integrated with NGEM. So that really was very helpful when we were bringing in digital innovations. So at the beginning when Niamh was not ready platform, we had many many of these digital AI companies coming in who said that hey I want to do this, do this, do this and then we had very separate siloed conversations right and it all came back to integration because our clinical users said that no it is not integrated, it is not efficient. I mean a lot of digital innovations is actually to help the productivity, right? Of things. So if it's not integrated, it is an additional step for our users to use. Because you know, you still need to cut and paste and then do extra steps. So they were not keen to adopt and deploy. So the neat part about the Endeavor AI is, because they already have pre-approval from Synex, so once you are identified or selected to be on Endeavor AI, it solves a lot of the problems and especially reducing costs as well, manpower and also the cost of integration because it is already integrated in a system, system wide manner. So it really makes a lot of sense for our innovators to come. And this is a differentiating point because the other clusters actually do not have this.

Yeah, and I think, so Ngiam was saying that there are conversations with NHG to also extend our endeavor AI to that. So it's something that is of value, right, to healthcare system. And we are also trying to see how we can scale this kind of model. It's going to be difficult, like, it's built around our data.

Yoann - 0:49:17 But it could be quite exciting for all the clinicians and the end user, you know, the patients, if this could be done and be kind of like shared, not within just our clusters, but with the rest of the clusters, right? So that could be quite exciting. I mean, it's not a small initiative, right? It's not a small pilot. It's going to, I guess, take time and a couple of conversations. But yeah, great to hear. But yeah, but it's technically on a technical side, it may be easy because it's just opening an auto. It's just opening an auto, right?

Priyah - 0:49:57 Because everything is virtual. Unlike the medical devices and all those, you have other problems coming up. And eventually, if the clusters agree, it can be a national kind of resource that we can tap on. And it will really make Singapore look very good.
Really, it is going to be, yeah. Okay. And it really took many years for him. Yeah. And then now we are so glad that, you know, we have this, so that our digital innovations can tag on. And we no longer have to tell people, you know, you have to go through Synapse,

Yoann But you still need to go to Synapse for some of these approvals, no? Or it could be kind of more like a straightforward process?

Priyah - 0:51:08 It's more straightforward because Niam already has a partnership with Synapse. So, yeah, on that side, they have settled all the... But we still have our internal approvals to go through. Still a bit of, couple of like hurdles, I guess, I imagine.

Yoann - 0:51:28 But you know, thanks a lot, Priyah. I don't want to take too much of your time, but thanks again for, you know, accepting and this invitation to be part of the study and to share your perspective, really insightful as always. So thanks a lot. And if there is anything else, Dr. Hon, that you want to share or anything like the playbook, as you said, feel free. And yeah, thanks again. Thanks for your time. And I hope you will have a great weekend in JB. Yeah, thank you. You too. Enjoy your weekend.

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Back Cover with Abstract

Despite their promising potential to revolutionize healthcare delivery, digital therapeutics (DTx) face significant market access and deployment barriers due to insufficient understanding of their economic value. This thesis addresses this critical knowledge gap through a comprehensive mixed-methods investigation examining what drives DTx economic value and how these factors are considered throughout product development.

Through a systematic literature review, group concept mapping with 62 stakeholders, and qualitative research with 17 researchers, this work reveals that while DTx can deliver cost-effective solutions in certain contexts, economic considerations remain systematically underemphasized during development. The research identifies 59 distinct economic value factors across eight thematic clusters, highlighting significant perception gaps between stakeholders regarding their importance and practical implementation.

The thesis uncovers three interrelated generative mechanisms—*Professional Norms*, *Researcher Experience*, and *Adoption Uncertainties*—that create persistent barriers to economic integration throughout the DTx lifecycle. Most importantly, it provides actionable recommendations for fostering interdisciplinary collaboration, embedding early economic considerations, establishing integration guidelines, enhancing professional training, and improving methodological rigor in DTx evaluation.

A strategic roadmap for transforming how economic value is conceptualized, assessed, and integrated in DTx development is proposed—ultimately supporting healthcare systems worldwide in realizing the full potential of these innovative interventions.

Key words: digital health; digital therapeutics; economic value drivers; cost-effectiveness, mixed methods-based approach, critical realism, qualitative study, group concept mapping.

Mots clés: santé numérique; thérapeutiques numériques; moteurs de valeur économique; rapport coût-efficacité; approche par méthodes mixtes; réalisme critique; étude qualitative; cartographie des concepts en groupe.