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**Development of a framework to support medical
technology innovation and
objective data usage in healthcare: a case study in the
prosthetics industry**

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Resumo

A indústria MedTech tem papel crucial na melhoria das condições de saúde e na preservação da vida de pacientes. Prevista para alcançar 595 mil milhões de dólares em 2024, a indústria observa um crescimento de novas tecnologias voltadas para o aproveitamento dos dados gerados no setor. Contudo, empresas de tecnologia médica enfrentam obstáculos na entrega de inovação. Se não forem geridos de maneira hábil, regulações, reembolso, dinâmicas de mercado e muitos outros desafios ao longo do desenvolvimento de um negócio MedTech podem impedir que até mesmo a melhor ideia chegue ao paciente. Complexidades inerentes às novas tecnologias, ao tratamento dos dados de saúde e à contenção de custos sem precedentes observada no setor da saúde tornam esta navegação ainda mais difícil.

Para responder à questão "O quão aplicável é o framework de Stanford Biodesign para os atuais negócios MedTech?", este estudo combina uma abordagem qualitativa exploratória baseada em entrevistas não estruturadas e semiestruturadas e uma revisão da literatura focada nos principais fatores que afectam negócios MedTech quanto ao aproveitamento de dados gerados no sector e à entrega de soluções inovadoras. O alicerce deste estudo é o framework de Stanford Biodesign apresentado no livro "Biodesign: The Process of Innovating Medical Technologies 2nd Ed." de Yock et al. (2015). Com contribuições de diversos especialistas, este livro apresenta um guia para identificar, inventar e implementar novas tecnologias médicas, influenciando empreendedores MedTech em todo o mundo.

Esta dissertação visa explorar as dimensões do framework de Biodesign original que foram mais significativamente impactadas pelas mudanças tecnológicas e socioeconómicas em quase uma década desde a publicação do livro, e a identificação das melhores práticas e tendências atuais de inovação em tecnologia médica e no uso de dados de saúde. O resultado desta dissertação é um Framework Atualizado para Negócios MedTech, que serve como complemento ao framework de Biodesign original. Sua aplicação prática é exemplificada em um estudo de caso também apresentado neste estudo, onde uma empresa MedTech é avaliada de acordo com seu alinhamento com o framework proposto.

O estudo identificou cinco dimensões de interesse a serem incluídas no novo framework, as quais complementam e atualizam um ou mais componentes do framework original: 1) Geração e Seleção de Conceitos inclui requisitos para soluções digitais e centradas em dados, como obter aceitabilidade e confiança dos provedores de saúde, e suporte infraestrutural para a inovação; 2) Propriedade Intelectual e Assuntos Jurídicos inclui vias para proteção de software e suas ramificações; 3) Assuntos Regulatórios e Gestão de Qualidade e Processos inclui caminhos regulatórios e recursos para produtos baseados em dados e ML/AI; 4) Reembolso inclui vias de cobertura para tecnologias emergentes; e 5) Modelos e Estratégias de Negócio inclui estratégias de apoio a tecnologias emergentes e acordos baseados em valor e resultados.

Esta dissertação visa apoiar a indústria MedTech moderna, introduzindo um framework prático e eficaz a ser seguido por empresas na invenção e implementação de soluções inovadoras – especialmente aquelas com negócios centrados em dados, como a empresa no estudo de caso. No entanto, o estudo reconhece suas limitações de natureza qualitativa exploratória, pequena população estudada e curto período de pesquisa. Melhorias futuras na pesquisa incluem uma rodada de feedback com os entrevistados e, idealmente, com os autores do framework de Biodesign original. Além disso, seria desejável avaliar mudanças em outros aspectos do framework de Biodesign através de contactos com mais e mais diversos stakeholders, incluindo seguradoras privadas e grandes corporações de tecnologia que estão a adentrar na área da saúde.

Abstract

The MedTech industry plays a crucial role in improving patient health conditions and saving lives. It is projected to reach 595 billion dollars worldwide in 2024 and shows exciting prospects as new technologies aimed at leveraging the abundance of medical data enter the sector. However, medical technology businesses face significant hurdles in the delivery of innovation. If not managed skillfully, regulatory approval, reimbursement, market dynamics, and many other challenges along the development of a MedTech business can prevent even the best idea from reaching patient care. Adding to that, the intricacies of emerging technologies, the handling of health data, and the unprecedented cost containment observed in healthcare as a whole only make matters more difficult to navigate.

To answer the research question “What aspects of the Stanford Biodesign framework may warrant additions to better support current MedTech businesses?” this study combines a qualitative exploratory sequential approach based on unstructured and semi-structured interviews with a literature review focused on main factors affecting a business’ ability to leverage health data and deliver innovation in MedTech. The cornerstone of this study is the Stanford Biodesign framework presented in the book “Biodesign: The Process of Innovating Medical Technologies 2nd Ed.” by Yock et al. (2015). This book leveraged expert input to create a roadmap for identifying, inventing, and implementing new medical technologies, teaching MedTech entrepreneurs all around the globe.

The main contribution of this dissertation is an exploration of the dimensions of the original Biodesign framework that have been more significantly impacted by the technological and socio-economic changes in what nears a decade since the book’s publication, and the identification of the current best practices and trends of medical technology innovation and data use in the industry. The output of this dissertation is An Updated Framework for MedTech Businesses, which serves as a complement to the original Biodesign framework. Its practical application is exemplified in a case study also presented in this study, where a MedTech company is evaluated according to its alignment with the proposed framework.

The study identified five dimensions of interest to be included in the new framework, each providing valuable insights that complement and update one or more components of the original Biodesign framework: 1) Concept Generation and Screening includes requirements for digital and data-centric solutions, such as provider acceptability and trust, and infrastructural support for the innovation; 2) Intellectual Property and Legal Affairs includes avenues for software protection and their ramifications; 3) Regulatory Affairs and Quality and Process Management includes regulatory pathways and resources for data-driven and ML/AI-based products; 4) Reimbursement includes coverage avenues for emerging technology; and 5) Business Model and Strategy includes discussing strategies to support emerging technology and value- and outcomes-based deals.

This dissertation aims to provide guidance to the MedTech industry by introducing a practical and effective framework with considerations and recommendations for businesses to follow in the invention and implementation of innovative solutions – especially those with data-centric businesses, such as the company in the case study. However, the study recognizes its qualitative exploratory nature, small population studied, and research the short period as limitations. Future research improvements include a feedback round with interviewees and, ideally, with authors of the original Biodesign framework. In addition, evaluating changes in other aspects of the Biodesign framework by engaging with more and more diverse stakeholders, including private insurers and major technologies corporations venturing into healthcare, would also be desirable.

Keywords: MedTech Innovation, MedTech Industry, Biodesign, Health Data, Value-based Healthcare, MedTech Digitalization.

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*“Take this kiss upon the brow!
And, in parting from you now,
Thus much let me avow —
You are not wrong, who deem
That my days have been a dream;”*

– Edgar Allan Poe (A Dream Within a Dream)

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Index

Resumo.....	1
Abstract	2
Acknowledgements	4
Index.....	4
List of Figures	7
List of Contents	8
Abbreviations	9
1. Introduction	10
1.1. Background.....	10
1.2. Motivation and objectives.....	11
1.3. Structure of the dissertation	12
2. Theoretical Background and Key Concepts.....	13
2.1. Medical Technology Innovation	13
2.2. Value-Based Healthcare (VBHC)	13
2.2.1. Real World Data	15
2.2.2. Value partnerships between providers and industry	20
2.3. Digitalization and Data-driven Solutions in MedTech	22
2.3.1. Artificial Intelligence.....	23
2.3.2. Cloud Technology.....	25
2.4. Barriers to digitalization and data use in MedTech.....	26
2.4.1. Privacy.....	27
2.4.2. Cybersecurity.....	28
2.4.3. Data Adequacy	29
2.4.4. Standardization of data	30
2.4.5. Infrastructure	31
2.5. The Biodesign framework	31
2.5.1. Drivers for change in the Biodesign framework	33
3. Investigational Methodology.....	44
3.1. Research Question, Objectives and Methodology	44
3.2. Research Design	46
3.3. Data Collection	46
3.4. Data Analysis	47
4. Results and Discussion.....	50
4.1. Current landscape of the MedTech sector: features, challenges, and opportunities ..	50
4.2. General considerations and best practices to ensure success as a MedTech business	53

4.3.	Key factors and best practices for the implementation of digital and data-driven solutions by MedTech businesses.....	58
4.4.	The future of the MedTech sector	63
5.	An Updated Framework for MedTech Businesses.....	65
I.	Concept Generation and Screening	66
II.	Intellectual Property and Legal Affairs	68
	Intellectual property strategy.....	68
	Beyond IP: dealing with legal affairs	73
III.	Regulatory Affairs and Quality and Process Management	73
	The current regulatory landscape	74
	General Strategies for Regulatory Compliance and Quality Assurance.....	74
	Strategies when Dealing with Innovative Devices.....	76
	Real-World Data (RWD) to Support Regulatory Decision-Making.....	78
	Software	82
	Privacy.....	84
	Cybersecurity	85
	Artificial Intelligence	87
IV.	Reimbursement	88
	Reimbursement Strategy	88
V.	Business Model and Strategy	93
	Creating value-based partnerships	95
	Leveraging new technology	100
6.	Case Study: Adapttech Prosthetics LTD.....	102
6.1.	The company.....	102
6.2.	Concept Generation and Screening.....	103
6.3.	Intellectual Property and Legal Affairs.....	104
6.4.	Regulatory Affairs and Quality and Process Management	104
6.5.	Reimbursement	105
6.6.	Business Model and Strategy.....	106
7.	Conclusions and Future Improvements.....	108
	References.....	110
Annex I:	The Future of MedTech – 5G Connectivity.....	I.1
Annex II:	Interviews	II.1

List of Figures

Figure 2. Common sources of Real-World Data (RWD).	15
Figure 3. Medtronic's seven step VBHC framework.	21
Figure 4. Interaction of communication technology, cloud and AI in digital MedTech solutions. Example of a Software as a Medical Device (SaMD) solution that analyzes patient monitoring data.	23
Figure 5. The Biodesign framework. Extracted from “Biodesign - The Process of Innovating Medical Technologies 2 nd Edition”.	32
Figure 6. An overview of the drivers for change in select dimensions of Stanford's Biodesign framework.	33
Figure 7. AI Act's risk-based classification of AI.....	40
Figure 8. Flowchart of the qualitative exploratory sequential research design.	45
Figure 9. Schematic representation of the methodology to analyze the results and discuss the findings.....	49
Figure 10. Activities of the original Biodesign framework that are discussed in each step of the proposed framework.....	66
Figure 11. Example of protection strategies for an automatic insulin pump (hardware and embedded software).	71
Figure 12. IS' multi-layer technical file.....	75
Figure 13. Flowchart from the guidance document “Deciding When to Submit a 510(k) for a Software Change to an Existing Device”.	84
Figure 14. Using Monetization and Offering to build Value-based partnerships with providers.	95
Figure 15. Medtronic's UNiD™ ASI cycle of services for spinal surgery	98
Figure 16. Proposed implementation plan for a Value-Based deal.	100

List of Contents

Table 1. Number of interviews made across relevant dimensions of the Biodesign framework.	47
Table 2. Features, challenges and opportunities of the current MedTech landscape identified by the interviewees.....	50
Table 3. Relevant topics, considerations and best practices to generally support innovation in MedTech according to interviewees.....	53
Table 4. Relevant topics, considerations and best practices to support digital and data-driven MedTech according to interviewees.....	58
Table II-1. Unstructured interviews: interviewees' profiles, key lessons learned and recommendations. shared in the interviews.	II.1
Table II-2. Semi-structured interviews: interviewees' profiles, key lessons learned and recommendations shared in the interviews.	II.5
Real-World Example 1: PeekMed®.....	67
Real-World Example 2: Interventional Systems	75
Real-World Example 3: RelieVRx® (part I).....	78
Real-World Example 4: PRO Instrument (from PRO Compendium Entry)	80
Real-World Example 5: PeraServer/PeraTrend software validation using EMRs	81
Real-World Example 6: ContaCT software validation using radiology reports.....	81
Real-World Example 7: RelieVRx® (part II)	89
Real-World Example 8: Coverage for the Canary Tibial Extension (CTE) With Canary Health Implanted Reporting Processor (CHIRP) System.....	90
Real-World Example 9: Coverage for the EchoGo Heart Failure 1.0 Software.....	91
Real-World Example 10: Coverage for Optellum Lung Cancer Prediction Software.....	92
Real-World Example 11: Interventional Systems' Crawl, Walk, and Run approach	96
Real-World Example 12: Medtronic's UNiD™ ePRO service and UNiD™ ASI platform.....	97
Real-World Example 13: PeekMed's Licensing of SaMD	101

Abbreviations

AI	Artificial Intelligence
API	Application Programming Interfaces
APM	Alternative Payment Methods
CAPA	Corrective and Preventive Action
CDRH	Center for Devices and Radiological Health
CMS	Centers for Medicare & Medicaid Services
CROM	Clinician-Reported Outcome Measure
EHR	Electronic Health Record
EMR	Electronic Medical Record
EU	European Union
FDA	Food and Drug Administration
FHIR	Fast Healthcare Interoperability Resources
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act
HTA	Health Technology Assessment Authority
ICHOM	International Consortium for Health Outcome Measures
ICT	Information and Communication Technology
IP	Intellectual Property
ISO	International Organization for Standardization
IT	Information Technology
IVD	In Vitro Diagnostics
MDIC	Medical Device Innovation Consortium
MDMA	Medical Device Manufacturers Association
MDR	Medical Device Regulation
ML	Machine Learning
NHS	National Health Service
O&P	Orthotics and prosthetics
OSS	Open-Source Software
PCO	Patient-Centered Outcome
PP	Patient Preference
PPI	Patient Preference Information
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
QS	Quality System
RWD	Real-World Data
RWE	Real-World Evidence
SaMD	Software as a Medical Device
SEP	Standard Essential Patent
SMEs	Small and Medium Enterprises
TPLC	Total Product Lifecycle
US	United States
VBHC	Value-Based Healthcare
VC	Venture Capitalist

1. Introduction

The MedTech industry is one of the main stakeholders in the healthcare sector, collaborating with payers, healthcare providers (i.e., hospitals, clinics) and patients in the delivery of medical solutions that improve people's quality of life and save lives. With such close ties to other stakeholders of healthcare, MedTech businesses are not only influenced by cross-industry technological and regulatory trends, but also susceptible to changes in provider, payer, and even patient behavior. The tightening budgetary constraints faced by the healthcare sector due to healthcare professional shortages and the aging of the general population accompanied by a rise in chronic conditions, as well as the never-before-seen advancements in technology – especially in the digital domain, aimed at leveraging the abundance of healthcare data – creates a unique and often challenging landscape for MedTech businesses to operate in.

This dissertation focuses on identifying the specific internal and external factors currently affecting the MedTech industry and their associated challenges and opportunities, culminating in the creation of a framework to help current MedTech businesses leverage technology and deliver innovation – from the conceptualization of a new solution to its development and deployment.

Medical technologies, or MedTech, can be defined as products, services and solutions used in the prevention, diagnosis, monitoring, and treatment of health conditions that may affect people's lives. MedTech encompasses both medical devices and in vitro diagnostics (IVDs), which are non-invasive tests used on biological samples to determine the state of one's health [1]. For the purposes of this study, the discussion of MedTech matters focus primarily on medical devices. The particular characteristics of IVDs would add yet another layer of complexity to an already intricate discussion, requiring the inclusion of biotechnology notions such as molecular diagnosis and genomic sequencing. This choice is also justified by medical devices constituting the major portion of MedTech – representing more than 80% of the sector's revenue in 2021 [2]. Nevertheless, many of the considerations pertaining to medical devices in this study may also be applicable to IVDs.

1.1. Background

The rise of digitalization and data-driven solutions has shaken the bases of all industries. Data analytics and AI have allowed companies to gain insight into the efficiency of their own operations, as well as identify and even predict market trends that have direct impact on their businesses.

The healthcare industry is no strange to this shift towards digitalization: electronic health records (EHRs), operating room and medical item procurement management software, digital storage of patient imaging results—these are only some of the tools or systems which have been widely used by hospitals and healthcare institutions in the past years. In this rapidly changing environment, however, existing solutions are quick to fall into obsolescence, or are simply not enough to tackle deep-rooted problems in healthcare.

The healthcare providers' inability to handle an increase in demand is one example of such deep-rooted problems. The aging of the general population, which is accompanied by an increase in chronic conditions, will only raise the demand for healthcare services, while the sector's workforce is expected to steadily decline. This trend is already being observed in healthcare, with immense pressure being put on healthcare providers, leading to workforce burnout, poor patient treatment and skyrocketing healthcare costs. According to a 2023

Accenture report [3], there are currently about 53.5 million people in the 60-90 year-old range in the US, a number expected to grow by 45% over the next two decades. Meanwhile, when it comes to healthcare capacity, in the US alone, nearly 500,000 nurses (17% of today's total workforce) are expected to leave the profession in the next five years. The International Council of Nurses projects that the current nurse shortage could balloon to 13 million by 2030, with more than 6 million nurses expected to retire over the next decade. With the decreasing workforce, many health systems have had to use outside resources to help deliver care, and the cost of replacing employed nurses with agency resources is significantly greater. Spending on agency staff rose 20% last year in England to reach £3 billion. NHS trusts have paid up to £2,500 to nurses to fill shifts. As the report puts it, "the unprecedented challenge for health systems is that we can never hire our way out of this problem".

To prevent the collapse of healthcare systems, innovative solutions that simultaneously reduce costs and improve patient outcomes – through a so-called value-based approach – must thus be found. The medical technology (MedTech) industry has shown signs that this is achievable by leveraging the power and abundance of health data in producing data-driven solutions capable of increasing the operational and clinical efficiency of healthcare systems.

The path to be followed by MedTech companies is not clear-cut, however. Companies of the sector must not only stay up to date with rapidly evolving, data-centered technologies (e.g., cloud and artificial intelligence tools), but also comply with emerging regulation that arise from that, including concerns with cybersecurity and data privacy, quality of sourced data, and data standardization. From a business standpoint, MedTech companies must also take into account the value-driven shift in reimbursement and procurement decisions of payers and providers in order to build robust business models and strategies.

In light of this challenging panorama, it is essential to offer guidance to MedTech companies through a complimentary framework that builds upon the core principles of medical product development as presented by authors Yock *et al.* (2015) in their industry-defining work *Biodesign: The Process of Innovating Medical Technologies*. Such a new framework should touch upon the best practices defined by the original work, while exploring the key new steps to be followed by MedTech companies in the creation of impactful data-driven solutions.

1.2. Motivation and objectives

The MedTech industry plays a pivotal role in the delivery of continuously improving solutions to improve the quality of life of patients and save lives. However, the complexity of regulatory, market, socio-economic and technological aspects that permeate the sector, especially in the way they interact with one another, often deter MedTech businesses from pursuing innovation – or lead to the failure of many that try. Navigating such complex environment is a challenge for all kinds of businesses, be it major MedTech enterprises, which have limited maneuverability in innovating within their well-established, bureaucratic structures, or small businesses, which have limited experience and resources to address all the factors influencing their business, and that constitute the vast majority of MedTech businesses within the industry [4].

The Biodesign framework developed by Stefanos Zenios, Josh Makower and Paul Yock aimed to provide guidance for MedTech businesses on such matters [5], leveraging the academic, clinical, industrial and business expertise of important stakeholders in and around the MedTech industry to create comprehensive roadmap for identifying, inventing, and implementing new medical devices and technologies. In spite of the completeness of the Biodesign framework, the healthcare sector and consequently the MedTech industry have gone through significant transformations since the publishing of the framework – namely its latest iteration, presented in the 2015 book *Biodesign: The Process of Innovating Medical Technologies* 2nd Edition [6] –

including the aggravation of cost containment within healthcare and the rise of new technologies aimed at leveraging the great amount of health data generated in the sector. Therefore, driven by the research question “*What aspects of the Stanford Biodesign framework may warrant additions to better support current MedTech businesses?*”, this dissertation aims to study and analyze the dimensions of the Biodesign framework most affected by recent changes in the industry, identify opportunities and disclose best practices to be followed by MedTech businesses across such dimensions, working as a natural extension of the Biodesign framework.

This study, which culminates in the creation of a framework in itself, is expected to have practical use, providing detailed information and highlighting useful resources for current MedTech businesses based on the inputs of diverse experts from areas relevant to the industry. This dissertation includes the application of the proposed framework to a real MedTech company – not only as a demonstration of the framework’s applicability, but also as a source of direct guidance for the company involved

1.3. Structure of the dissertation

This dissertation is structured around 7 chapters in total. Starting at Chapter 2, each chapter is briefly described in the following paragraphs.

Chapter 2 provides a literature review of the theoretical background and key concepts related to MedTech innovation, delving into aspects of Value-Based Healthcare (VBHC), the different sources of real-world data (RWD) in healthcare, and the opportunities and challenges faced in the implementation of digital and data-centric solutions within the MedTech industry. The chapter also discusses the original Biodesign framework and, based on the other information provided in the chapter, presents the dimensions of that framework that may warrant a revision given the current landscape of healthcare and the MedTech industry.

Chapter 3 describes the research methodology, which comprised a qualitative exploratory sequential approach based on unstructured and semi-structured interviews. The interviews were analyzed using thematic coding, which generated the themes used in the following chapter.

Chapter 4 presents and discusses the results of the interviews, comparing them with the initial literature review findings and exploring new information brought by the interviewees. The chapter mostly validates the changes through which healthcare and MedTech have gone in the past years, presents suggestions and best practices pertaining to innovation in the industry as a whole, specific considerations for digital and data-centric businesses, and provides notions on the future of the industry.

Chapter 5 synthesizes the previous information to propose An Updated Framework for MedTech Businesses, effectively building upon the original Biodesign framework on matters concerning Concept Generation and Screening, Intellectual Property and Legal Affairs, Regulatory Affairs and Quality and Process Management, Reimbursement, and Business Model and Strategy. The updated framework introduces new considerations while highlighting some aspects of the original framework that are particularly applicable to the current MedTech landscape.

Chapter 6 presents a case study in which the MedTech company Adaptech is evaluated through the lenses of the framework proposed in the previous chapter. The case study constitutes a practical implementation of the framework, analyzing whether Adaptech is aligned with the best practices and recommendations of the proposed framework across all its dimensions. In case of misalignment, suggestions based on the framework are provided.

Finally, Chapter 7 draws conclusions on the main contributions and implications of the study, discusses its limitations, and presents suggestions for further improvements in future research.

2. Theoretical Background and Key Concepts

2.1. Medical Technology Innovation

From a general standpoint, innovation can be defined as the implementation of adaptive solutions motivated by commercial and/or societal motives that create value, harness new technology, and contribute to competitive advantage and economic growth [7]. The introduction of new cross-industry technologies, changes in investor behavior and shifts in the dynamics of the healthcare sector have caused significant changes in the way medical technology is thought of and rolled out, prompting the resurgence of innovation in the sector. The average global R&D investment rate (R&D spend as a percentage of sales) in the medical technology sector ranks amongst the highest, being estimated to be around 8% [8]. The quick pace of medical technology development is further evidenced by product lifecycles of only 18 to 24 months before improved products become available [9].

MedTech innovation is motivated at its core by grave shortages in medical personnel and mounting demands for medical services due to factors such as the aging of the global population. Increasing capacity and workforce productivity, and the delivery of effective, personalized care are amongst the driving forces of the industry. This is why, according to Accenture [10], 92% of health executives rank delivering a highly personalized experience as a top strategic priority.

On the other hand, overarching technology advancements seem to be some of the main drivers for innovation within MedTech. To put this into numbers, an Accenture [11] report revealed that 97% of healthcare executives believe continuous advances in technology are becoming more reliable than economic, political or social trends in informing their organization's long-term strategy. While the pursuit of increasingly more advanced technologies allows for the delivery of solutions to glaring problems within the industry that could not be previously tackled, the introduction of new, fast-evolving technologies has intensified competition and raised the bar for companies wishing to maintain their space in the market. As previously stated, innovation may be birthed out of societal or commercial motives, with both aspects being evident and often intertwined in MedTech.

2.2. Value-Based Healthcare (VBHC)

The MedTech industry finds itself in a phase of transition as new technologies arise. However, though new technologies are able to tackle clinical problems in better, more effective ways, it is important to highlight foundational problems in the healthcare system that prevent innovation from reaching its intended users and contribute to the financial strain currently faced by healthcare providers, namely hospitals and clinics.

The US healthcare system is based on a traditional fee-for-service payment model in which healthcare providers – such as physicians, hospitals and outpatient clinics – are paid for each service they provide. This essentially rewards providers for the volume of provided services, even if the desired outcomes are not reached. The use of such models for the past decades has often resulted in providers adopting inefficient or marginally-enhanced solutions for which the costs are not translated into patient wellbeing. With a diminishing workforce and higher demands for care, such a model becomes unsustainable: as patients' needs are not truly addressed, they end up accumulating and crowding the system. Providers' financial resources are thus drained, since the solutions for which they paid are not enough to satisfy the stream of both old and new patients.

In the past years, these issues have pushed for a change in the definition of “value” within healthcare. Although MedTech solutions are still valued by their potential to improve clinical outcomes, a new dimension of cost has been added to their valuation: now, value is much more tied to whether the marginal benefit brought by a MedTech solution over other available solutions is enough, in terms of a cost/improvement ratio, to warrant its adoption. Parallely, the assessment of value is evolving from being product specific to outcomes-oriented, often evaluating total solution offerings across an episode of care [6, p. 2]. Healthcare could be considered as having always been “value-based”, though the sector’s current understanding of “value” pushes solutions to deliver improved outcomes in broader, more substantial ways than before, and with tighter budgetary considerations.

A recent trend of value-based models in payer-provider relationships is one that ties the amount healthcare providers earn for their services to the results they deliver for their patients, serving as a more sustainable alternative to fee-for-service [12]. It incentivizes providers to achieve the best possible patient outcomes while streamlining operations and minimizing wasteful spending, which has become a necessity given the current panorama. The National Academy of Medicine has described a useful framework for quality in healthcare, which may serve as measures of performance for providers in value-based care models:

- **effectiveness:** care is based on evidence and is designed to get results
- **efficiency:** providers don’t use resources that are not needed
- **equity:** care does not vary in quality based on personal characteristics such as race, gender, and income
- **patient centeredness:** each patient’s values, preferences, and needs are respected
- **safety:** treatment does not cause harm
- **timeliness:** treatment is available without long delays.

The applicability of the value-based model relies on the implementation of value-based payments as opposed to fee-for-service. Value-based payment models, or alternative payment methods (APMs), have been gaining more traction among payers in the past few years [13]. Upside rewards, that is, paying providers for exceeding expectations on quality, cost, or equity targets, appears to be one of the more popular APMs. Upside & Downside incentives go one step further by penalizing providers that do not meet expected outcomes; also known as two-sided risk APMs, these have been shown to lead to better outcomes, such as fewer patient hospitalizations [12].

According to a report by The Health Care Payment Learning & Action Network (HCPLAN or LAN), an active group of public and private healthcare leaders dedicated to supporting the adoption of value-based models, in 2021 19.6% of U.S. healthcare payments fell into two-sided risk APMs, with public payers showing the biggest adherence: 35.2% for Medicare Advantage, 24% for traditional Medicare, 16.6% for Medicaid and 12.7% for commercial insurers [13]. That same report revealed that 83% of payers thought APM activity would increase in the following years, with the vast majority agreeing that APM adoption will lead to better quality of care, more affordable care and improved care coordination.

Still on HCPLAN’s report, payers listed health plan readiness and government influence as some of the top facilitators to the implementation of APMs, which may serve as indicators that the widespread use of value-based systems may soon become a reality. Conversely, payers cited provider willingness to take on financial risk as one of the top barriers to APMs. This sentiment is understandable given the financial strain at which most providers find themselves in, which might detain them from taking even more financial risk; however, the necessity for value-based systems and the pressure from payers and government may eventually cause providers to yield. This is likely to impact the relationship between providers and MedTech companies, as many of

the solutions provided by the latter will be rigorously evaluated (even more stringently than today) in their potential to maximize patient outcomes at a reduced cost.

2.2.1. Real World Data

To improve clinical and patient outcomes – a long-standing part of MedTech innovation and the central component of value-based systems – the performance of providers, procedures and solutions should be evaluated in the real-world context in which they are inserted. As per the FDA, Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, including electronic health records (EHRs), claims and administrative data, data from product and disease registries, patient-generated data, and device-generated data [14]. Spanning from data generated in actual clinical settings outside of controlled trials (e.g., death rates and time of hospitalization associated with a certain procedure or therapy), to data generated by medical devices in the home setting, RWD are important resources in ascertaining the effectiveness of procedures using certain MedTech solutions, or the performance of MedTech devices themselves.

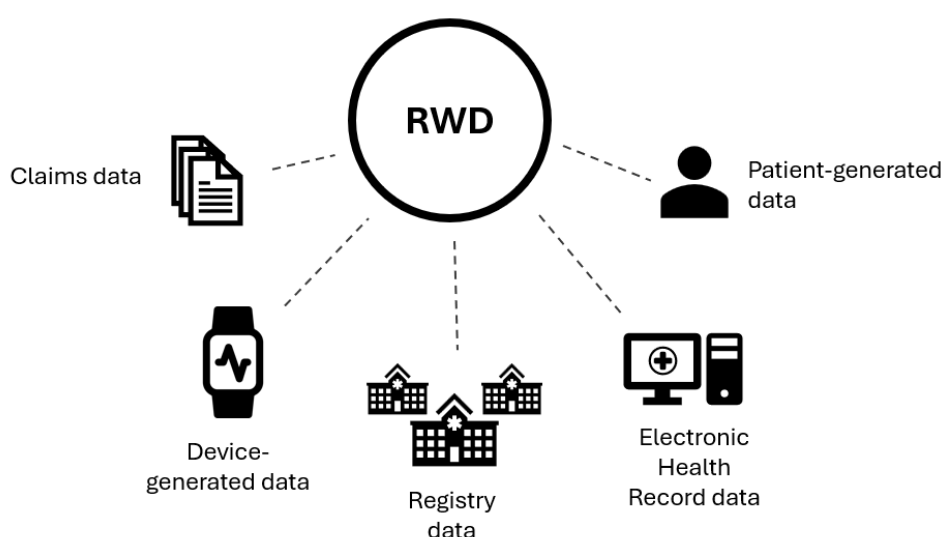


Figure 1. Common sources of Real-World Data (RWD).

The abundance of RWD may not only be used in reimbursement decision-making but also applied, in the broader sense of the value-based system, on previous steps of MedTech product lifecycles, namely in the regulatory approval of new medical devices. The consideration of RWD by regulators and payers has the potential to streamline the arrival of innovative MedTech products to the market while making sure that only the best solutions – that is, the ones which produce the best patient outcomes more efficiently – are actually incorporated.

In a 2017 guidance on the Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, the FDA’s Center for Devices and Radiological Health (CDRH) clarified how they evaluate the relevance and reliability of RWD to determine whether they are sufficient for generating the types of Real-World Evidence (RWE) that can be relied on for FDA regulatory decision-making for medical devices [15]. The document Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions [14] further expands on that, where the CDRH presents 90 examples of submissions that illustrate RWE usage in support of regulatory decision-making from fiscal years 2012 through 2019, with examples coming from the full continuum of clinical and device areas and across the medical device total product life cycle.

Defining how to best leverage RWD to inform regulatory and especially payment decisions in an institutionalized way will require sustained dialog involving regulators, product developers,

clinicians, payers, and other stakeholders. In 2021 MDIC hosted a public forum on real-world evidence in the context of payer decision-making. The forum, which was co-hosted by the FDA, discussed the CMS-FDA collaboration on real-world data (RWD), provided examples of RWE used by the FDA in regulatory decisions, and presented the perspective of CMS and other stakeholders on RWE.

The forum evidenced that the use of RWD and RWE is still in an incipient state. Although the FDA and CMS agreed that clinical data, claims data, disease databases or registries, and data from personal devices have great potential in being used to assess safety, efficacy and reasonable necessity of medical technology, it was also determined that RWE must meet rigorous methodologic standards. A major private payer further expanded on the topic, saying that published evidence about RWE is often lacking or has bias or unsound methodology, and that well-defined standards are needed in order to identify clinically meaningful outcomes from RWE.

It is important to note that the FDA has been working with stakeholders to develop metrics, maturity models, and standards for data quality. For solely regulatory considerations, FDA's Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices 2016 guidance document goes over how the agency evaluates RWD in its decision-making.

Amongst other initiatives pertaining to the consideration of RWD by both regulators and payers, the National Evaluation System for Health Technology Coordinating Center (NESTcc) should be highlighted. Created by the MDIC through an FDA grant in 2016, it is intended to catalyze real-world evidence generation and establish a research network devoted to that purpose [16]. NESTcc has recently deployed 21 Test-Cases aimed at assessing the feasibility for medical device ecosystem stakeholders to work with RWD and helping identify areas where transaction costs could be reduced (e.g., data sharing agreements) [17]. The Test-Cases span the medical device total product lifecycle (TPLC) and include projects that have regulatory (i.e., pre-market and postmarket pathways) and coverage applications. NESTcc Network Collaborators contribute to the execution of the projects by leveraging multiple data sources – device registries, electronic health records (EHR), claims, mHealth, patient-generated health data, and patient reported outcomes. NESTcc also established a multi-stakeholder Active Surveillance Task force to more quickly detect emerging safety signals related to medical devices in the post-market setting. The task force is intended to demonstrate the feasibility of deploying active surveillance tools within the NESTcc Data Network, resolve methodological issues and explore scalability of active surveillance to include a large number of devices [18].

Over the coming years, a growing number of collaborations is expected to emerge between many different stakeholders in healthcare, including providers, payers, IT companies, and MedTech companies, large and small. These new types of partnerships are likely to focus on accessing and processing real-life outcome data with the objective of sharing accountability on patient outcomes. Without RWD data, it is difficult to find actionable ways to improve, and thus to overcome the serious operational and economic pitfalls of the healthcare system.

Ultimately, the use of RWD is something to be kept in mind by the MedTech industry. New technologies are likely to support the generation of reliable data, which may serve as objective validation of a product's performance in a practical scenario. This can increase the value of MedTech solutions and may facilitate their navigation through regulatory and reimbursement avenues as new standards for RWD are developed.

2.2.1.1. Patient-Reported Outcomes (PROs) and Patient-Centered Outcomes (PCOs)

Patient centeredness is at the core of the value-based system, where solutions are first evaluated by how well they can satisfy patients' needs. The only way to evaluate the true value of care is thus to measure patient health gains according to what they consider most important in their daily life [19]. Patient-Reported Outcomes (PROs) are used for that purpose. Defined by the FDA as “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else,” [20] PROs typically include information about health-related quality of life, symptoms, function, satisfaction with care or symptoms, adherence to prescribed medications or other therapy, and perceived value of treatment [21]. Patient-Centered Outcomes (PCOs) may be determined through the evaluation of PROs, allowing providers and other stakeholders to highlight outcomes most relevant and comprehensible to patients [22]. PROs are a subset of real-world data (RWD), which have been explored in the previous section.

PROs and PCOs are not new to the healthcare system, but their adoption has often been overshadowed by the use of clinical outcomes (e.g., PSA levels tied to prostate cancer). In their 2016 book *Redefining Healthcare*, authors Michael E. Porter and Elizabeth O. Teisberg presented the argument for using health outcomes data to redefine the nature of competition in health care, leading to better patient outcomes and reducing inefficiencies [23]. Nowadays, the necessity for such improvements has brought PROs closer to the spotlight.

As a practical example, we can look at the National Health Services (NHS) in Wales. NHS Wales found – through patient reporting – that 19% of cataract surgeries do not improve visual disability. With a cost of £615 per surgery (€731), it was questioned whether the procedure actually added value to the patient if it had no impact on activity limitations in daily life. As complication rates for cataract surgery are low (1.6% on average), but unnecessary treatments are significant (19%), patient-reported outcome measures are now strategically used by the NHS and clinicians in triage to determine the optimal care pathway for each patient. This case illustrates that though solutions may be of high quality (low complication rates), they might not necessarily add the highest amount of value to patients, leading to wasteful expending. PROs can thus play an instrumental role in determining the judicious deployment of resources [19].

Patient-Reported Outcome Measures (PROMs) are measured before, during and after care through the employment of questionnaires, often called PRO instruments. These instruments are generic and condition specific, multidimensional and risk-adjusted, allowing for the determination of endpoints of care and relevant milestones. They undergo rigorous psychometric and statistical validations and must be calibrated to each specific setting in which they are applied to ensure validity and allow for proper benchmarking; translations and cultural adaption of PRO instruments must follow the guidelines adopted by the Professional Society for Health Economics and Outcome Research (ISPOR) [24]. PRO instruments are essential for evaluating patient priorities and provide standardized measures for improvement [25] with the ultimate goal of involving patients in clinical decision-making. PROMs are thus relevant, actionable data [26] that can be coupled with clinical outcomes measures for a thorough assessment of healthcare performance [27].

The somewhat slow adoption of PROMs by different stakeholders of the healthcare sector can be attributed in part to the difficulty of their measurement, especially since adjusting outcomes to case-mix variables is essential when analyzing variations across patient populations [19]. To remedy that, the International Consortium for Health Outcome Measures (ICHOM) [23] has partnered with many public and private stakeholders, including patient representatives, leading physicians and registry leaders, in the development of Sets of Patient-Centered Outcome

Measures. As of 2023, ICHOM had published 45 Sets of Patient-Centered Outcome Measures covering different conditions and for specific patient populations, all of which are under continuous review. For each condition, a data dictionary clearly defines sources of data and time points for data collection. Standard sets are accessible online for free and can easily be integrated into Electronic Medical Records, allowing for seamless collection of PROMs and clinical information by providers. ICHOM Sets are in the process of being made compatible with FHIR/HL7 data standards (see chapter 2.4.4), which may allow for even more interoperability across health electronic systems.

From an industry perspective, knowledge of the ICHOM Sets and PROMs in general may help guide the development of new solutions, as these will directly affect the care pathway of patients. Considering patient-centered outcomes in addition to clinically-relevant outcomes may increase the value of MedTech solutions in the current panorama of the healthcare sector.

e-PROMs

Most healthcare facilities have a data platform designed to collect patient-reported and clinician-reported outcome measures (PROMs and CROMs, respectively). When it comes to PROMs, the data integration process is simple: after checking in, patients complete an online PROM survey while waiting for the appointment. The survey results are then made immediately available to both patient and clinician during the consultation and, after the visit, stored along with other patient records (i.e., EHR) in a searchable database [28]. Such online surveys are conducted at different points of the care pathway in order to assess the impact of the treatment on the patient according to their own perspective.

From the provider's side, the use of well-designed data collection tools may significantly impact the amount of PROM and CROM data collected, contributing to more robust improvement cycles [29]. As an example, the cleft lip and palate department at the Erasmus Medical Centre in Rotterdam, the Netherlands, established its own electronic data capture tool, which was built through the contribution of clinician and IT teams. It consisted of customized ergonomic dashboards designed to appeal to patients, caregivers and hospital managers [30]. With visuals that engage users and prompt actionable discussions, the dashboards achieved 95% compliance for PROMs and 100% compliance for CROMs for the department.

Data platforms for providers do not need to be developed in-house, as these require time and resources for IT development. A growing number of software as a service (SaaS) solutions aim at filling this niche within the healthcare sector, with vendors proposing integrated solutions with libraries of questionnaires for each care pathway including checklists, PROMs, CROMs, alerts, etc. to standardize treatment and learn from improvement cycles.

The collection of PROMs may be directly incorporated into patient-monitoring medical devices themselves, helping offload provider duties. The Israeli start-up Sivan has developed a digital biomarker integrated in an electronic patient reported system (e-PROM) to telemonitor patients in lung cancer remission. The e-PROM device/app, Moovcare, which has been validated through evidence-based results published in scientific journals such as the American Journal of Clinical Oncology and JAMA, asks that patients report on 12 symptoms on a weekly basis. When their health status deteriorates (with recurrent reports of breathing and sleeping difficulties, for example) an automatic alert is sent to a doctor or nurse. Compared to the traditional care cycle with regular CT scans to monitor early symptoms of lung cancer relapse, Moovcare was shown to increase overall survival by eight months and has demonstrated a €12,127 increase in the cost-effectiveness ratio per life-year gained [31]. Due to its proven clinical and economic impact, the French Health Technology Assessment Authority (HTA) ranked Sivan's solution as one of the most innovative medical devices eligible for reimbursement in 2019. This was followed by the establishment of strategic partnerships

between Sivan and leading French public and private hospitals for the integration of Moovcare into new patient pathways to improve patient survival rates and reduce unnecessary imaging and hospitalization costs [32]. This VBHC example illustrates a novel type of relationship between e-PROM companies, providers and a national HTA body and highlights the relevance of such unprecedented approaches to measuring health status.

2.2.1.2. Patient Preference Information (PPI)

The FDA defines patient preference information (PPI) as “qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions”. PPI are therefore meant to capture the value that patients place on aspects of a treatment option while also accounting for their perspectives on trade-offs they are willing to make for the benefits and risks that come with the treatment. The role of PPI extends across the total lifecycle of a healthcare technology, influencing decisions in design, clinical trial protocols, regulatory pathways, payer coverage, product and service acquisition, marketing, clinical education, adoption, and more. Although explicit, quantitative data contribute to PPI, what sets it apart from PROs and PCOs is the inclusion of qualitative, hypothetical, and aspirational components [33].

Companies that have mastered the nuances and intricacies of conducting patient preference (PP) surveys early are well positioned to obtain insights that can improve their products, bring them to market sooner, and yield a significant return on investment [34]. The impacts of preference studies throughout the development and roll out of medical products are numerous:

- **Needs finding and screening:** perhaps most important of all, patient preference studies applied at the early stages of product development may uncover unmet needs amongst patients and providers. Such studies will inform if an innovative product is likely to be embraced by the market or not, and may spare companies from investing in solutions for which there is no actual interest.
- **Prototype design:** patient preferences can inform which attributes are most relevant to patients in a new product, and may shorten the time of development of a product.
- **Clinical trial design:** patient preferences can help identify unique endpoints and performance goals, which can be built into pre-market clinical study designs as primary or secondary outcomes. This can reduce the burden on patients participating in the trial, which may result in improved recruitment, retention, and compliance.
- **Benefit-risk decision-making:** patient preference information can provide insights on maximum acceptable risk—including minimum acceptable benefit, net clinical benefit, quality-adjusted time without symptoms and toxicity, and benefit-less-risk analysis.
- **Regulatory pathway:** as it will be further discussed, the FDA encourages the inclusion of PPI in the development of medical devices as patient voice becomes more important in the approval process.
- **Post-market coverage decisions:** although the use of PPI in coverage decisions is relatively new, US payers have demonstrated interest in its use. International HTAs have also shown keen interest in data from patient preference studies.
- **Marketing and labeling:** PPI can be critical to informing marketing strategies and informational materials directed towards patients, and can ensure receptiveness and effective use of products with the adequate label or indications.

It is relevant to note that developing a survey to collect patient information can require expertise in areas such as marketing research and statistical analysis. Surveys must elicit the needed information while promoting the recruiting and retention of respondents to be successful – for example, the use of a discrete choice experiment that allows respondents to evaluate multiple

attributes at a time may be beneficial to the researcher but burdensome to the respondent, leading to dropouts or inaccurate answers. Such knowledge may not always be available to smaller MedTech companies, which should instead secure services from external consultants.

Patient preference has long been considered in regulatory decision-making. Since the creation of the Patient Centered Benefit-Risk (PCBR) Framework by the Medical Device Innovation Consortium (MDIC) – an independent organization composed of government and industry stakeholders, such as federal agencies CDC and CMS, the Medical Device Manufacturers Association (MDMA) and major life sciences corporations Medtronic and Johnson & Johnson – in 2015, the FDA has been able to reliably assess patient preference in the evaluation of multiple medical devices, with the agency even incentivizing MedTech companies to include PPI in their development of new solutions. In accordance with the 21st Century Cures Act, the FDA has been working on a series of guidance documents titled “Methods to Identify What Is Important to Patients” to help standardize the collection and submission of patient-focused information [33].

Although the FDA has shown willingness to use PPI data generated by industry to support regulatory purposes, payers and health technology assessment (HTA) organizations seem more reluctant to do so. In 2020 MDIC sponsored a series of interviews with representatives from public and private payers, integrated delivery networks and HTAs to ascertain the value attributed to PPI in reimbursement decision-making. Interviewees uniformly expressed interest in PPI, but remarked that its implementation is held back by concerns about the lack of standardization in PP studies as opposed to what is seen in PRO and PCO questionnaires, and the potential bias stemming from who funds, designs and conducts PP studies. Nevertheless, the same stakeholders concurred that there are times when PPI would be more likely to inform their assessments and coverage decisions, notably when multiple approved technologies are available that appear comparable in safety, effectiveness, and cost. In those cases, PPI may help to point decisions toward interventions that patients express would benefit their adherence, quality of life, or other outcomes. MDIC’s initiative revealed that creating standardized methods for evaluating PPI, conducting independent PP studies, and increasing the awareness of patient preferences on the part of the HTAs may help inform payer decisions, offering an opportunity to leverage their credibility to increase the role of PPI beyond regulatory avenues.

MedTech companies can work to ameliorate payer skepticism. Transparency on industry funding and partnering with patient advocacy groups are great ways of lessening concerns towards PP study bias. Companies should maintain a conversation with regulatory agencies, payers, and HTAs in order to gain insights into how those bodies would use patient preferences in their processes, or in what situations they find patient preference data valuable, which can inform their development and use of patient preference studies [34].

2.2.2. Value partnerships between providers and industry

In such rapidly changing times, companies in the healthcare sector understand that they can remain competitive only by demonstrating how their products and services help providers and medical teams deliver superior outcomes for patients at lower total costs. However, the promise of better outcomes is different from accepting accountability for those outcomes. The shift from being paid for promises to being paid for outcomes requires the routine measurement of real-world outcomes using digital solutions and registries [29].

The biopharmaceutical sector has been making significant strides in this sense. For example, in 2016 American multinational Amgen launched in Finland the development of a VBHC ecosystem for multiple myeloma in collaboration with hematology units of academic medical centers as well as with other technology partners. Such partnerships allowed Amgen to collect

real-world data through an e-PROM tool, which included nine patient symptoms for patients with relapsed and/or refractory multiple myeloma. Hospitals covered the license costs of using Amgen's IT platform, with the company committing to refund treatment costs for its innovative treatment option if expected outcomes based on the PROMs were not delivered. Since then Amgen has scaled this initiative to other clinics and disease areas in the country. MedTech companies are also developing their expertise in clinical care and reimbursement services to demonstrate the value of their devices and services, as will be seen further.

2.2.2.1. Medtronic's VBHC framework

In 2017 Medtronic adopted operational principles to accelerate VBHC projects in an effort to strengthen its relationship with providers [19]. According to this seven-step framework (Figure 2), a value-based healthcare project should:

- Specify a procedure or condition with a significant and defined population of patients who could be treated more effectively and efficiently through an innovative care model
- The condition must have measurable outcomes and Medtronic managers must be able predict the improvements in outcomes and costs from implementing the VBHC project.

Seven step VBHC framework	Product: antibacterial envelope for implantable cardiac devices (TYRX™)
1. Select disease or condition	Cardiac arrhythmia
2. Develop patient cohorts based on risk and protocols	Patients undergoing a cardiac electronic device implant at high risk for infection
3. Define outcome measures that are meaningful to patients	Reduction in device-related infections
4. Define the time frame required to achieve optimal outcomes	6 months, post device implant
5. Quantify baseline outcomes and costs for each patient cohort	3.6% infection rate in high risk patients and average cost of \$50,000 per infection
6. Determine prospective performance and cost objectives	0.4% infection rate with TYRX utilised
7. Develop the business model	Shared accountability (risk share) programme with providers

Figure 2. Medtronic's seven step VBHC framework.

This framework was applied to Medtronic's TYRX™ absorbable antibacterial envelope, which helped to stabilize device implants and prevent infections associated with pacemakers and defibrillators. The use of TYRX™ had shown to reduce 70-100% the rates of infection for high-risk patients and to lower total costs. Based on this value-based operational approach, Medtronic developed a shared accountability business model based on the estimated savings from using the device, meaning that if such savings were not reached, Medtronic would incur financial penalties. The programme proved successful with nearly 1,000 hospitals beginning to purchase TYRX™ under the shared accountability programme in the following year.

Medtronic's framework touches upon core components of VBHC and showcases the relevance of VBHC programmes in the current state of healthcare. Steps 1 and 2 are common initial steps in the development of MedTech solutions, consisting of narrowing down the condition and specific group of patients which the solution is supposed to tackle. The first VBHC aspect of the framework is observed in step 3, where outcome measures meaningful to patients – or patient-centered outcome (PCO) measures – are identified. Steps 4 through 6 define the practical aspects of implementing the solution, clearly stating the kind of real-world data associated with the PCO to be collected, as well as establishing both the baseline and target values for the collected data (performance indexes). Finally, step 7 proposes the development of a VBHC business, which in the case of TYRX™ took the form of a shared accountability model. Such model signals the company's confidence in its own product and takes away some of the

financial risks normally incurred by providers; it thus promotes a relationship of trust with providers and makes them more willing to acquire the product even under financial strain.

Since the implementation of the aforementioned program, Medtronic has rolled out a series of value-based projects with the same approach – ranging from therapy optimization, episodic care bundles, and chronic care management.

2.2.2.2. Consulting services in support of product delivery

Going beyond the selling of a product is an important aspect of value-based partnerships between MedTech companies and providers. By supporting doctors and administrators in the implementation of new care pathways based on VBHC, companies may acquire valuable knowledge on provider operations and patient preferences, allowing them to collaboratively tailor their solutions to deliver the best possible outcomes. Offering guidance and consultancy services to providers thus realizes the full value of the delivered product and demonstrates its medical and financial impact through real-world evidence. Leading MedTech companies such as Siemens Healthineers have been systematically applying these kinds of services as a way of establishing long-lasting partnerships [19].

In 2015 Medtronic went substantially beyond its traditional product-based business by acquiring Diabeter, a private network of Dutch medical centers that develop personalized approaches to the treatment of children and young adults with diabetes. The company also acquired the Dutch obesity center in order to address metabolic syndrome, which is one of the main factors involved in type 2 diabetes [35]. Fresenius, another large MedTech company, acquired two large private hospital operators in Germany and Spain, allowing them to impact care pathways more directly, improve patient outcomes, and take part in the entire value chain [36]. Though the previous two examples focus on larger companies moving into care delivery, it is important to note that MedTech companies of all sizes can diversify their business models to more closely engage with providers and, by extension, their patients.

2.3. Digitalization and Data-driven Solutions in MedTech

Digital healthcare refers to tools and services that use information and communication technologies to improve prevention, diagnosis, treatment, monitoring and management of health and lifestyle [37]. The rapid expansion of digital tools in MedTech can be justified by their capacity to further promote the creation of health data (e.g., through EHRs and connected medical devices), and, simultaneously, to allow the seamless sharing and processing of that data. Insights extracted from health data shared through the digital medium can then be used to improve the access to and quality of care, optimize processes and generally increase the efficiency of the healthcare sector – much needed improvements at a time of growing shortages in the healthcare workforce, ageing populations, and rising rates of chronic conditions.

Pre-COVID-19 findings attribute up to one-third of the world's data to healthcare, and projections put the growth rate of data for healthcare ahead of that of any other industry [38]. As the sector advances towards more personalized, predictive, precision healthcare, leveraging all this data will be key – and so will the digital tools to handle it. A survey by Deloitte revealed that 51% of the surveyed MedTech leaders see digital innovation as a long-term bet, with the majority of them being guided by a strong, leadership-driven digital innovation agenda [39]. When asked to identify innovative digital technologies' greatest value, 76% said enabling better patient/customer experiences, 57% said enabling greater connectivity of devices, and 55% said development of new products.

Partnerships between MedTech companies and digital solution providers are on the rise as both sectors strive to create innovative solutions to enhance healthcare outcomes. These

collaborations frequently leverage AI, machine learning, and other advanced technologies to develop innovative medical devices, diagnostic tools, and treatment methods. For instance, Medtronic and NVIDIA are teaming up to expedite the integration of AI into the healthcare system and introduce new AI-driven solutions into patient care. This could allow Medtronic to scale the development of algorithms to enhance real-time procedures and improve patient care [40].

Speaking of specific technologies, artificial intelligence and cloud computing and wireless communications are at the forefront of the digital revolution, being frequently implemented in conjunction. While AI algorithms are capable of analyzing large amounts of patient data to detect patterns and make predictions beyond human capacity, cloud and communication technologies enable the rapid collection and distribution of large amounts of patient data, often with the added benefit of removing the necessity for in-loco IT infrastructure. Calling back to Deloitte’s survey on how MedTech companies are employing digital technologies to grow, innovate, and develop a competitive edge, more than 80% of the surveyed leaders said their organization’s largest digital investments go toward AI. Cloud was the second highest area of investment, with more than 70% of the surveyed leaders’ organizations identifying it as an area of interest [39]. The following sections delve deeper into AI and Cloud.

As for communication technologies, these have an important role in wireless transfer of information across devices and electronic systems. The introduction of 5G technology holds the promise of transforming healthcare delivery by significantly improving speed, capacity, and reducing latency. 5G is poised to support the expanding network of interconnected devices and wearables for remote patient monitoring [41] [42]. However, 5G is yet to see widespread adoption in MedTech, contrary to other technologies explored in this chapter. This is mostly due to current challenges in the deployment of 5G infrastructure [43] [41] and in the way it may impact the performance (especially battery-wise) of cellular devices [41]. Nevertheless, early indications are that MedTech leaders are taking up this new technology, and have either embedded 5G into their product roadmap or are beginning to do so [44]. More information about 5G is explored in Annex I.

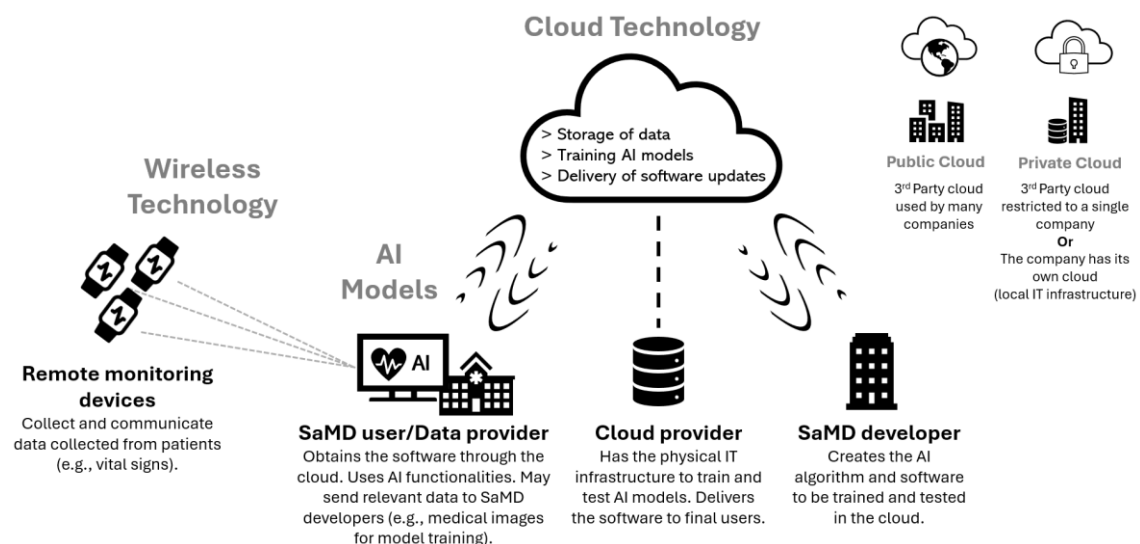


Figure 3. Interaction of communication technology, cloud and AI in digital MedTech solutions. Example of a Software as a Medical Device (SaMD) solution that analyzes patient monitoring data.

2.3.1. Artificial Intelligence

In its 2022 technical document “Machine Learning-enabled Medical Devices: Key Terms and Definitions”, the International Medical Device Regulators Forum (IMDRF) defines Artificial

Intelligence (AI) as branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions and making predictions. Machine Learning (ML), a subset of AI, allows models to be developed by ML training algorithms through data analysis, without models being explicitly programmed.

Artificial intelligence has been producing drastic changes across all industries, especially in the way AI models are capable of extracting information from large volumes of data. Though the use of AI in healthcare is only in its infancy, applications of that technology within that sector are greatly anticipated: according to Accenture's 2022 Digital Health Technology Vision [11] report, 57% of healthcare executives believe artificial intelligence will have a positive transformational impact on their organization in the future. In terms of market size, healthcare AI is expected to reach almost 188bn U.S. dollars in 2030, an astonishing jump from 2021's \$ 11bn market [45]. Such massive predicted increase can be justified by continuous advancements in ML algorithms, wider production and access to data, cheaper hardware and the availability of communication technologies such as 5G [46].

Artificial Intelligence may be used to improve the efficiency of all kinds of processes, from back-office tasks (e.g., administrative workflow, fraud prevention) to patient care. For working with data, AI data analytics tools can help providers and MedTech developers gather, store and analyze high volumes data from medical devices, EHRs and disease registries, allowing them to acquire actionable, information-driven insights from vast numbers of people.

From an industry standpoint, the possibilities for AI-enabled MedTech solutions are near endless: from AI-enabled robots and surgery navigation tools that may allow for less invasive procedures, to early diagnosis and prevention tools based on medical image analysis and patient monitoring. In fact, it is in that latter field that AI may find its greatest application: with robust results already seen in the use of ML and Deep Learning tools for the prevention of cancer and other conditions, estimates show that using AI to aid diagnosis may reduce treatment costs by up to 50% and improve health outcomes by 40% [47]. Unsurprisingly given such good results, sources report that over 90% of US healthcare leaders believe AI's leading application is in predictive analytics for early intervention [48].

Further practical examples of AI being used in healthcare include:

- **Decreasing radiation dose and shortening examination time in radiological examinations:** A systemic review of AI for radiation dose optimization in pediatric radiology found that AI – through strategies such as Deep learning imaging reconstruction – could reduce radiation dose by 36–70% without losing diagnostic information [49].
- **Reducing administrative burden for healthcare professionals and systems:** Through smart speaker devices and AI algorithms, virtual scribes are able to transcribe clinical data recorded between physicians and people living with medical conditions. These voice-to-text applications can be used to take notes about symptoms, write prescriptions, order additional tests, arrange follow-up appointments, classify, and enter everything into the patient's EHR. Estimates show that such solution could reduce the burden on healthcare professionals by up to 507.2 million hours, translated into a yearly opportunity cost of almost €8 billion [50].
- **Reducing human error in surgeries:** AI-enabled robot hands can use data from past operations to perform new surgical techniques, reducing the risk of human error. Estimates show that AI-enabled robotics could potentially reduce post-surgery stays by up to 21% and save up to 35.9 million days of hospital stay overall, resulting in upwards of €12.9 billion in savings per year [50].

2.3.2. Cloud Technology

Cloud technology is a core part of the infrastructure required to sustain digitalization across all industries, including the healthcare sector. Such is the importance of cloud technology in the current panorama that according to the International Data Corporation, over 70 percent of executives consider large-scale cloud adoption to be a strategic business decision for survival, innovation and competitive differentiation [51].

Cloud computing and associated solutions provide access through the web to computing resources and products, including business applications, development tools, data storage, compute services, and networking solutions. By moving its operations to the cloud, a company gives up its own IT infrastructure, using instead the cloud provider's offsite data center. For customers, cloud computing offers more agility, scale and flexibility, as it removes the necessity for investment in legacy IT systems and reduces operational expenses related to maintaining it, all while being able to quickly access computing resources from multiple locations. Cloud computing models can be separated into the following:

- **Public cloud.** In a public cloud, the entire computing infrastructure is located on the premises of the cloud provider, and the provider delivers services to the customer over the internet. Customers do not have to maintain their own IT and can quickly add more users or computing power as needed. In this model, multiple tenants share the cloud provider's IT infrastructure.
- **Private cloud.** A private cloud is used exclusively by one organization. It could be hosted at the organization's location or at the cloud provider's data center. A private cloud provides the highest level of security and control.
- **Hybrid cloud.** As the name suggests, a hybrid cloud is a combination of both public and private clouds. Generally, hybrid cloud customers host their business-critical applications on their own servers for more security and control, and store their secondary applications at the cloud provider's location.
- **Multicloud.** The main difference between hybrid cloud and multicloud is the use of multiple cloud computing and storage devices in a single architecture.

According to an Accenture report [52] from 2023, on average, 50% of workloads are committed to the public cloud, while 32% of workloads are destined to private clouds. However, almost all cloud users reported using both public + private (hybrid) clouds and a large percentage are using multiple public cloud providers (multi-cloud), which may be attributed to companies' weariness on committing mission critical domains to public clouds.

2.3.2.1. Cloud Computing Services

Cloud services are varied, and companies should choose which are more adequate for their objectives [53]. The main difference between the following services is the degree of involvement of the cloud subscriber in the configuration of the cloud, though in every case the physical IT infrastructure remains under the cloud provider's management:

- **Software as a service (SaaS).** SaaS is a cloud-based software delivery model in which the cloud provider develops and maintains cloud application software, provides automatic software updates, and makes software available to its customers via the internet on a pay-as-you-go basis. Many businesses find SaaS to be the ideal solution because it enables them to get up and running quickly with the most innovative technology available. Automatic updates reduce the burden on in-house resources. Customers can scale services to support fluctuating workloads, adding more services or features as they grow.

- **Platform as a service (PaaS).** PaaS provides customers with the ability to deploy onto the cloud infrastructure customer-created or acquired applications created using programming languages and tools supported by the provider. PaaS solutions provide ready-to-use programming components that allow developers to build new capabilities into their applications, including innovative technologies such as artificial intelligence (AI), chatbots, blockchain, and the Internet of Things (IoT). PaaS often includes solutions for analysts, end users, and professional IT administrators, including big data analytics, content management, database management, systems management, and security. The cloud subscriber does not manage or control the underlying cloud infrastructure including network, servers, operating systems, or storage, but has control over the deployed applications and possibly application hosting environment configurations.
- **Infrastructure as a service (IaaS).** IaaS enables customers to access infrastructure services on an on-demand basis via the internet. IaaS provides the ability to provision processing, storage, networks, and other fundamental computing resources on-demand through a console or Application Programming Interfaces (APIs). Customers are then able to deploy and run arbitrary software, which can include operating systems and applications. The consumer does not manage or control the underlying cloud physical infrastructure but, unlike with PaaS, has control over operating systems, storage, networking, and deployed applications.

2.4. Barriers to digitalization and data use in MedTech

With demographic changes, geopolitical instability and technological advancements, there is increasing pressure on MedTech companies to adopt new business models, defined as the way an organization creates, delivers, and captures value. As previously seen, change comes to MedTech mainly through two often interconnected dimensions, both of which leverage data generated in the sector: value-based healthcare and digitalization. The latter, explored in the previous chapter, involves a series of practical considerations that, when properly addressed, are bound to generate a lot of value in the form of improved efficiency in healthcare processes and in the delivery of care. The practical or technical barriers to the full realization of digitalization and data use by MedTech companies are addressed in this chapter.

Even though nearly two thirds of healthcare leaders acknowledge that the value brought by data in areas such as digital health records, patient monitoring, and medical devices are worth the investment of time and resources, 46% of them view data as more of a burden than an asset [54]. Barriers such as limited technology infrastructure and concerns about privacy and security are amongst the reasons behind that view. In regard to the treatment of data itself, there is usually intense work associated with navigating and gathering patient consent, cleaning data sources, and standardizing data structures and units [55]. Apart from aggregating data from multiple sources (e.g., different hospital electronic systems), companies often have to deal with data use and export regulations for collecting data across multiple regions.

It is worth noting that other non-technical, corporate- or customer-level limitations hamper the development of digital businesses models. At the provider level, staff reluctance or data literacy have been cited as preventing digital solutions from achieving their optimal goals [54], while leadership alignment and understanding how digital innovation can impact the business are some of the main gaps preventing MedTech organizations from becoming more digitally mature [39].

2.4.1. Privacy

Across all industries, the sharing of data amongst stakeholders is at the core of the digitalization process. The information being transferred may be extremely varied, ranging from physical data collected from accelerometers in the automotive industry to an individual's credentials within banking systems. Privacy concerns arise the closer the collected (and shared) data carries information about a particular individual, allowing that information to be traced back to its originator. In healthcare, a vast amount of data that is produced and processed pertains to patient information, be it their health condition (e.g., presence of chronic disease), physiological indicators (e.g., a patient's blood sugar), medical imaging results or even demographic and personal data entered at hospital electronic systems upon a patient's registration (e.g., name, social security number, occupation, etc.)

Generally, privacy is concerned with the collection, storage, and use of personal information, and examines whether data can be collected in the first place, as well as the justifications, if any, under which data collected for one purpose can be used for another purpose [56]. The bioethics principle of nonmaleficence requires safeguarding personal privacy. The disclosure of personally identifiable health information can cause a certain individual to be a target of stigma or discrimination by their social or professional circle. Breaches of privacy may not only affect a person's dignity, but can cause harm in a practical sense. The absence of safeguards to one's privacy may lead to patients withholding relevant information from physicians, resulting in the latter being unable to provide adequate care to the former [56].

The need for privacy in regard to patients' data is thus evident. However, the demand for safeguards in that dimension of patient information invariably makes the collection, sharing and processing of patient data more intricate. The fair information practices endorsed by the Organisation for Economic Co-operation and Development (OECD), include principles to be followed by any entity dealing with personal information. These principles, which are shared by Europe's stringent General Data Protection Regulation (GDPR) [57] and many others, are:

1. **Lawfulness, fairness and transparency** — Processing must be lawful, fair, and transparent to the data subject.
2. **Purpose limitation** — You must process data for the legitimate purposes specified explicitly to the data subject when you collected it.
3. **Data minimization** — You should collect and process only as much data as absolutely necessary for the purposes specified.
4. **Accuracy** — You must keep personal data accurate and up to date.
5. **Storage limitation** — You may only store personally identifying data for as long as necessary for the specified purpose.
6. **Integrity and confidentiality** — Processing must be done in such a way as to ensure appropriate security, integrity, and confidentiality (e.g. by using encryption).
7. **Accountability** — The data controller is responsible for being able to demonstrate compliance with all of these principles.

The US' Health Insurance Portability and Accountability Act of 1996 (HIPAA) echoes these principles and was responsible for the creation of national standards to protect sensitive patient health information from being disclosed without the patient's consent or knowledge [58].

2.4.1.1. Pseudonymization of patient data

Pseudonymization is a method “used to replace the true identities (nominative) of individuals or organizations in databases by pseudo-identities (pseudo-IDs) that cannot be linked directly to their corresponding nominative identities” (Claerhout and De Moor, 2005) [59].

Pseudonymization is often used for health research and analytical purposes as it allows

individuals' identities to remain concealed while associated with pseudo-IDs. These pseudo-IDs are internally linked with patients' personal data across time and place, which allows researchers and analysts to still extract relevant information from a certain patient cohort or group.

Most pseudonymization methods use a trusted third party to perform the pseudonymization process. There is the data source that has access to nominative/protected personal data, the trusted third party, which associated that data to pseudo-IDs, and the entity (e.g., a MedTech company or data register) that analyzes the pseudonymized data or uses it in research.

2.4.2. Cybersecurity

The rapidly evolving technological landscape marked by interconnectivity and the sharing of data has the potential to bring transformational changes to all industries, including the healthcare segment. With great opportunities, however, come great risks. Ill-intended individuals are bound to find ways to exploit emerging technologies and to cause harm to their users, a particularly dangerous thing to happen when working with people's health, as is the case with healthcare. Healthcare is highly valuable to cyber attackers—almost 10 to 20% more than other information, such as credit card data [60]. However, healthcare organizations on average spend less on cybersecurity than other sectors, like financial services. For these reasons, healthcare systems and services have been placed at the epicentre of malicious cyber activities — 60% of ransomware attacks throughout 2021 targeted healthcare facilities or healthcare industry services [61].

Such is the gravity of cybersecurity threats to the healthcare system that regulators have made moves to ensure that stringent safeguards and mitigations are deployed throughout the total product lifecycle for new MedTech solutions. Specific guidance documents from the FDA will be explored in further sections of this dissertation.

Cybersecurity concerns permeate the whole suite of new technologies being implemented in rising MedTech solutions, from 5G and other forms of communication, to cloud computing, software development and deployment, and interface with provider electronic systems. Security areas to cover generally include, but are not limited to [60]:

- **Journey to cloud:** build security from the ground up as healthcare organizations shift to cloud.
- **Ransomware and incident response:** detect, defend against and recover from threats from advanced cyber adversaries.
- **Medical data security and patient privacy:** protect patient and member data and infrastructure across the enterprise.
- **Digital identity:** streamline identity and access management across multiple integrations.
- **Internet of Medical Things (IoMT) security:** secure medical devices by managing risk from pre-procurement to decommissioning.

It is important to note that these areas are not to be addressed by a sole stakeholder, but rather as a collective of healthcare providers, infrastructure providers and MedTech medical device manufacturers.

2.4.2.1. Connectivity Risks

Cyber-attacks targeting communications may directly affect the way a medical device functions, or may be used as a way to steal confidential or clinically-relevant information stored at electronic systems. The following types of attack have been observed in different network types, and may also apply to more modern technologies such as 5G:

- **Signal Jamming** – This can be physical jamming of the physical down- link / uplink control channel, physical broadcast channels, etc., as well as signal degradation. Signal jamming attacks increase latency or interrupt critical use cases, such as in remote surgery robots.
- **MITM attacks** – MITM is a common strategy to intercept data and potentially disseminate malicious commands to connected devices/receivers. For example, a bad actor could send signals that rapidly drain the batteries of critical connected medical devices, potentially causing physical hazards (e.g., during surgical operations or in ambulatory monitoring devices).
- **Mobile Network Mapping (i.e., device fingerprinting)** – Wireless devices connected to a private network can “sniff” identifying data of other devices connected to the network and ascertain potentially sensitive information about those devices (e.g., manufacturer, capabilities, etc.)
- **DDoS** – DDoS attacks are attempts to disrupt normal traffic by overwhelming a network, server, or service with a flood of internet traffic, using compromised computer systems or IoT devices. This is particularly harmful in newer 5G-based solutions, as 5G supports a greater number of connected devices on a high-speed network.
- **Bidding Down** – This attack causes devices to “bid down” to lower-quality network protocols, causing a degradation in the quality of their service, which can significantly disrupt time-sensitive and carefully scheduled operations.
- **Authentication and Key Agreement (AKA) Attack** – An AKA attack exploits a vulnerability in the 5G “Authentication and Key Agreement” security protocol. The attack enables a malicious actor that compromised the long-term key of a user to then impersonate that user to a Serving Network.
- **Dynamic Spectrum Sharing (DSS) Attack** – 5G networks require several physical short-range cell towers and support DDS and “network slicing.” However, an attack on one of these physical devices, or the virtualized infrastructure, may allow a bad actor to jam the network, or access as well as move between network slices.

By securing the equipment providing network connectivity, as well as ensuring the security of the endpoints of communication networks (more specifically in 5G private networks), one reduces the risks of a network-based attack from the moment of deployment.

2.4.3. Data Adequacy

The large volumes of data produced and shared around the healthcare sector carry valuable information that can be used to optimize processes and improve care delivery. AI data analytics tools are able to extract insights from seemingly disparate sources and drive actionable outputs from them. However, for these outputs to be reliable, it is essential to “feed” such analytical tools with complete, unbiased information. Ensuring that data is properly collected from its sources and that irrelevant data is filtered out in the data analysis process is a challenge in the implementation of data-driven solutions.

In a landscape where real world evidence (RWE) is becoming more influential in regulatory decision-making, data must be adequate in terms of its accrual and overall quality. Procedures for data accrual and quality assurance must be put in place during data source design and development stages to optimize the reliability, quality and usefulness of the data. Further information on FDA guidance documents relating to data adequacy can be found in following sections of this dissertation.

2.4.4. Standardization of data

The current technological landscape in healthcare is inherently tied to the large amounts of data being produced from a myriad of sources. Apart from guaranteeing that data is properly collected and that its quality is ensured, one must also consider that multiple data sources are bound to provide data with different formats. In order to extract relevant information from data, thus, one must find ways to standardize the way data points are formatted for them to be processed, compared to one another and analyzed (e.g., by automated data analytics tools).

2.4.4.1. Terminology system: SNOMED CT

SNOMED CT is the world's most comprehensive clinical terminology [62]. It determines the standards for a codified language that represents groups of clinical terms, which allows conditions and procedures to be registered and processed automatically. Without the existence of a standardized terminology, healthcare stakeholders would all speak in their own terms, leading to misalignments and mistakes.

A practical example of the use of SNOMED CT can be found in IVD devices intended to detect influenza A or B infection through the presence of viral antigens in a nasopharyngeal swab [63]. There is a device identifier tied to the IVD device to be used in the examination. Then, there is a LOINC (another terminology standard more closely related to laboratory applications) code associated with the question of whether the nasopharyngeal swab contains influenza A or B antigens. Finally, there is a SNOMED CT code associated with the detection or non-detection of influenza A or B antigens. This SNOMED CT code is then registered, and can be used in epidemiology tracking applications and/or claims documentation sent to an insurer.

2.4.4.2. Health data standard format: HL7's FHIR

The Health Level Seven International (HL7) is a not-for-profit, American National Standards Institute (ANSI)-accredited standards developing organization supported by over 1,600 public and private members that has been releasing standards for the exchange, integration, sharing, and retrieval of electronic health information for the past decades. The Fast Healthcare Interoperability Resources (FHIR) is HL7's latest data exchange standard, being intended to be easier to implement and having backward compatibility with older HL7 standards [64]. By adopting existing standards and technologies already familiar to software developers, FHIR significantly lowers the barriers of entry for new software developers to support healthcare needs. In addition, it provides the following advantages to software developers [65]:

- Unrestricted, free to use.
- Support from major vendors including Apple, Microsoft, Google, Epic, Cerner, and most other EHR vendors.
- Many free, online, and downloadable tools, including reference servers and implementation libraries.
- A multitude of publicly available examples to help kick-start development of new applications.
- A strong foundation in web standards including XML, JSON, HTTP, and OAuth.
- Concise and easily-understood online specifications.
- A human-readable serialization format for ease of use by developers
- A global community to assist implementers.

In 2020, the U.S. Centers for Medicare & Medicaid Services (CMS) issued their *Interoperability and Patient Access final rule*, which requires the use of FHIR by a variety of CMS-regulated payers, including Medicare Advantage organizations, state Medicaid programs, and qualified health plans in the Federally Facilitated Marketplace. More specifically, CMS

established that payers are required to implement FHIR-based APIs to allow patients to easily access their claims and encounter information, as well as a subset of their clinical information through third-party applications [66].

The implementation of FHIR by payers is moving the sector as a whole towards the use of that standard, including providers and the MedTech industry. Emerging businesses such as 1upHealth [67] are working to facilitate the integration of existing systems with FHIR. Through its FHIR Platform, 1upHealth allows digital health MedTech clients to convert a variety of older files from EHRs to FHIR, even offering data analytics tools to extract insights from the data once it has been standardized in FHIR. The company also offers similar solutions to providers and payers.

2.4.5. Infrastructure

2.4.5.1. Cloud

As previously stated, cloud computing significantly offloads companies' necessity for IT infrastructure and reduces the investment needed for maintaining a dedicated IT team. Apart from higher cost efficiency, cloud solutions also allow companies to more quickly launch new services.

There is still, however, some resistance in moving business-critical operations to the cloud, be it in the healthcare sector or in other industries. For many enterprises, approximately 60 percent or more of applications and workloads still remain on-premises, and a majority of which is mission critical in nature [51]. There are many frictions to overcome for cloud migration associated with data stored in legacy systems, such as interface dependencies, system scale and complexity, and lack of technology currency.

According to an Accenture report [52], the number of companies reporting full achievement of expected outcomes in regard to cloud usage has grown from 37% in 2020 to only 42% in 2023, even though cloud investments have significantly increased. Cloud value outcomes were below 50% for even “high cloud adopters”. Barriers for cloud adoption, especially in mission critical domain were shown to be the following [51] [52]:

- **More stringent regulations.** Regulations concerning data sovereignty and security are strict, and often do not provide the necessary guidance for companies to follow.
- **Architectural control.** Business and operational change (e.g., integration of cloud with on-premise systems) are too complex.
- **Operational control.** Companies lose control over infrastructure operations (attributed to the cloud provider) and expose their data to the increased risk of unauthorized access, data theft, and data tampering.
- **Financial control.** Investment in legacy systems is “lost” upon the implementation of an alternative in the form of cloud, for which usage requirements are often not known upfront.
- **Knowledge gap.** Companies lack the necessary cloud skills or are uncertain over where to place workloads (on-premise, public cloud, private cloud, etc.)

2.5. The Biodesign framework

The Stanford Byers Center of for Biodesign – or Stanford Biodesign – is a worldwide reference center for the training of MedTech innovators and a hub of knowledge for the creation of MedTech solutions. With over 20 years of existence, the center has helped launch 56 companies and reached 9.4 million patients through Biodesign-originated products. On the educational side, Stanford Biodesign trains more than 500 fellows, students, faculty, and executives every year in a variety of courses [68]. The book “*Biodesign: The Process of Innovating Medical*

Technologies” by authors Stefanos Zenios, Josh Makower and Paul Yock, first published in 2010, was created to support the Biodesign innovation and fellowship programs at Stanford University, establishing a comprehensive framework – referred to as the Stanford Biodesign framework – for the implementation of new MedTech solutions. The book provides a step-by-step guide on how emerging businesses should approach the three main dimensions of the innovation process: identification, innovation and implementation. It offers a realistic, action-oriented roadmap for the successful innovation in MedTech, building upon the inputs of hundreds of industry leaders and specialists. A second edition, released in 2015, added further resources to the original work in an effort to expand on more recent trends of industry globalization and value-conscious healthcare.

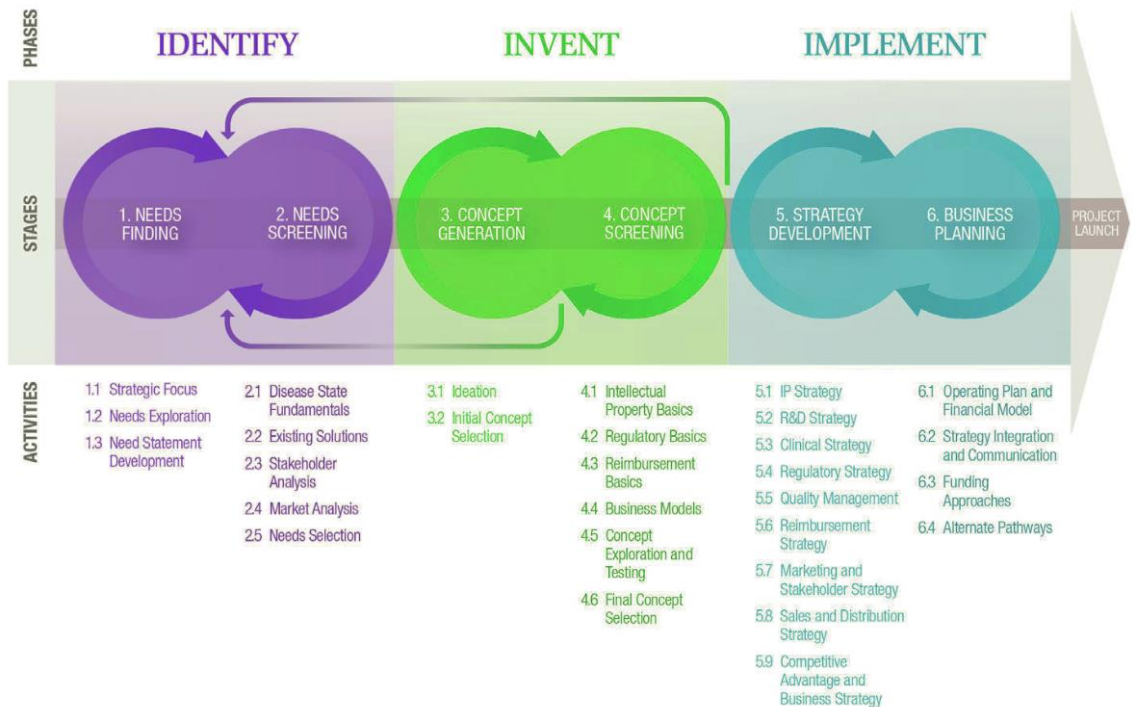


Figure 4. The Biodesign framework. Extracted from “Biodesign - The Process of Innovating Medical Technologies 2nd Edition”.

As previously mentioned, the Stanford Biodesign offers an ever-expanding number of courses and fellowship programs which explore the Biodesign framework and take it to new directions. The Digital Health Course at Stanford University is one such example, which adapts concepts of the original framework to the context of digital technologies within healthcare. Nevertheless, the book by Yock *et al.* is the only widely available piece of literature produced by the Biodesign center that compiles all relevant information about the Biodesign framework in a structured format, serving as an invaluable guide to innovators worldwide regardless of their participation in one of the center’s programs. For those reasons and for the purposes of this work – as explored in the Investigational Methodology chapter – mentions of the “Stanford Biodesign framework”, “Biodesign framework” or “original Biodesign framework” all pertain to what is presented in the latest edition of Zenios, Makower and Yock’s book.

Although the value of the Stanford Biodesign framework is unquestionable, it is evident that with the passing of the years, new developments in technology, economics, politics and market dynamics have raised the need for new guidance in domains not fully explored or even considered in the original framework.

2.5.1. Drivers for change in the Biodesign framework

Fundamental aspects of the Biodesign framework, such as the separation of the innovation process into three big steps (identify, invest and implement) and their respective subdivisions remain as valid as ever, with the purpose of this dissertation being to provide new insights on specific steps that may be relevant to emerging digitally-enable, data-driven MedTech businesses. Technological advancements seen in the incredible rise of software as a medical device (SaMD), AI and data analytics, accompanied by changes in stakeholder relationships in the midst of value-based ecosystems prompt changes and additions to the original framework, as it will be explored in this chapter (see Figure 5).



Figure 5. An overview of the drivers for change in select dimensions of Stanford's Biodesign framework.

2.5.1.1. Intellectual Property

The Biodesign framework presents IP at two distinct moments: first, it focuses on the initial steps required for obtaining a patent, going over the basic concepts of IP; and second, it more intricately describes how to build an effective medical device patent portfolio and associated strategies. The information contained in these two sections is very thorough, including explaining relevant terms, providing guidance on patent search and patent risk assessment, patent filing, patent application timelines, and even on how and when to seek legal advice.

Here, the main addition to the original framework lies in further emphasizing intellectual property considerations for software-based products, as emerging MedTech companies that provide either software or software-enable devices as their main products – a rising trend in the industry – may wonder if the protection given to traditional medical devices also applies to them. The core IP assets of such products go beyond hardware (if applicable), but include things like software, proprietary algorithms and even datasets. The integration of these components adds yet another layer of complexity to a company's IP strategy – often consisting of a combination of patents for hardware and software components, copyrights for software, and

trade secrets for proprietary computational techniques – often requiring the attention of highly specialized attorneys [48].

A horizon of new collaborations within the industry, encompassing both large and small players, should also be taken into account. Joint patents, cross-licensing agreements and co-developed technologies are alternatives to IP strategies based solely on offense or defense that may become more frequent as medical technologies become more and more interconnected and interdependent [48]. In an extreme example within healthcare, the establishment of a Technology Access Pool for the development of vaccines by the World Health Organization allowed biotech and pharmaceutical companies to share their findings in a single space, and for third parties to obtain multiple licenses from that single source through a unique, simplified transaction (patent pool) [69]. Though this is an abnormal event, it shows the feasibility and potential benefits of such deals, which could eventually come to the MedTech industry.

Standard Essential Patents (SEPs) are patents created to cover a technology standard that is essential to the functioning of an industry. These technology standards are selected through an industry-wide decision, and the licensing of that technology must be conceded to users of that standard on Fair, Reasonable and Non-Discriminatory (FRAND) terms. Though amply used in the information and communication technologies industry, SEPs are slowly making their way into other industries where data traffic is concerned, including digital health [70]. MedTech businesses in the fields of telemetry and biometric analysis and diagnostics may be particularly prone to seeing SEPs arise, and should consider the impact of those deals in their IP strategies [71].

2.5.1.2. Regulation

Though many of the original Biodesign framework's considerations regarding the US regulatory landscape are still applicable, especially for more traditional, hardware-focused medical devices, in the past few years US regulators have made efforts to accelerate medical product development and bring new innovations and advances faster and more efficiently to the market, which mainly came in the form of the 2016's 21st Century Cures Act [72]. For medical devices as a whole, new regulation brought advancements in the way real-world evidence may be used to support regulatory decision-making, both in pre- and post-market settings [15]. Patient preference information also seems to be gaining more relevance in helping regulators in the evaluation of the benefit-risk profile of certain devices [73]. Moreover, general Quality System regulation has been updated to better align FDA requirements with that of other standards in an effort to streamline regulatory processes while incentivizing good manufacturing practices [74].

Specifically for software as a medical device (SaMD), regulatory pathways have been substantially changed. These changes have not only impacted the classification of some software functions – including the removal of some of those from the definition of medical device [75] – but also the contents of premarket submissions for device software functions [76]. Initiatives such as the software precertification pilot program point to even deeper changes in the way FDA may process SaMD applications in the future [77].

Other recent US regulations tackled matters adjacent to digitally-enabled devices, such as cybersecurity [78], interconnectivity [79] [80] and data collection [79], with requirements usually spanning the total product life cycle. Further expanding on data use, the EU's General Data Protection Regulation (GDPR), put into effect in 2018, had significant worldwide impact on how patient data should be handled, including in the US. As for regulations on digitally-enabled technology, namely AI, there are many initiatives on the horizon, with EU's Artificial Intelligence Act being the first-ever legal framework to be put in place and with great potential of influencing AI governance and policy-making around the world [81]. Initiatives to guide the use of such tools are, however, already in place [82].

The 21st Century Cures Act

The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, was designed in an effort to keep up with the rapid changes within healthcare, reflected in the way different stakeholders interact with one another and in the popularization of software-based solutions and related technologies. The Cures Act is seen as a major move in the modernization of FDA regulations, and has authorized \$500 million over 9 years to help FDA cover the cost of implementing the law [72].

Patient Preference Information

The FDA has been working on incorporating the perspectives of patient into the development of medical devices in FDA's decision-making process. The FDA acknowledges that patients and care-partners who live with a disease or condition on a daily basis and utilize devices in their care may provide valuable insights into the benefits and risks of devices reviewed under the premarket approval, humanitarian device exemption (HDE), or *de novo* classification pathway. Patient preference information (PPI), such as patient tolerance for risk and perspective on benefit, may be used in conjunction with evidence from clinical and nonclinical testing in FDA's assessment of the benefit-risk profile of certain devices, and may even condition clinical trial design requirements for pre-market approval. Guidance documents have been released to help sponsors understand what constitutes PPI (e.g., its difference compared to patient-reported outcomes (PROs)) and how that information may be considered by the Agency, as well as the recommended qualities for PPI studies [73].

Quality Management System Standardization

As previously stated, the FDA has been working on integrating the different quality system requirements across its jurisdiction and relevant surroundings, so long as substantial similarities are found. Recently, the FDA has issued the Quality Management System Regulation (QMSR) Final Rule, which essentially harmonies the FDA's old quality system framework, CGMP, part of the Quality System (QS) regulation, with that of the international standard specific for medical device quality management systems set by the International Organization for Standardization (ISO), ISO 13485:2016 Medical devices – Quality management systems – Requirements for regulatory purposes [74]. Effective February 2, 2026, manufacturers will be able to cover much of the US regulatory ground by complying with the ISO standard, thereby removing much of the current inefficiency of providing duplicate documentation for complying with both FDA's QS and ISO's 13485 standards.

Real World Evidence

The Cures Act contributes to the FDA's modernization of clinical trial designs through – amongst other factors – the consideration of real-world evidence (RWE) [72].

Examples of real-world data considered by the FDA include EHRs, claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices. The FDA has issued guidance documents on the use of real-world evidence (RWE) to support regulatory decision-making for medical devices [15], which provide an overview of the factors that should be considered for acquiring real-world data in an accurate and reliable manner, and with sufficient clinically relevant time intervals through a device's lifecycle. Under proper conditions, the FDA considers that RWE may be suitable to support the clearance of new devices, or the expansion of the indications of use of devices already on the market.

The Agency has gone as far as compiling a list of practical examples of products that have obtained clearance with the support of RWE in a recent document “Examples of Real-World

Evidence (RWE) Used in Medical Device Regulatory Decisions” to showcase their commitment to the use of RWE in regulatory decision-making [14].

NESTcc

The National Evaluation System for health Technology Coordinating Center (NESTcc), created by the Medical Device Innovation Consortium (MDIC) through FDA funding, aims at engaging public and private initiative in the creation of standards and guidelines to support the use of RWE in regulatory decision-making [16]. In 2019, NESTcc announced the execution of a series of test-cases involving members of its network and external organizations with the objective of determining how to leverage RWE across medical devices’ total product lifecycle (TPLC), including a pioneer prospective research projects utilizing patient-generated health data (PGD) and an active surveillance project. NESTcc Network Collaborators, which include major medical device manufacturers, registries, and patient associations, contributed to the projects by leveraging multiple data sources device registries, electronic health records (EHR), claims, mHealth, PGD, and Patient Reported Outcomes (PROs) [83].

Software as a Medical Device (SaMD)

The 21st Century Cures Act changed the way some software functions may be defined as medical devices [75]. As per the current regulation, the term device does not include software functions intended:

- **For administrative support of a healthcare facility** including the processing and maintenance of financial records, claims or billing information, appointment schedules, business analytics, information about patient populations, admissions, practice and inventory management, analysis of historical claims data to predict future utilization or cost- effectiveness, determination of health benefit eligibility, population health management, and laboratory workflow;
- **For maintaining or encouraging a healthy lifestyle**, so long as it is unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition;
- **To serve as electronic patient records**, such as software functions intended to transfer, store, convert formats, or display electronic patient records that are the equivalent of a paper medical chart;
- **For transferring, storing, converting formats, displaying data and results**, unless such function is intended to interpret or analyze clinical laboratory test or other device data, results, and findings.

In addition to those changes, which have been made public through guidance documents, additional resources specifically clarify which clinical decision support (CDS) software functions have been excluded from the definition of device, and restate the applicability of existing FDA digital health policy to software functions that meet the definition of device [84].

In addition to changes in classification, regulators have made efforts to facilitate premarket submissions for device software functions – that is, device functions that meet the definition of a device (SaMD). Guidance documents have been released with more detailed recommendations on what submissions for SaMD should include, such as demonstrating that risk assessment and testing plans were employed [76]. Additionally, the FDA has made moves to align its terminologies and recommendations with that of more recent software-related consensus standards. In fact, to accompany the rapidly evolving nature of digital health, the FDA has kept close ties with some of the aforementioned consensus standards, which can be found at FDA’s Recognized Consensus Standards Database [85].

The Pre-Cert Pilot program

The FDA has recognized on numerous occasions that its regulations are not optimally suited to the manner in which SaMD and related digital health technologies are designed, validated, and improved over time. The fast cycles of innovation through which these technologies go are hardly accompanied by the current statutory framework, making it difficult for the Agency to provide reasonable assurance of safety and effectiveness in regard to such devices [86].

To explore innovative approaches to the regulatory oversight of medical device software, the FDA launched the Software Precertification (Pre-Cert) Pilot Program (“the pilot”) in July 2017. The pilot enrolled 9 participants with a demonstrated culture of quality and organizational excellence, which were tasked with monitoring and reporting the real-world performance of their (software) products upon market entrance. Throughout the pilot, the FDA assessed, for each participant, the association between the organization’s software design, development, verification, and validation processes and the organization’s general business processes and key performance indicators (KPIs). Upon the completion of the pilot, it was learned that organizational appraisal and ongoing monitoring focused on KPIs – which aimed at demonstrating how processes used for the development and maintenance of medical device software are effective and sustained over time – provided a consistent, holistic view of the organization’s software development processes. The FDA found that this was more informative than a review of the organizational procedures that govern the creation of such data alone, as is the case with current regulatory requirements [86].

The pre-cert pilot points to a future in which companies themselves may be able to prove their operational robustness and efficiency on the development and sustenance of medical software through specific KPIs, thereby greatly streamlining the regulatory process for such devices. Staying in tune with some of the relevant KPIs identified in the pilot may not only be good practice in the current landscape, but actually prove relevant in the years to come.

Data Collection and Interoperability

Data collection from electronic sources may be necessary as a means of providing real-world evidence on the performance of a device to support regulatory decision-making. Data may also be collected from EHRs, medical devices and registries for the purposes of clinical investigation, or may be at the very core of digital health solutions whose outputs are based on AI and data analytics.

The FDA’s current stance on the utilization of real-world data has been explored in “Real World Data”. In that section, it is said that the FDA has issued guidance on how sponsors should evaluate the data they collect according to principles of accuracy, reliability and adequacy. However, the FDA has also been more specific about what measures should be put into place when extracting information from real-world data sources, especially in regard to EHRs [79]. EHRs and other sources of health electronic data have seen the emergence of data standards to facilitate interoperability amongst healthcare stakeholders, a matter to be considered by medical device manufacturers that wish to engage with such sources.

The ONC Health IT Certification Program

The Office of the National Coordinator for Health Information Technology (ONC) Health IT Certification Program (Certification Program) is a voluntary certification program established by the ONC to provide for the certification of health IT. The Certification Program is run as a third-party product conformity assessment scheme for health information technology (health IT) based on the principles of the International Standards Organization (ISO) and International Electrotechnical Commission (IEC) framework [87].

EHRs that adhere to ONC Health IT Certification Program are standardized in their data format (namely, using the FHIR standard), thus facilitating the interoperability of EHRs and electronic data collection systems. Certified EHR technology is also required to meet certain privacy and security requirements. For all of those reasons, the FDA encourages the use of such certified EHR systems as sources of electronic data.

Data and Privacy

It can be a delicate operation to expand the use of data – which is at the basis of digitally-enabled MedTech – while remaining in compliance with privacy regulation. The original Biodesign framework made it a point that patient health information should be approached with caution, with the Health Information Portability and Accountability Act of 1996 (HIPAA) being the main piece of legislation at the time to ensure comprehensive protection of patient health information (PHI) in the US. The framework highlighted HIPAA's more recent Security Rule (effective 2003), which established technical and non-technical safeguards that must be put in place to secure individuals' "electronic protected health information" (e-PHI) [88] [6, p. 77]. Most facilities and providers require that an agent that wishes to access patient data (e.g., a MedTech firm) to become HIPAA certified [89].

A factor not considered in the Biodesign framework with great implications for modern MedTech developers is the emergence of the European General Data Protection Regulation (GDPR). Put into effect May 25, 2018, the regulation has had substantial worldwide impact on privacy matters, going as far as affecting companies operating within the US under HIPAA.

General Data Protection Regulation (EU)

The GDPR is the toughest privacy and security law in the world [57]. GDPR compliance is required for any entity that collects personal data from an EU citizen, be it for clinical studies, clinical trials planning, medical device model training, and other purposes.

With the globalization and digitalization of healthcare, accessing information from all over the world has not only become easy, but also attractive. The European MedTech market is still the second largest in the world [9], and companies, even if US-based, are often interested in extracting insights from the local population. Of course, US companies that do not engage with patient data from the EU do not need to comply with the GDPR.

For US MedTech companies that need to worry about both the GDPR and HIPAA, it is important to note that the former has much broader requirements. While HIPAA deals only with Protected Health Information (PHI) – that is, information that can be used to identify a patient, such as name, address, social security number and insurance information combined with health information – the GDPR sets standards for all sensitive personal data, or personally identifiable information (PII) [90] [91]. This means that all information that can be used to directly or indirectly identify persons, including race, religion, sexual preferences, biometric or genetic data, in addition to any other health-related information, fall under GDPR protection.

Cybersecurity

The regulatory landscape has evolved to account for the technological advancements of the past years. The transition of medical devices towards digitalization required regulators to design new ways of accessing the quality of such devices as to ensure their reliability and safety. It quickly became clear, however, that digitally-enabled medical devices could bring harm to patients due to the actions of ill-intended individuals capable of exploiting the digital infrastructure of devices, be it in causing device malfunctions or in stealing sensitive information.

The FDA has put cybersecurity in the spotlight in the midst of serious cyber-attacks targeting the healthcare sector, with specific cybersecurity requirements being included in premarket

submissions [92]. The Agency has stressed the importance of incorporating cybersecurity safeguards in medical device design, ensuring protection across the total product lifecycle (TPLC). Guidance documents have been issued that go over security objectives for digitally-enabled devices (e.g., devices containing artificial intelligence and machine learning (AI/ML) and cloud-based services), as well as quality controls that should be put in place prior to the premarket submission of these devices [78].

EU-US Cyber Dialogs

Since its inception in 2014, with the first EU-US Cyber Dialog held in Brussels, the US and the EU have been conducting annual meetings to discuss policy-related cyber issues [93].

Throughout the years, the two regions have continued to underline their strong transatlantic partnership on cyber issues and expressed their concern about the increase of malicious cyber activities targeting supply chains, critical infrastructure, and intellectual property, as well as a rise in ransomware attacks against businesses and citizens. Cyber Dialogs have made strides to influence legislation in both the EU and the US in an effort to address cybercrime and ransomware attacks, enhance global cyber resilience, and promote responsible state behavior in cyberspace [94]. In the latest EU-US Cyber Dialog (9th edition), the EU and the US advanced discussions on a Joint CyberSafe Products Action Plan to work in the alignment of parallel cybersecurity labelling programs and regulations for Internet of Things (IoT) within the two regions, namely the EU Cyber Resilience Act and the U.S. Cyber Trust Mark. Future developments should be monitored as they might impact cybersecurity requirements across all industries, including MedTech products.

Artificial Intelligence

An increasing number of countries worldwide are designing and implementing AI governance legislation and policies [95]. In October 2022, the US government addressed potential concerns arising from the widespread use of AI by releasing a Blueprint for an AI Bill of Rights. The document constitutes a series of suggestions for the proper development, use and deployment of AI systems through principles meant to ensure the effectiveness and safety of AI systems, avoid discrimination and bias in the design and training of AI models, safeguard privacy, and promote model explainability [96]. Since then, federal guidelines have also been issued to regulate AI. An Executive Order on Safe, Secure, and Trustworthy Artificial Intelligence signed in October 2023 requires AI systems developers to share their safety test results with the U.S. government if such results show that the AI could pose a risk to national security, and requires that several federal agencies release guidance and develop standards specific to AI safety and security [97].

For what concerns medical devices, the FDA released on March 2024 a paper in which it discusses how its different product Centers, among which is the Center for Devices and Radiological Health (CDRH), are working together to regulate the use of AI in medical products [98]. Amongst the future measures to be taken by the FDA in that regard, the following are particularly relevant for medical device manufacturers:

- Release of final guidance on marketing submission recommendations for predetermined change control plans for AI-enabled device software functions
- Publishing of draft guidance on life cycle management considerations and premarket submission recommendations for AI-enabled device software functions
- Development of a framework and strategy for quality assurance of AI-enabled tools or systems used in the medical product life cycle, emphasizing continued monitoring and mitigation of risks.

EU's Artificial Intelligence Act (AI Act)

On March 2024, the European Parliament passed the Artificial Intelligence Act (AI Act), which constitutes the world's first binding horizontal regulation on AI. The regulation establishes a classification for AI systems with different requirements and obligations tailored on a risk-based approach. AI systems – which refer to a range of software-based technologies using specific techniques and approaches, such as machine learning' logic and knowledge-based systems, and statistical approaches – are classified according to the potential risk they may pose to individuals.

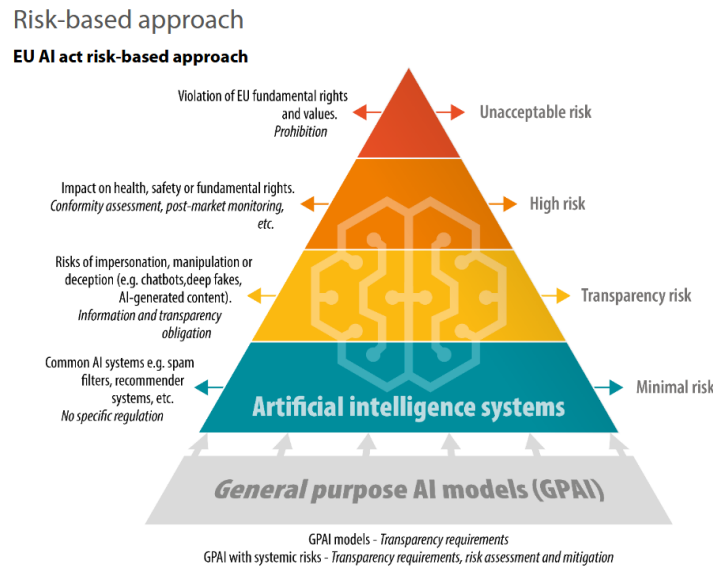


Figure 6. AI Act's risk-based classification of AI.

Prohibited AI systems, which have to be phased out within six months after the act has entered into force, are those that go directly against EU rights and values. High-risk AI systems, on the other hand, are still permitted but must comply with multiple requirements and undergo a conformity assessment prior to release on the market [95]. These systems are also required to be registered in an EU database which shall be set up [95] [99]. Many AI-enabled medical devices may fall into this category, as AI systems in these applications are capable of creating adverse impacts on the health of their users.

The relevance of the AI Act to worldwide policy making remains to be seen, though precedents opened by the 2016 General Data Protection Regulation (GDPR) point to many other countries possibly following in its footsteps [100]. The so-called “Brussels Effect” was evidenced by the role the GDPR took in shaping policies on privacy around the globe, even though it only applied to data collected from European territory. The AI Act brings some of the same characteristics, such as its enforcement over any actor that implements an AI system within the EU, as well as its overarching, rigorous requirements. However, it is important to keep in mind that factors such as the way tech investors will react to the restrictions imposed by the AI Act, and the effort put by China into establishing standards parallel to AI legislation – something yet to be done by the EU – may work against EU’s legislative supremacy over other countries in AI matters [100].

Regulatory Sandboxes

A regulatory sandbox refers to a limited form of regulatory waiver or flexibility for firms, enabling them to test new business models with reduced regulatory requirements. Such mechanisms enable exploration, evaluation and insight into how to properly regulate new, rapidly evolving technology, as current regulatory pathways are often not well suited or even unable to consider all aspects of an innovative product within their established frameworks

[101] [102]. For AI systems, for example, a sandbox could allow for the testing of such systems in real-world conditions outside of a laboratory for a limited period prior to their introduction into the market [95]. It is important to note, however, that although deviating from standard regulatory pathways, sandboxes still employ mechanisms to ensure overall regulatory objectives, including consumer protection. Regulatory sandboxes have been used somewhat extensively in finance, but are also gaining traction in other sectors like health [102] [103].

Real-World Examples of Regulatory Sandboxes in Health

On May 9, 2024, UK's Medicines and Healthcare products Regulatory Agency (MHRA) launched its pilot regulatory sandbox for AI as a Medical Device (AIaMD), AI Airlock [104]. The sandbox will initially support 4-6 projects with aims to identify regulatory challenges to AIaMD and understand and potentially mitigate any risks that may be uncovered. The pilot project will go over a range of medical device regulatory issues, with different sections of healthcare or clinical disciplines and levels of product regulatory maturity [105]. Some of the objectives of AI Airlock revolve around understanding the safety, validation and design implications of:

- Detecting and reporting product performance errors (including drift) and failure modes in post market surveillance data.
- Increased automation and decision-making responsibilities within clinical workflow and producing pre-market evidence of safety.
- Breaking down the complexities of generative AI based medical devices.

Health regulatory sandboxes have also been implemented by Eastern nations to great avail. In 2018, Singapore's Ministry of Health (MOH) established a regulatory sandbox for telemedicine and mobile medicine applications in an effort to understand the risks and develop risk mitigation associated the use of these service delivery models prior to licensing under Singapore's Healthcare Services Act of 2023. The programme, which received industry input throughout its life, was concluded in 2021, having successfully achieved the objectives set out [106].

2.5.1.3. Reimbursement

The Biodesign framework contains a very large portion dedicated to reimbursement, as that topic ties into a company's ability to economically sustain itself in the delivery of medical technology. The framework goes into detail about the fundamentals of reimbursement in the US, including entities involved, particularities of public and private payers and coding. In the case of the latter, the framework goes as far as discussing the modification of existing coding or the creation of new coding for brand new technology for which current coding is inadequate [6, p. 575] – something that remains very relevant in the current technological landscape, where changes are rapid and seldom accompanied by other aspects of the sector, such as reimbursement and regulation. Perhaps most significant to current developments in healthcare, more recent editions of the Biodesign framework account for the cost containment pressure to which the sector is subjected. The Affordable Care Act (ACA) of 2010, which is discussed in the framework's latest edition, brought significant changes to the financial panorama of healthcare, including the creation of the Independent Payment Advisory Board (IPAB), capable of making changes in Medicare payment rates and programs without Congress approval, the establishment of the Patient Centered Outcomes Research Institute (PCORI), meant to evaluate the comparative effectiveness of new innovations, the experimentation of different mechanisms for containing costs through the CMS, and the expanded implementation of provider reward systems linked to cost savings achieved in the delivery of healthcare [6, p. 585].

Possible additions to the Biodesign framework in regard to reimbursement considerations come in the form of further expanding on these value-based notions, such as going over more recent

tendencies of Alternative Payment Methods (APMs) that tie provider payments to quantifiable patient outcome improvements, and other related matters discussed in chapter 2.2 Value-Based Healthcare (VBHC). Real-world evidence (RWE), patient reported outcomes (PROs) and patient preference information (PPI), which have been discussed in chapter 2.2.1, have started to elicit interest from payers in the past few years, through a certain degree of weariness remain over the use of such information in their coverage decision-making due to the lack of standards surrounding those matters. Nevertheless, the aforementioned PCORI funds research that aims to include patients – be it via PROs or PPI – throughout research processes, which is meant to influence payment decisions [107].

As a final note, the Institute for Clinical and Economic Review (ICER) should be highlighted as a relevant player in matters relating to reimbursement. Founded in 2006, ICER is an independent non-profit organization that evaluates the clinical and economic value of prescription drugs, medical tests, and other healthcare innovations. ICER has been gaining increased notoriety in the past few years [108], especially after the release of its Emerging Therapy Assessment and Pricing program in 2015. Through its initiatives, ICER fills a similar role to that of a health technology assessment (HTA) body, a concept widely implemented in European and other developed nations, but that is wholly absent in the US.

2.5.1.4. Business Model and Business Strategy

Important considerations about how a company should establish its own business model are explored in detail by the Biodesign framework. MedTech business models revolving capital equipment, disposables, implantables, fee-per-use and others are discussed according to their strengths and weaknesses, as well as the types of MedTech products commonly associated with them [6, p. 373]. Sales and distribution insights are also given, tying into a company's business model. Going further into a company's business strategy, the framework presents a variety of well-established strategies that have been used to great avail by companies large and small [6, p. 663].

As it was the case with the other themes presented in this chapter, in spite of the thoroughness of the guidance provided by the Biodesign framework in Business Model and Business Strategy matters, that framework could not possibly account for the most recent developments in the MedTech sector. Here, some of the points raised by the Biodesign framework will be further expanded upon, as they have gained more relevance in the current landscape of the industry, while other considerations will be added – namely digital- and SaMD-centered business models and related strategies.

Business Models in the MedTech industry are conditioned by dynamics inherent to the healthcare sector accompanied by the profound changes brought by digitalization. Regarding the former, the mounting need for care and the shortages of care personnel – as well as the inefficiencies of the traditional US healthcare system – have forced budgetary constraints upon providers. MedTech companies have thus come up with monetization models to fight off customer hesitancy [40] [109]. These models include pay-per-procedure or use of the MedTech device or service, leasing, or subscription-based models that put the control of expenditures on the hand of the provider. MedTech suppliers have also offered refunds when specific clinical or economic objectives are not met, or have agreed to reduce price point in exchange for a financial upside when providers achieve a successful outcome using their product. The popularization of such models was further evidenced by a survey by Simon-Kucher, in which 85% of the 60 participating MedTech suppliers reported already having experience experimenting with monetization models [109].

At the intersection of appealing to providers and taking advantage of digital tools lie integrated or so-called end-to-end solutions. Going beyond the product and focusing on offering a holistic

solution to solve clinical and economic needs through a combination of devices, data, hardware and software, MedTech companies have been able to establish long-lasting relationships with consumers. This approach creates a win-win situation whereby a healthcare provider can get immediate value from their investment while the supplier opens up a new revenue stream [109]. Solutions based on this model could leverage real-time connectivity, data analytics, and artificial intelligence to enhance patient care, streamline processes, and optimize outcomes [39]. An example of this all-in-one approach is Thermo Fisher's Instrument Connect, a device-monitoring application that collects and displays information on laboratory equipment [110].

Leaning more into digitalization, digital business models – that is, business models revolving around leveraging technology to deliver new digital products, therapies, or services to engage with patients – are becoming more and more attractive to MedTech businesses [39] [111]. A survey by Deloitte with 100 MedTech executives from across the United States, Europe, and Asia revealed that 46% of leaders put digital health as their most important area of technological focus. When asked about the ways digital technologies could benefit MedTech, over half of the leaders ranked new digitally-enabled “as-a-service” business models among the top biggest opportunities for the sector. Seventy percent of respondents were interested in investing in such models to target new markets and customers, 69% to increase operational margin, and 60% to diversify revenue streams. Software-as-a-service (SaaS) was taken as the most promising of the “as-a-service” business model options, with many MedTech leaders disclosing that they will invest more in software in the next years [39].

In a landscape where software has a central role, usually in the form of SaMD, business models and strategies should account for the particularities of that format. The scalability of software-centric business models through strategies like licensing to providers and industry partners, the lack of reimbursement coding for innovative digital solutions and the introduction of new intermediaries in product deployment (e.g., mobile app platforms like AppStore for mHealth applications), should all be considered in the construction of an updated framework to guide emerging MedTech businesses.

3. Investigational Methodology

3.1. Research Question, Objectives and Methodology

The current landscape of the healthcare sector has brought new challenges and opportunities for MedTech companies in terms of what solutions they can offer. Technological advancements and new stakeholder dynamics pushed by budgetary constraints and the search for value, combined with an unprecedented abundance of medical data being generated in the sector, significantly impacted the way MedTech businesses are expected to operate, warranting guidance on current product expectations, IP, regulation and business models and strategies.

The cornerstone of this dissertation is the Stanford Biodesign framework presented in the 2015 book *“Biodesign: The Process of Innovating Medical Technologies 2nd Edition”* by Yock *et al.* As discussed in chapter 2.5, the Stanford Biodesign framework is at the core of many courses and programs offered by the Stanford Byers Biodesign Center, a center of worldwide renown in the creation of MedTech solutions and the tutoring/training of MedTech innovators. The center has inspired the creation of MedTech innovation courses around the globe – including the Management and Innovation in Bioengineering course at the Faculty of Engineering of the University of Porto, which first introduced me to aspects of the Biodesign framework. The Stanford Biodesign framework has been expanded upon through the many courses and programs provided at Stanford University, as is the case with the Digital Health Course, which explores the framework’s application to digital technologies. Nevertheless, the aforementioned book by Yock *et al.* constitutes the most recent iteration of a structured compilation of the Stanford Biodesign framework made available to innovators worldwide, regardless of their enrollment in programs offered by the Stanford Biodesign center. With the aim of this dissertation being to provide widely accessible guidance to MedTech businesses on how to navigate the current landscape of healthcare, it only made sense to start from the most comprehensive, successful piece of literature on the topic of MedTech innovation – even if slightly dated – and to build upon the framework presented therein.

Alongside a thorough examination of the Biodesign framework presented in the book *“Biodesign: The Process of Innovating Medical Technologies 2nd Edition”*, a preliminary literature review from January 2024 to March 2024 was conducted to identify and understand the newest trends in MedTech with a focus on the use of data, and, relating to that, points of the original framework that warranted a fresh look. Keywords (Biodesign, MedTech Innovation, MedTech Regulation, Data MedTech, Medical Data, Medical Software Regulation, Artificial Intelligence in MedTech, Software Intellectual Property, MedTech Reimbursement, Future of MedTech, Business Strategy MedTech, Business Models MedTech, Cloud in Healthcare, MedTech Industry, MedTech Trade) were used in this research, with sources encompassing journal articles, consultancy firm reports, trade organization reports, governmental webpages and documents, and more.

A qualitative approach followed the literature review to identify and explore best practices of medical technology innovation and use of objective data for MedTech businesses, building on top of the Biodesign framework. Qualitative methods aim to understand a phenomenon through the meanings, experiences, and perspectives of individuals and communities, especially when conventional sources of information are insufficient or partial to support a comprehensive understanding of the context or geography [112]. The aim of this dissertation was to provide an updated framework to support MedTech businesses in their pursuit of innovation and objective data use, tying into the research question of this study:

What aspects of the Stanford Biodesign framework may warrant additions to better support current MedTech businesses?

The methodology aimed to investigate dimensions of the Biodesign framework that were more significantly impacted by changes in the healthcare landscape, and focus on important considerations for current MedTech businesses that wish to deliver innovative solutions, especially through the leveraging of medical data. The interviews document practical experiences and perceptions of involved agents, identifying challenges, success factors, best practices, opportunities, and pointed at useful resources for MedTech business to use and avenues to follow. Based on the interview findings, the study proposed An Updated Framework for MedTech Businesses, providing important considerations and recommendations for the successful implementation of innovative, data-centric businesses in the MedTech industry. The flowchart in Figure 7 depicts the steps and methods followed to achieve the final objective.

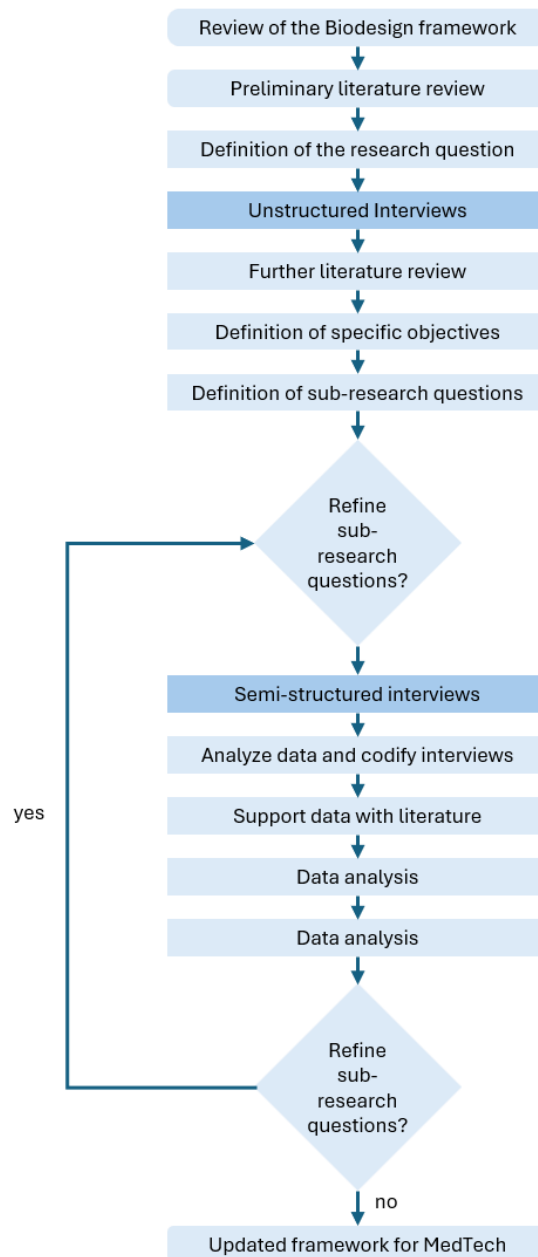


Figure 7. Flowchart of the qualitative exploratory sequential research design.

3.2. Research Design

This study utilized an exploratory sequential design inspired by the works [112] [113], which discuss the establishment of a research question, the choice of a data collection method and its structuring (namely the latter work, which goes into detail about the purposes and features of unstructured and semi-structured interviews), how to compile and codify collected qualitative data, and the importance of comparing emergent concepts (interview outputs, in the case of this dissertation) with the extant literature to draw robust conclusions. As depicted in Figure 7, this study was grounded on a review of the literature and both unstructured and semi-structured interviews to compare and compile agent perspectives and identify best practices for supporting medical technology innovation and objective data use in MedTech businesses. This research design involved two rounds of interviews with professionals involved with the MedTech industry, following a preliminary literature review. Consistent with the mixed method suggested by Yin [113], the first round of interviews served as preparation for the subsequent semi-structured data collection, ensuring the reliability of the research conducted. From the outset, the sample of interviewees was designed to include professionals from different backgrounds that are directly involved with MedTech and that cover different dimensions of the Biodesign framework (e.g., IP and regulatory affairs). The detailed selection criteria is shown in chapter 3.3.

The first phase of the study consisted of unstructured interviews with five professionals from varied fields, covering most themes presented in the original Biodesign framework. These unstructured interviews were open-ended and lacked preconceived notions, conducted with minimal planning [113] to acquire preliminary insights into the topic. These interviews aimed to validate and refine the research objectives, questions, and scope, as well as to identify key challenges, needs, and opportunities related to innovation and the leveraging of data in MedTech businesses.

The second phase involved a review of additional literature and a second round of semi-structured interviews. These semi-structured interviews followed a flexible set of questions to further explore, validate, and gather additional information. This phased approach allowed for the comprehensive collection and analysis of data, ensuring that the research was thorough and grounded in a diverse set of perspectives [112].

3.3. Data Collection

This research employed a four-step process to investigate best practices for medical technology innovation and use of objective data amongst MedTech businesses, using the Biodesign framework as a basis. The first step involved a preliminary literature review to identify key concepts and the theoretical background of the topic, drawing from various sources such as previous research, literature, reports, articles, news, and interviews. In the second step, unstructured interviews were conducted to validate and refine this preliminary review. Five individuals with distinct professional backgrounds were chosen in an attempt to cover most of the dimensions of the Biodesign framework, and to provide insights on current socio-economic and technological trends in MedTech: one member of academia with extensive experience in entrepreneurship and familiarity with the Biodesign framework; one CEO of a highly-innovative, rising MedTech business; one specialist in medical device regulatory affairs and QS; and two clinicians from a major Dutch hospital network, with one being and advisor for the VBHC department, and the other specializing in clinical data science in addition to having previous experience in a major MedTech corporation. These individuals – all based in Europe but with significant experience with US matters – were interviewed to validate the current challenges (what to study), the need to address them (why to study) and the measures implemented to overcome them (how to study).

The third step involved a more comprehensive literature review to refine research objectives and questions, followed by semi-structured interviews to compile recommendations, best practices, lessons learned, and findings. Semi-structured interviews were conducted with professionals either based on the US or with experience applicable to that region, as the US still constitutes the biggest market for medical devices and is the focus of the original Biodesign framework.

The fourth step consisted of further literature review to supplement interview data, ensuring validity and promoting a well-founded discussion of results. This involved a rigorous selection of current articles, reports, news, and press releases (ideally no later than 2019) to provide a timely and informed analysis. Interviews were conducted confidentially and professionally, with participant consent and respect for privacy. Face-to-face meetings were preferred, but written testimonials were accepted when necessary. The interviews, lasting approximately 60 minutes, involved 15 agents. Each agent was chosen based on a main dimension of the Biodesign framework, though their insights sometimes encompassed other areas. Table 1 details the number of interviews per dimension of the Biodesign framework. Triangulation of these sources provided reliability and strengthened the results, ensuring a well-founded discussion [112] [113]. A summary of key lessons learned, recommendations, and best practices from each interview is recapitulated in Annex II.

Table 1. Number of interviews made across relevant dimensions of the Biodesign framework.

Main dimension of focus	Number of interviews
Concept Generation	3
Intellectual Property	3
Regulatory and Quality Assurance	4
Reimbursement	1
Business Models and Strategies	3
General	1

3.4. Data Analysis

Based on the preliminary literature review and unstructured interviews, the dimensions of the Biodesign framework that appeared to warrant the most attention given the current state of the healthcare sector were studied. This analysis refined the specific objectives and questions and identified the professionals/organizations to be interviewed in a second round of semi-structured interviews. Between the two rounds of interviews an evaluation of how the aforementioned dimensions of the Biodesign framework have been affected by technological advancements and socio-economic changes – and by what specific factors – was conducted. The collected data from the interviews were organized and summarized to update and refine the research objectives and questions, as well as to corroborate and support the data analysis with the literature review. It is relevant to note that considerations and recommendations discussed in the interviews that aligned with notions of the original Biodesign framework were considered as impactful as brand new notions, as they corroborate specific aspects of the original framework that remain relevant to innovation in MedTech businesses to this day.

To address the ambiguity, subjectiveness, and breadth of the research question, which spans the past, present, and future, additional research questions were formulated to divide the main topic into subtopics:

- *What factors not accounted for in Stanford's original Biodesign framework are relevant to current MedTech businesses?*
- *What are the current best practices to follow in order to successfully deliver innovation as a MedTech business?*
- *What are the main barriers to digitalization and data use currently faced by MedTech businesses?*
- *How to future proof a framework intended for fast-evolving MedTech businesses?*

A thematic coding approach was employed to analyze the interviews [114]. To ensure the reliability and validity of the qualitative data analysis obtained from the interviews, the MAXQDA 2024 software was utilized. This software facilitated the organization and management of data, coding of themes and concepts, and generation of visualizations to support the analysis. The data analysis was guided by the research questions, with codes and themes derived from them, as illustrated in Figure 8. Given the specificity of some information, sub-codes within codes have been used. For example, under the theme “*General considerations and best practices to ensure success as a MedTech business*”, one may find the code “*Regulatory Affairs*” and its sub-code “*Company Management Involvement*”. The themes, representing the patterns and trends in the data, were used as the titles of sections 4.1. to 4.4. in Results and Discussion to structure the analysis.

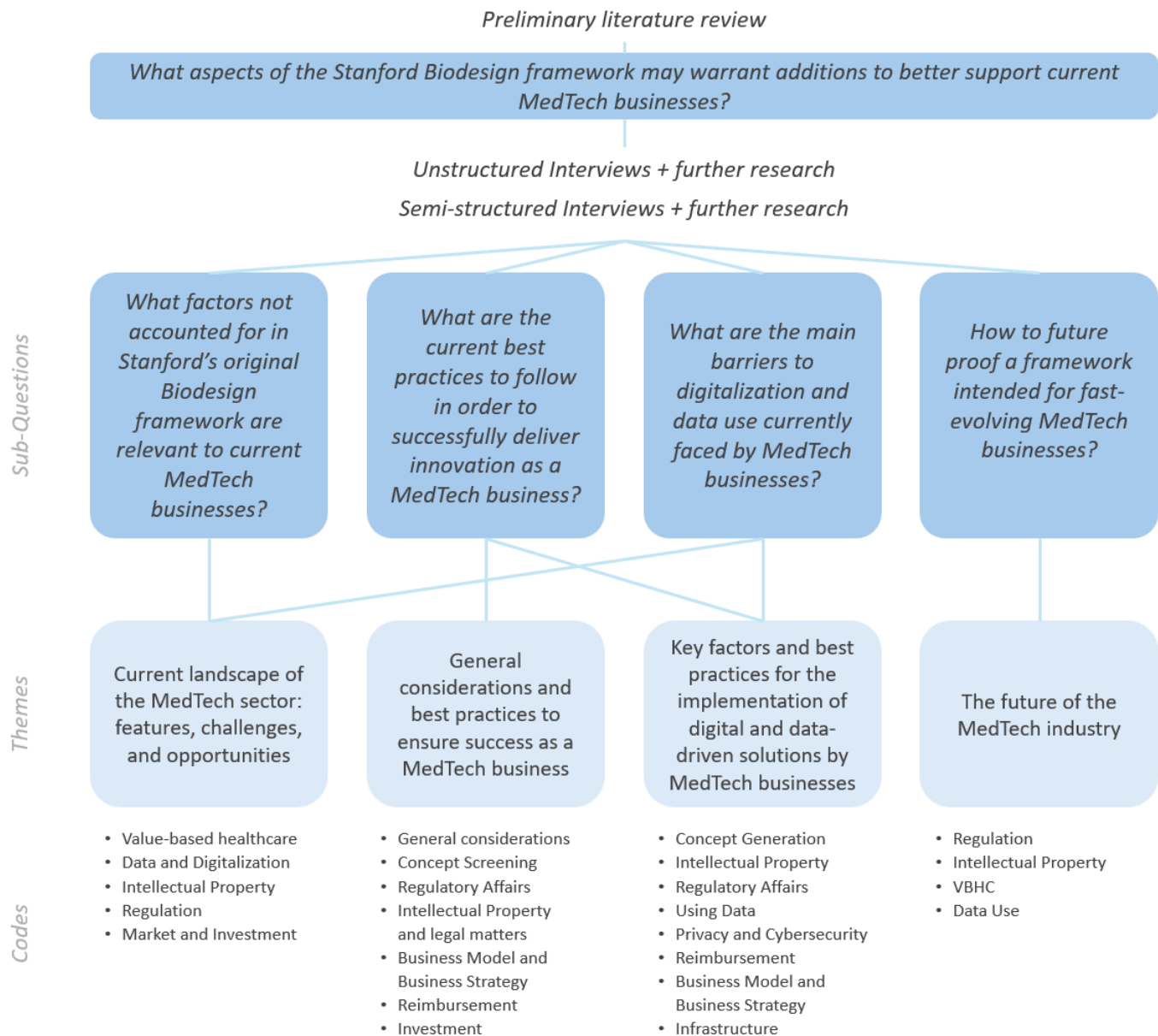


Figure 8. Schematic representation of the methodology to analyze the results and discuss the findings.

4. Results and Discussion

This dissertation aims to identify current challenges and opportunities in MedTech, and to produce an updated MedTech development framework to support businesses in the delivery of innovation and in the leveraging of data. To accomplish this, semi-structured interviews were conducted with 15 professionals hailing from diverse backgrounds including MedTech business professionals, hospital advisors and data analysts, attorneys, payers, regulators, and industry experts. The interviewees were based in different geographical locations between the EU and the US. Most of their inputs were applicable to the two regions, with the majority of interviewees from the EU having experience with US matters in their respective fields of expertise. More information about the choices of interviewees and the structuring and objectives of the interviews can be found in the previous chapter.

This chapter discusses the findings derived from the interviews and the literature review presented in chapter 2, aiming to address the overarching research question: “*What aspects of the Stanford Biodesign framework may warrant additions to better support current MedTech businesses?*” The results validate and often build upon previous recommendations and expositions while also presenting fresh insights and challenging existing notions. Given the complexity of the research question and the diverse array of stakeholders involved, the main research question was broken down into four research objectives. As discussed in Investigational Methodology, each of these research objectives encompasses a series of thematic codes used to classify and segment interview outputs.

This chapter is thus structured to reflect the aforementioned objectives, showcasing insights gleaned from the interviews and reporting the outcomes of the data analysis based on the thematic coding. As will be seen in the next chapter, these insights were combined with the literature review to produce a framework intended to serve as a modern complement to Stanford’s Biodesign framework – providing guidance on current matters only briefly explored or not accounted for in Zenios, Makower and Yock’s original work.

4.1. Current landscape of the MedTech sector: features, challenges, and opportunities

From the thematic coding of interviews, the main features, challenges and opportunities of the current landscape of the MedTech sector were identified. These were distributed between five subjects – Value-based healthcare (VBHC), Data and Digitalization, Intellectual Property, Regulation, and Market and Investment. Table 2 presents these subjects and the insights associated with them.

Table 2. Features, challenges and opportunities of the current MedTech landscape identified by the interviewees.

Current landscape of the MedTech sector	Features, challenges and opportunities reported by the interviewees

Value-based healthcare (VBHC)	- Healthcare providers are under unprecedented budgetary constraints. - Providers have been making efforts to identify products and procedures that lead to the best patient outcomes, leading to cost-effectiveness. Patient- and Clinician-Reported Outcome Measures (PROMs and CROMs), as well as Patient-Reported Experience Measures (PREMs) are very relevant for provider improvement cycles. - VBHC has brought providers and payers together. Both are committed to producing the best patient outcomes, prompting new reimbursement deals based on therapy performance. - VBHC establishes a chain of responsibility: payers set performance expectations for providers, and providers transmit these expectations to MedTech manufacturers. Providers often want proof that a new product is able to improve outcomes in clinical application prior to committing to a full deal. - Real world data (RWD) and evidence (RWE) play a fundamental role in the assessment of therapy and product performance. There is interest in using RWD both primary (within the clinic) and secondary (research) goals.	
Data and Digitalization	Hospitals and healthcare providers	- There is a lack of human resources in the IT area (quantitative and qualitative) of hospitals to carry out complex projects. Hospitals do not have the financial resources to invest in well-qualified specialists. - The in-house development of digital solutions is not a focus for hospitals; they expect such solutions to be presented by the industry. - Hospital data platforms are continuously subject to changes in standards and regulation. - Clinical data has been used for benchmarking the performance of providers and individual therapies, procedures and MedTech products. - Electronic health records (EHRs) gather increasingly more information, and some companies' solutions revolve around the processing of EHRs.
	MedTech industry	- Many aspects of the healthcare sector are unable to accompany the rapid changes brought by digitalization. Regulatory and economic matters around MedTech are based on older interactions, and there is considerable inertia associated with them. - Software products do not reach the market as easily in MedTech as they do in other industries due to specific requirements of the sector, namely regulatory compliance. - Innovation is inherently tied to digital technologies: blockchain, cloud, data analytics and other technologies have created great opportunities for innovation within MedTech. Artificial intelligence is at the forefront of MedTech digitalization. - Major tech companies have been expanding into healthcare, influencing MedTech businesses to pursue digitalization and invest in software. Oftentimes, MedTech digitalization is achieved by leveraging resources from major tech companies (e.g., Amazon's cloud services). - Players usually seen in other industries that are now involved with providing the infrastructure to support MedTech digitalization must be accounted for. These include telecom companies for wireless applications, cloud providers for software deployment, and data and application gathering platforms.

Intellectual Property (IP)	• MedTech currently falls between the Pharma (heavy focus on patent protection) and ICT (different intellectual property rights are combined including patents, copyrights, trademarks, databases and trade secrets to protect the distinct layers of the technological solution) industries when it comes to IP protection, but there has been rising concern towards patent protection. • Technological advancements have not substantially changed the approach to IP conceptually: having an understanding of how one's products add value to their medium guide IP decision-making just like it did before. • For software-based products, there are many well-established IP protection strategies, but there is some complexity involved in the protection of products coupling hardware and software.
Regulation	• The US has become an entry point for many global companies prior to obtaining regulatory approval in Europe due to the stringent nature of the European MDR (especially for lower risk devices). In addition, US regulations on medical affairs are updated much more frequently than they are in the EU. • The separation of sectoral regulation from technology regulation, and the existence of legislation tied to each member-state creates a very complex regulatory environment in the EU. • On a global perspective, regulatory pathways specific to medical devices are generally not well suited for evaluating emerging MedTech solutions. There is need for a more holistic review of such devices. • On a global perspective, regulations on data, artificial intelligence and other matters surrounding digitalization are generally struggling to keep up with changes across all industries, including MedTech. • The “Brussels Effect” points to Europe influencing the creation of future regulations and standards around the world, as was the case with the recent GDPR.
Market and Investment	• Venture capital is one of the drivers for MedTech innovation. As is the case in all industries, the priority given by investors to certain technologies and solutions in MedTech will guide the sector. • MedTech investors expect high returns and have become more demanding, usually asking for “fully baked” solutions before committing to an investment. High percentages may be asked of a company even if they already have somewhat well-established products. • Between the US and Europe, the latter remains considerably more risk-averse. Venture capital is much more abundant in the US.

Interviewee insights were generally aligned with the notions presented in the literature review (chapter 2). Unprecedented budgetary constraints were described as drivers of VBHC in hospitals, as discussed by members of Santeon, a major Dutch network of hospitals that promotes cross-site data sharing and benchmarking of conditions and procedures. The use of RWD and RWE was deemed important in the assessment of therapy and product performance, having value both in primary (clinical) and secondary (investigational) applications [**Dr. Jos Hendrikx, Annex II**]. Within RWD, PROMs were cited by providers as extremely useful tools alongside Patient Reported Experience Measures (PREMs) [**Dr. Lea Dijkman, Annex II**], which had not been previously discussed; as explored in an Accenture report, in a more human-centric healthcare, providers' growth and customer retention is increasingly tied to experience [115]. The choice of PROMs and PREMs to collect were mostly based on the International Consortium for Health Outcomes Measurement (ICHOM). Patient preference information (PPI) was not directly mentioned by interviewees, though PROMs and PREMs were discussed as tools to give patients voice within the clinical setting. Within the topic of VBHC, pay-for-performance deals were mentioned [**Dr. Lea Dijkman, Annex II**], as well as the transmission

of performance expectations from payers to providers, and from providers to MedTech manufacturers [Pedro Costa, Annex II].

In terms of the digitalization of healthcare, interviewees reported a lack of IT resources in hospitals, which look at MedTech manufacturers for solutions [Markus Neuer, Annex II]. The vast majority of interviewees discussed how digitalization and software are being used in MedTech to leverage medical data in the sector. Cloud was seen as fundamental infrastructure for the deployment of digital solutions, and AI was regarded as a field of great potential. Perhaps most importantly, how the industry deals with this new technological paradigm, especially in regard to regulation, was seen as the biggest gap in the suggestions presented by the Biodesign framework, which is otherwise still largely applicable nowadays [João Claro, Annex II].

On that note, multiple interviewees involved with IP and legal matters remarked that new technologies did not substantially change the general approach to IP protection [Iakovina Kindylidi, Annex II][Robert Harrison, Annex II], with that being still tied to the value a solution provides to its medium, be it a tangible product or not, but recognized that the combination of hardware and software and the different modalities of protection can be an intricate matter to address. Interviewees also pointed out the inadequacy of regulatory pathways to account for innovative products in the past years [Marco Rafael, Annex II] [Pedro Costa, Annex II], but acknowledged that regulators have put in place decent measures to make processes clearer [João Ribeiro, Annex II] – especially in the US, which disposes of more frequent updates to its regulation than the EU [Marco Rafael, Annex II]. Further research on the ease of navigating US regulatory pathways *versus* EU regulation points to a paradigm shift where smaller companies are now turning their attention towards the US [116].

Finally, interviewees brought new insights into investor behavior. MedTech investors were generally described as having become more demanding in the last years, giving more attention to solutions that have been validated by regulators and the market. The US was pointed out as still being the best place to obtain funding from VCs, with European investors being considerably more risk-averse [Jeffery Ryan, Annex II]. Those insights were confirmed by further research, as evidenced in a 2021 study by Deloitte and AdvaMed [4].

4.2. General considerations and best practices to ensure success as a MedTech business

For establishing practical guidelines to support innovative MedTech businesses, it is crucial to evaluate some of the best practices and important considerations for companies across the whole industry, regardless of the type of product they wish to explore. These more broadly applicable directions, collected from the literature and the interviews (see Table 3), contemplate many of the dimensions of the MedTech sector explored in the last section.

Table 3. Relevant topics, considerations and best practices to generally support innovation in MedTech according to interviewees.

Relevant Topics	General considerations and best practices for MedTech businesses
General considerations	Companies must set proper expectations across all dimensions of their business, especially when it comes to resource expenditure. Lack of planning is likely to result in there not being enough resources to support relevant dimensions (e.g., hiring an IP specialist, conducting clinical trials, growing the team) and cause the business to fail.

Concept Screening	• Market studies should be performed right in the beginning of a company's journey when the product is first conceptualized. Actively engaging with stakeholders (e.g., through interviews, surveys) may help a company assess how their solution is to be used and how receptive stakeholders are to the new product in the company's region(s) of interest. • Conducting a large, structured market study may be expensive, depending on the number of people targeted by it. The company may rely on a third party to conduct a proper study.	
Regulatory Affairs	Company Management Involvement	• Knowledge of regulations and relevant standards must be within the company. When building a MedTech company from the ground up, the managing team should read and inform themselves about regulatory requirements, including requirements for consensus standard. • Being involved in regulatory affairs will help company management to avoid mistakes down the line and give them agility in dealing with issues that may arise, saving resources. It will also help the company implement consensus best practices from the start, leaving them in good standing with regulators and even investors. • External consultants are an option, especially as the company gets larger, but these are not as committed to the company's vision as its employees are. Internal teams may learn from consultants and come up with more valuable insights.
	Quality Assurance and Control	• Implementing quality control systems is not particularly complicated. • Adopting a Security-by-Design approach to product development alleviates conformity concerns down the line, and helps to achieve the desired device classification. • The use of Corrective and Preventive Action (CAPA) processes presents a way to more deeply address issues with a company's operations. • A complaint management system allows a company to readily identify problems in the post-market setting. Keeping close post-market surveillance is a must. • The use of harmonized standards helps identify risks and force companies to have a clear notion of their product's intended use, must-haves associated with its use, and non-essential components. There is a variety of international standards relating to usability, electronic componentry, shipping, and more that are also backed by the FDA. • A company may consider creating a multi-layered technical file for its products as a way of summarizing their features and standards associated with their development.
	Cybersecurity and Privacy	• Any device that connects to a healthcare provider's system must follow extensive steps to ensure cybersecurity. • Cybersecurity standards are being used more often, which help with regulatory compliance.

	Strategic Approach to FDA classification	- FDA's 510(k) process can be very burdensome in the way a company has to prove that its device relates to existing technology in the market. - De Novo classification can take a lot of work, but is generally more transparent than 510(k). - A De Novo classification can be used as a defensive tactic against competition. Since there is no predicate for a new technology, a De Novo sponsor may define special requirements for the use of a new technology, which might deter other companies from pursuing applications for similar technology under 510(k).
	Use of RWD to support regulation	- Up until recently, the FDA did not seem to put a lot of weight into RWD for regulatory decisions. - Sponsors for De Novo devices could justify the use of RWD as there is no predicate.
	Technological resources to facilitate regulatory affairs	- Digital Quality Management tools for handling complaints and keeping QS design up-to-date. - FDA digital interface: sponsors can already submit documents and accompany ongoing processes, and a portal for filling applications has recently been launched.
Intellectual Property and legal matters	General legal strategy	- Having big clients and working on highly regulated industries require both technical and legal know-how. - Oftentimes it is the commercial team that deals with legal matters, causing legal affairs to drag for much longer. - Investing in a lawyer right in the beginning for the creation of internal policy, term sheet and licensing agreement templates is very valuable, as it streamlines future operations. A lawyer/legal team may also contribute to the legal literacy of company employees through workshops or similar measures. - Legal compliance leads to operational benefits and may increase a company's value in an acquisition deal.
	IP professional support	- Patent attorneys should be involved right from the get-go; counseling may help assess freedom to operate and even prevent inventors from disclosing their invention. - A patent attorney should work with a company's management to define an IP strategy. An attorney that works with limited knowledge about the company's business model and technology will only be able to offer limited contribution. - Patent managers are lower-cost alternatives for counseling, though they are not legal professionals. - There are highly specialized legal professionals in the market, and choosing one that is aligned with the company's technology is a priority.
	Company Management Involvement	- For newer companies, it is important that the company management does their job in looking for threats to the IP they wish to develop. - Legal counsel becomes essential as a company grows. An internal attorney could work as a manager for legal affairs across the company.

	Trade secrets and confidentiality	• Some trade secrets are born from companies not wanting to put the effort into a patent application process. • MedTech expositive regulatory requirements work against trade secrets. • Trade secrets are endangered by partnerships with other companies, which increase the chances of information breaches. • It is essential to implement measures to ensure confidentiality within the company: NDAs, access restriction and labelling of documents.
	IP strategies	• Companies must define an IP strategy from the start. • Smaller companies usually have two levels of protection: one for its core business, and one for complimentary activities/tools. • Companies should invest in a scope of protection. Divisional patent applications (US and EU) help safeguard business models through spin-offs from the main patent. • If a company has the resources, they should protect alternatives to their main business model. • Having a firm understanding of the company's place in the value chain and protecting that will reduce the possibility of turning to alternative models in the future. • Continuing patent applications (US) play a big role in expanding patent claims and context for initial, central patents. They offer a good way of reflecting changes in a company's priorities. • Companies that wish to be acquired need to their patents as valuable as possible: that means investing in a wide scope of protection and cutting off licensing deals.
Business Model and Business Strategy	Popular strategies for MedTech businesses	• Licensing has been gaining popularity. It allows companies to capitalize on patents for which they spent substantial resources. • Most companies make licensing deals with a small number of companies, as it is hard to administer deals for many licensees. Doing so may require a dedicated team. • Pay-per-procedure and pay-for-performance models are becoming more common, contributing to cost reductions and improved outcomes for providers.
	Practical example	• The Crawl, Walk, Run approach: business model for a surgical robot. It allows companies to address gaps in their portfolio without having to invest internally into such a tool. • During Crawl, the company co-designs features for its based product with prospective partners; during Walk, prospective partners are able to test the device, paying a periodic fee that they can drop at any time; during Run, the partnership is solidified through a licensing deal.
Reimbursement	General considerations	• The MedPAC Payment Basics series are a digital resource for understanding Medicare's payment system. • The CMS relies solely on its internal team and assessments from the FDA to evaluate health technology. ICER has gained ground as a pseudo-HTA body in the US, but its assessments are more relevant to the Pharma and Biotech industries.

	Reimbursement strategy	- Companies should be strategically aware of reimbursement from the first conceptualizations of a product. - Market studies may be used to assess whether reimbursement is likely in a given region considering how stakeholders reacted to the product's concept.
Investment		- Venture Capital is still the best way for a company to get funding in the early beginning. - Companies must look for a strategic fit when dealing with VCs. This process must be exhaustive. - Though most VCs may have experience due to multiple investors, they rarely have the in-depth knowledge of the MedTech panorama and its technologies.

Interviewee outputs on general best practices to support innovation covered a myriad of areas, with most considerations revolving around regulatory and IP and legal matters. “Setting proper expectations early” on was discussed as an advice for businesses as a whole, as that will help define a company’s business model, IP and legal strategy [Franz Möltgen, Annex II][Iakovina Kindylidi, Annex II][Robert Harrison, Annex II], reimbursement considerations, and approach to investors [Jeffery Ryan, Annex II].

On regulatory matters, interviewees from the industry highlighted the use of international quality system and cybersecurity standards to streamline regulatory processes. To further support compliance, interviewees mentioned the use of software to monitor QS activities [Anonymous, Annex II], as well as other digital assets that help with operations. Interviewees also mentioned the important role of the company’s management in having a good understanding of regulatory requirements, especially at the early stages of business, as a way of ensuring good compliance measures are implemented. Somewhat contrary to what is presented in the literature, an interviewee reported that the FDA did not give proper consideration to the RWE they used in support of their application, though they acknowledged that the FDA’s stand on the matter could have changed in the past years, especially for De Novo applications [Jeffery Ryan, Annex II]. These types of application were given especial strategic relevance, as sponsors of a new technology under a De Novo application may set the requirements – including the use of RWE – for all future sponsors of similar technologies.

Defining an IP strategy at the early stages of a business was seen as extremely important for multiple interviewees. They defend the alignment of legal and IP strategies with a company’s business model, as well as more involvement of the company’s management with the former. Pursuing a patent scope was presented as a particularly effective strategy for companies that wish to protect around their business model, and for companies that want to increase their attractiveness for acquisitions [Franz Möltgen, Annex II]. Patent scope may be an old strategy as presented by the literature [117], but have remained relevant as new technologies increase the competitiveness of the market.

When discussing business strategies, interviewees from the industry addressed the rise of pay-for-performance deals and provided examples on how to establish value relationships with providers through measures of co-creation and testing of products alongside potential customers [Pedro Costa, Annex II], similarly to what is presented in chapters 2.2.2 and 2.5.1.4.

The use of a market study by companies in the earliest stages of concept generation were presented as an important way of ascertaining customer acceptance, intended use of the solution, and potential reimbursement avenues [Jeffery Ryan, Annex II]. Though not directly mentioned, similar studies directed to patient preference may be applied throughout a product’s life cycle to support product conceptualization, clinical trial design, regulatory labelling, and

reimbursement decisions [34]. Market and patient preference studies may be hard to implement, with companies usually resorting to external services. In terms of investment, interviewees cautioned MedTech businesses to only deal with VCs aligned with their business strategy, and to beware of investors without proper knowledge of MedTech.

4.3. Key factors and best practices for the implementation of digital and data-driven solutions by MedTech businesses

As stated in previous chapters, the framework presented in this dissertation intends to build upon a pre-established Biodesign framework through the inclusion of current matters that permeate innovation and the use of data in the MedTech industry. Therefore, in addition to the more general considerations and suggestions presented in section 4.2., this section aims to explore recommendations and facts specifically relevant to the implementation of digital and data-driven MedTech solutions. The literature and interview outputs shown in Table 4 highlight important factors to MedTech businesses aiming to leverage the abundance of data in the sector.

Table 4. Relevant topics, considerations and best practices to support digital and data-driven MedTech according to interviewees.

Relevant Topics	Considerations and best practices for digital and data-driven MedTech businesses	
Concept Generation		• Prior to looking for a new solution, it may be more intelligent to analyze data and find ways to optimize the cycle of care by removing unnecessary steps. • Requiring providers to actively collect large volumes of data to use it as input for a solution will result in low adherence. • Solutions meant for providers to use and that interact with the provider's electronic system must ensure seamless integration. Accessing external resources may be cumbersome for providers. • Hospitals are interested in solutions that are compatible and integrated with their hospital information system, as that allows patient data to be optimally used. • Solutions for patient monitorization and condition tracking are desired. Monitoring medical devices require a great volume of data. • A bottom-up approach to the introduction of a new solution within a hospital leads to better acceptance from providers. • Solutions should be able to explain how and from what sources they collect data, and their methods for extracting insights from that data must be validated by competent regulators. • Solutions leveraging data should produce actionable outputs for providers.
Intellectual Property	General considerations	• For companies coupling complex software and hardware tools, it may be hard to find specialized IP support in a single professional. • Within a company, a patent attorney will be closer to the CTO than to the legal department due to the technical knowledge required.

	Software protection	• Software is easily patentable in the US, but has to be coupled with hardware to be patentable in the EU. • Software copyright is the most common form of software protection. It safeguards the source code, but does not prevent the creation of new software with similar functions. Software copyright is automatic upon creation in the EU, while in the US, copyright needs to be registered, and ownership of copyright can be transferred. • A copyrighted software may rely on licensing agreements or be open source. The source code of a software may also be kept as a trade secret. • APIs are eligible for copyright protection in the US, but not in the EU. Fundamental APIs (e.g., Java SE APIs) can be freely used in the development of digital solutions in the US through “fair use” provisions.
Regulatory Affairs	Quality Assurance for software products	• Software adds another layer to regulatory requirements for medical devices. A company should implement software quality controls from the beginning to rapidly identify and correct errors in the development of code. • Quality standards specific to software, namely Software Lifecycle Management, are not hard to follow. There is a problem with the mindset of software developers in the implementation of Quality Assurance measures. • Larger standards for MD development include Quality systems for SaMD. • The MDR and FDA offers good guidance on how to ensure the safety of SaMD.
	Building on top of existing solutions	• It is very common to introduce a product in the market with a basic functionality that can easily be approved from a regulatory standpoint. • A device already in the market may collect data beyond its functionality to support new features. • A product that wishes to add new functionalities must undergo another regulatory process, but that process is much more streamlined. • Data collected from an approved device can be used to support the approval of an unrelated device through RWD.
Using Data	General considerations	• It is of utmost importance to understand which are the different entities handling patient data. • Companies working with patient data should ask themselves questions of what patient data is being accessed, what will be done with that data, and whether the company is able to remove that data from its possession. • Patient consent is extremely relevant when dealing with patient data.
	Data sources	• Companies should have a good notion of its sources of data from the beginning. • Registries are an important source of data for both pre- and post-market studies. • For ML/AI applications, retrospective real-world data is required for training models. Training data for ML-based

		devices may come from public databases, directly from hospitals, or medical devices.
	Data Accrual and Adequacy	• Data is needed for training, testing and validating AI. • Depending on the application of the technology, varying amounts of data may be needed. Only the strictly necessary patient data must be used and shared. • Data must be as complete and as close to unbiased as possible. Demographic and peripheral data should be collected alongside main data to prove variability. • The data used to support the approval of a product must be adequate for the intended application of that product.
	Interoperability, Data Format and Standardization	• There is an overall lack of compatibility between hospital electronic systems. There are a handful of big companies which dominate the market for hospital systems. • Well established MDs from major companies sometimes produce data with unique formats as a strategy to keep customers tied to their devices/systems. • SNOMED CT is the most widely used terminology standard in hospitals and clinics. There is usually concept mapping from EHR to SNOMED CT for reimbursement claims. • FHIR is the most widely used data standard in healthcare. Providers are required to use FHIR in the US. FHIR allows for the standardization of EHR information and benefits data analytics.
	Data Governance	• Responsible personnel for each phase of data collection, processing and sharing need to be defined. • When multiple stakeholders are involved in the processing of data, looking at the different health information system communication protocols may help find sources of risk and error.
Privacy and Cybersecurity	• Data security is one of the biggest hurdles to collecting and analyzing medical data; there are extensive regulations relating to privacy that go beyond medical information. • Any kind of product that stores sensitive information must, by regulatory authority, have cybersecurity measures. • There are groups of organizations devoted to sharing concerns and occurrences in cybersecurity. Partaking in such groups signals to regulators that a company is committed to addressing cybersecurity issues.	
Reimbursement (US)	• The process of creating a new reimbursement code for a new solution is long and burdensome. • The CMS is experienced with SiMD, but standalone SaMD coverage is harder to justify due to their lack of “tangibility”. • In the inpatient setting, coverage of procedures generally do not discriminate against SaMD used in procedure optimization, so long as there is proof of its benefits. In the inpatient setting, SaMD may be considered for New Technology Add-on Payment (NTAP) coverage. If the technology becomes the standard of care in a procedure, then existing codes may be changed to accommodate it. • In the outpatient setting, coverage is often requested by the device’s manufacturer. Some are interested in standalone coverage for their SaMD, while others want it to be included in a bundle within procedure in which it is used. In the outpatient setting, SaMD and digital MedTech solutions usually	

	qualify for the New Technology Ambulatory Payment Classification, meant for products for which there is no precedent. • Documents have been issued by the CMS that summarize the most recent coverage decisions in both inpatient and outpatient settings. • On a global perspective, apart from regulatory requirements, payers may require that a certain solution be applicable to their population of interest (e.g., an American insurer choosing not to reimburse a software tool that was not trained with sufficient American patient data).
Business Model and Business Strategy	• Strategy-wise, providers must be convinced of the value of digital solutions, as they often have no defined digital strategies. Communicating and co-developing with end-users (e.g., clinicians) is key to the delivery of digital solutions to providers, as that will increase acceptance. • Licensing of SaMD is becoming increasingly more popular. • Licensing deals can be made with hospital and clinics, individual physicians, or partner companies that wish to integrate the solution into their own. Choosing to deal with one or all of these stakeholders depends on the company's vision for their product. • One advantage of licensing SaMD to intermediary companies is taking advantage of their sales force. • A fully digital business model based on licensing is very scalable. As new deals are struck, the company only basically needs to expand its cloud capabilities for the deployment of their software.
Infrastructure	• Clouds are absolutely necessary for the implementation of digital solutions. They are used for storage and transmission of data, as well as the deployment of software and updates. • External (public) clouds are almost unparalleled in the compliance of their services with requirements of particular industries, including MedTech. Public clouds usually provide ready-to-use functionalities that may streamline operations for newer businesses and reduce the need for local IT-infrastructure. • Private clouds require investment in IT-infrastructure but provides the company with the most control over which agents access the cloud and how. • SaMD may be deployed for desktop or mobile either as a downloadable app or through the web. For mobile apps, companies will have to conform to mobile platform (e.g., AppStore) requirements

When discussing the factors that must be considered in the conceptualization and delivery of data-driven, digitally-enabled MedTech solutions, interviewees highlighted the importance of creating appealing solutions to healthcare professionals **[Dr. Lea Dijkman, Annex II] [Dr. Jos Hendriks, Annex II] [Markus Neuer, Annex II]**. They talked about how the implementation of data collection systems in their hospital only worked on a bottom-up approach, where physicians were educated and made aware of the benefits of the solution, and also presented interoperability and the use of reliable data sources as major factors for establishing convenience and trust, respectively. Focusing on the improvement of current inefficient processes was also brought up as a priority. All these aspects tie into the creation of value partnerships between MedTech businesses and providers shown in “Consulting services in support of product delivery” – based on the education of MedTech users – and into the offer enhancements presented in chapter 2.5.1.4, where MedTech businesses make extra effort to facilitate the integration of their products into provider systems.

Interviewees from the industry pointed out more technical aspects to the implementation of data-driven solutions, including advising that companies define their expected data sources and formats from the beginning, and devising a strategy for standardizing said data **[João Ribeiro,**

Annex II]. According to interviewees, data used to train ML-based MedTech solutions should reflect demographic variations, and may be obtained from a variety of sources [**Célia Cruz, Annex II**]. They also addressed necessary infrastructure to support digital solutions, including the particularities of cloud and access to mobile platforms.

In terms of regulation centered around data use and digital MedTech products, interviewees once again mentioned the existence of standards that help ensure conformity, with some also relaying that FDA guidance documents has proven useful [**João Ribeiro, Annex II**] (chapter 2.5.1.2 discusses some of them). Cybersecurity and privacy concerns were brought up as major challenges for the use of medical data. In addition to complying with regulatory requirements, interviewees suggesting partaking in cybersecurity groups to strengthen their understanding of cyberthreats and show diligent work on that matter.

As for IP, choosing a specialized IP professional was deemed necessary, confirming what was presented in chapter 2.5.1.1. Interviewees presented copyright as the most common way of protecting software-based MedTech (including APIs), and raised concerns about confidentiality and the use of trade secrets [**Robert Harrison, Annex II**]. Patenting was also discussed in the protection of software, with interviewees stating that software must be coupled with hardware to be granted protection in the EU [**Franz Möltgen, Annex II**]. Further research on the matter revealed that an European software patent claim must contain at least one technical feature, and only the technical features are evaluated for the “inventive step” part of a claim [118]. Framing the software into a method claim, the inclusion of “computer-implemented method” wording in generally enough – in this case, the method (software) necessarily makes use of a computer (which is a technical thing) and thus the method is patent-eligible. Determining if a software-based functionality is “technical” – especially when not involving an effect on hardware, as is the case with many SaMD – is not clear cut, however, and professional counsel is advised [118] [119]. In terms of choosing avenues of protection for software – patenting, copyright, or both – further research points to copyright being indeed prominent, as the process for obtaining patents is usually slow and costly [120]. Nevertheless, a digital technology related to a considerably unconventional and inventive (i.e., novel and non-obvious) transformation or system may benefit from a patent, as the idea/functionality behind it will be protected, as opposed to copyright [120] [121] [122].

Moreover, upon discussing the commercialization of software, the subject of open-source software was brought up [**Iakovina Kindylidi, Annex II**]. Research on the topic revealed that though open-source software (OSS) can be freely used and modified, there are still license requirements in place to control their commercialization, or the profiting over modified versions of the software [123]. That raised concerns about a company’s ability to commercialize software that has OSS components in it. Strong copy-left licenses are of particular interest in this matter, as if an OSS component under strong copyleft is included in a composed work with other software components, these other components should also be distributed under the same or compatible strong copyleft license with full access to their source code [124] [125].

Reimbursement considerations for innovative solutions came mostly from CMS [**Susan Janeczko, Annex II**], which pointed at the most relevant documentation for MedTech companies to keep in mind. The CMS also discussed how coverage is usually harder to justify for standalone medical software (i.e., SaMD), as there is no tangible product, but provided sources for consulting examples on SaMD reimbursement decisions. Industry interviewees pointed out that for newer solutions, new reimbursement codes often need to be required in a long, burdensome process [**Pedro Costa, Annex II**] [**João Ribeiro, Annex II**].

Finally, interviewees pointed to the licensing of SaMD as being a popular [**Franz Möltgen, Annex II**] [**Robert Harrison, Annex II**], scalable strategy for MedTech businesses [**João**

Ribeiro, Annex II]. According to them and to insights from the previous section, such strategy would only require investments in better cloud infrastructure and potentially personnel to manage the licensing agreements.

4.4. The future of the MedTech sector

Some of the interviewees' inputs regarding the dimensions explored in the previous sections related not to the current state of things within the MedTech industry, but short- and long-term expectations they had. Interviews revealed emerging trends in regulation and intellectual property, and discussed the next steps in achieving interconnected, value-based healthcare.

In matters of regulation, interviewees restated that different sectors of healthcare – such as biotech, pharma, MedTech – are well covered by legislation if considered in isolation. *“The problem arises at the interplay of sectors”* [Marco Rafel, Annex II], when a product encompasses many different technologies, including some that have only recently entered healthcare (e.g., a drug-delivery solution with medical device hardware and AI-enabled controlling software). These products must comply with many different regulations that have conflicting timeframes and standards, or that have similar but distinct requirements, leading to “duplicate” efforts. Products are changing in such a way that soon there will not be a regulatory basis to support innovation: *“as a policy maker, I could tell you that today, there isn't a product that won't be able to reach the market due to regulatory barriers – though I'm not saying the process will be easy. However, I'm not sure I'll be able to say the same in 5 to 10 years from now”* [Marco Rafel, Annex II]. Regulatory sandboxes, as seen in chapter 2.5.1.2, were presented as a potential response to that dilemma by offering complementary regulatory pathways meant to cover exceptions. Interviewees mentioned how EU's AI Act (also in chapter 2.5.1.2) requires member states to implement sandboxes for the testing of AI across all industries, with countries like Germany and Spain soon expected to open applications for companies [Iakovina Kindylidi, Annex II]. Priority will be given to SMEs and Start-ups, as well as companies operating in critical industries, such as healthcare. Whether EU's example will be followed by the rest of the world remains to be seen.

Within intellectual property, the emergence of standard essential patents (SEPs) was discussed by the interviewees. As discussed in chapter 2.5.1.2, SEPs ensure that indispensable technology within an industry can be used by all companies of the medium through fair licensing agreements set by industry players themselves. Interviewees acknowledged that though SEPs are still rare outside of ICT, they are gaining ground in other industries [Franz Möltgen, Annex II] [Robert Harrison, Annex II]. MedTech companies usually do not need to worry about SEPs, as they purchase communication/interface modules rather than create them – however, as MedTech solutions become more intricate, SEPs could become a near reality for connected MedTech segments [Franz Möltgen, Annex II]. MedTech patent pools were disregarded by the interviewees, though cross-licensing was mentioned as a somewhat common practice across industries that could be considered in MedTech.

A very long-term scenario where medical records could be pulled from many healthcare organizations to provide a thorough picture of a patient's state was discussed in the interviews. Such interconnectivity could be achieved through the widespread use of the FHIR data standards, but there are still many roadblocks in the way, with strict requirements on data security being one of their main staples: *“the Dutch had the option to create a unified EMR in the past – around 10 years ago – but decided against it due to privacy concerns”* [Dr. Jos Hendriks, Annex II]. Value-based strategies and the use of PROMs were also discussed in the short- to medium-term. Interviewees stated that they wish to see increased patient and clinician involvement in the collection of PROMs in order to extract more actionable insights, as well as expand VBHC initiatives across a larger portion of the industry to fully realize their potential –

“I am an epidemiologist. I find it difficult to settle with the current results as absolute proof. We need more data from more sources to quantitatively determine how better we are performing under the VBHC framework.” [Dr. Lea Dijksman, Annex II].

5. An Updated Framework for MedTech Businesses

As previously stated, the framework presented in this dissertation intends to build upon the Stanford Biodesign framework, initially developed by Zenios, Makower and Yock [6]. The Stanford Biodesign framework stands out for its innovative and needs-driven approach, and has proven its practical clinical significance across various medical fields including cardiology, gastroenterology, nephrology, pediatrics, and radiology [5]. Utilizing this framework, medical products have the potential to enhance healthcare delivery, leading to saved lives, reduced medical complications, and better patient well-being. Through its needs-centric approach, the Biodesign framework has guided healthcare innovators in the successful adoption of the ‘Identify, Invent and Implement’ framework and in developing new healthcare innovations products to address patients’ needs. Though Zenios, Makower and Yock’s framework still plays a pivotal role in advancing patient care, enhancing clinical outcomes, and transforming the healthcare landscape, there are some aspects of this rapidly-changing sector that were either not considered or given the proper weight in the original framework.

The rapid aging of the population and decreasing workforce of care providers accompanied by ineffective traditional fee-for-service compensation models have imposed significant budgetary constraints on payers and providers, which now look for ways to deliver more precise, personalized, patient-centered care (see chapter 2.2). These limitations have spurred the emergence of value-based deals, and changed the way payers, providers, regulators, and MedTech businesses interact – or should interact – with each other in the creation and roll-out of innovative products.

Intermingling with socio-economic factors, technological advancements aimed at leveraging the abundance of medical data being produced in the sector, particularly in the form of data analytics and artificial intelligence, have been employed to enhance diagnostic accuracy, streamline administrative processes, and enable personalized treatment approaches. These technologies, their associated risks and concerns – data interpretability, provider adoption, data collection and interoperability concerns – and their capacity of growing rapidly in a largely unregulated environment are all matters that warrant additional guidance complementary to the original framework [João Claro, Annex II].

Understanding that the Biodesign framework is still large applicable [João Claro, Annex II], the following sections will explore important new considerations pertaining to two of the three pillars of the Biodesign framework – Identify, Invent, and Implement – and some of their subthemes. Figure 9 shows which activities from the original framework are addressed in each step of the proposed framework.

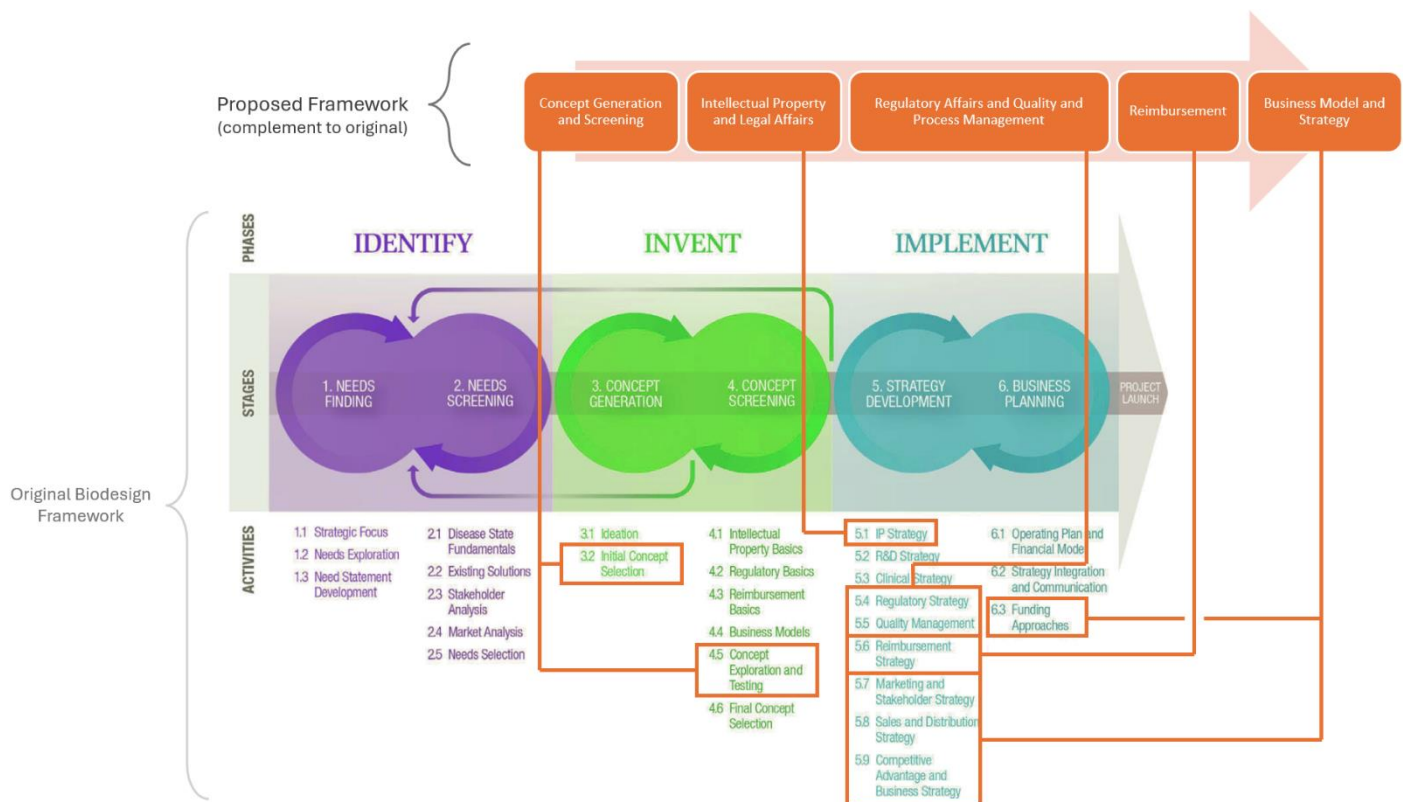


Figure 9. Activities of the original Biodesign framework that are discussed in each step of the proposed framework.

It is important to note that the following sections do not make direct reference to the aforementioned activities, but rather present topics that pertain to those activities, sometimes combining multiple activities under a single theme. For example, the section Regulatory Affairs and Quality and Process Management section touches upon the Regulatory Basics activity of the original framework, as it explores new standards relevant to industry, but also combines the Regulatory Strategy and Quality Management activities given that maintaining quality management systems are often part of regulatory requirements. This organization allows readers to rapidly identify all relevant aspects associated with a topic (e.g., Intellectual Property), and to easily couple that information with points of the original Biodesign framework that also pertain to that topic (e.g., Intellectual Property Basics and IP Strategy).

I. Concept Generation and Screening

After an innovator identifies the clinical need they wish to tackle, it is time for them to generate concepts for solutions that will address that need. When determining the features for the new product, innovators must not only consider requirements tied to specific stakeholder needs, but also define important technical specifications to ascertain the products viability.

When talking about data-centric and digitally-enabled solutions, two main characteristics must be incorporated into the conceptualization phase to secure provider interest: trust and convenience. To establish trust, a solution that extracts insights from clinical data should use reliable data sources and clear, auditable data collection methods, and must explicitly relay those control methods to providers [Dr. Lea Dijkman, Annex II] [Dr. Jos Hendriks, Annex II] (e.g., in a software's interface, add an option that explains how data is collected and what is done to it). Convenience, in the other hand, may come in the form of having interoperable solutions which communicate with hospital systems [Markus Neuer, Annex II] (e.g., PACS) and has access to EHRs – “hospitals like solutions that incorporate patient data, as they can be

integrated in their own systems” [Jeffery Ryan, Annex II]; “If doctors need to access a resource external to the hospital’s system, they will most likely not access it at all. It’s just too much for them to do while engaging with a patient” [Dr. Lea Dijksman, Annex II]. Integration touches upon another aspect of convenience which is reducing the amount of data providers actively need to pursue and introduce as input into the solution – “if you (a provider) have to collect too much data, it ends up being a waste of time” [Dr. Lea Dijksman, Annex II]. Data-driven solutions that are too intricate (e.g., implement complex ML models) may be convenient by providing objective, actionable outputs, but may be harder to explain; in this case, trust must be established through demonstration of adequate performance and validation [Dr. Jos Hendrikx, Annex II].

As for technical requirements for data-driven solutions, innovators must be able to identify what the potential sources of data for their solution will be, the format of said data, how they intend to store the data, and how they plan to convert all that disparate data into a uniform format, if applicable. *“Data standardization is one of the cornerstones of the business. One needs to focus on a type of data to work with, and then work on how to convert other types of data into the desired format” [João Ribeiro, Annex II].* On that note, knowledge of digital health system standards is relevant to creating interoperable devices. For accessing medical images, for example, integration with a hospital’s picture archiving and communication system (PACS) and compatibility with the DICOM image standard may be necessary, while access to a patient’s EHR would likely require the use of a FHIR-based API. Note that for solutions leveraging AI/ML, defining where training, testing and validation data will come from is also necessary; innovators may obtain these from a variety of sources, including public databases, deals with hospitals, and collected by medical devices themselves (in case the innovator already has another product in the market) [Pedro Costa, Annex II].

Innovators should also be aware of technical considerations surrounding the product itself, such as the use of a cloud and/or engaging with mobile app platforms. Cloud infrastructure is an absolute requirement for the deployment of digital solutions [João Claro, Annex II] [João Ribeiro, Annex II], and an innovator that wishes to pursue this sort of solution will need to decide between developing their own IT-infrastructure (private cloud) or use an external one (public cloud), or something in between. Innovators that want to offer mobile services will also have to consider the specifications of each mobile platform.

Real-World Example 1: PeekMed®

Implementing a SaMD: data sources, data transmission and cloud

PeekMed is medical device company specialized in software for orthopedic surgery pre-planning. PeekMed’s software allows orthopedic surgeons to plan for a surgery based on 2D and 3D environments, and to define best-fit medical implants to be used in the intervention, for which the positions of placement in the bone are calculated by the software based on the patient’s exams and the surgeon’s measurements. The solution minimizes surgery duration and risk of complications, and informs implant manufacturers of the specific components that will be required, reducing expenses with stock.

According to the company’s CEO, João Ribeiro, the company identified early on what the sources of data for their software would be, as well as the stakeholders involved in the transmission of data. In PeekMed’s case, data comes in different image formats from different picture archiving and communication systems (PACS). To deal with that, the software was built to be able to access all the different types of PACS, with the data being transformed into a uniform format for the training, testing, validation and proper function of the software. In terms of how the data is transmitted, a doctor or associate radiologic clinic directly uploads the image to PeekMed’s cloud, and, after a medical implant

is defined based on the processing of the image and the surgeon's inputs, PeekMed sends the manufacturing directives to implant manufacturers (also through the cloud).

Two of PeekMed's platforms, Desktop and Web, are tied to their cloud (with the Desktop one being downloadable), while their iPad app is inserted in the Appstore platform. PeekMed uses a private cloud (developed in-house) mainly to be able to control who accesses their information. The company initially used public clouds as they provided ready-to-use functionalities and reduced the need of investment in IT infrastructure. On the scalability of cloud, João warns: *"Private clouds may be more cost-effective when it comes to testing models, but may create a bottleneck in deployment"*.

A note on the "SMART on FHIR" API for EHR-based applications

As explored in chapter 2.4.4, FHIR is a data exchange standard whose adoption by CMS-regulated payers and US hospitals is required by law. FHIR was developed in close collaboration with the SMART API, culminating in what is called the "SMART on FHIR" API. As per the 21st Century Cures Act, EHR vendors are mandated to implement support for SMART on FHIR Core Capabilities [126].

MedTech digital businesses that wish to leverage EHR data should have a good understanding of the SMART on FHIR API from product conception, as that API allows developers to embed and launch apps from within the EHR itself [127]. The SMART on FHIR API is built into the major EHR products, has been used by Apple to connect its health app to hundreds of healthcare systems, and is used for apps launch on the Microsoft Azure product [126] [128].

Conducting market research

Beyond evaluating technical aspects, innovators are encouraged to conduct a market study early in the development process to validate their concept. By engaging with providers across different regions, they can assess market receptivity and competition, and understand how their solution is likely be utilized. Tapping into VBHC, market studies may be useful for ascertaining how a prospective solution may affect (in practice) the episode of care surrounding the target condition, and may even help identify new features to be added to the solution so that its impact in the episode of care – and thus in final outcomes – is more significant. Market studies also offer an opportunity for evaluating how the prospective solution may address economic issues of providers, which has been discussed as a metric for value (see chapter 2.2). However, it's important to be aware that such studies can be costly – potentially exceeding €50,000 in Europe – depending on factors like the scope and the number of stakeholders targeted, and whether or not a specialized service is hired [Jeffery Ryan, Annex II].

As will be seen in the Reimbursement section, beyond market insights, a well-executed study can also inform reimbursement considerations by revealing customers' perceptions of value and willingness to pay.

II. Intellectual Property and Legal Affairs

As new technologies emerge, there's often a "land grab" to secure intellectual property rights. The field of Medtech is currently witnessing a proliferation of synergies with other scientific disciplines. Advancements in information technology, data processing, and artificial intelligence are expanding the capabilities of Medtech, prompting companies to adopt new IP strategies and to reinforce legal measures as ways of ensuring sustainable growth in such a fertile landscape.

Intellectual property strategy

The first thing MedTech companies need to realize is that the general approach to IP has not changed with recent technology advancements [João Claro, Annex II][Iakovina Kindylidi, Annex II][Robert Harrison, Annex II]: a company must still have a firm understanding of

how their product – software, hardware, or whatever it is – adds value to the medium where it is inserted. Doing that early on will guide a company’s IP strategy: “*defining an IP strategy right from the beginning is an absolute requirement for all MedTech companies*” [Jeffery Ryan, Annex II]. The importance of creating a robust IP strategy has been true for a while, but should be reiterated here as companies fight over new technological niches – many of which deal with technologies for which protection is not clear cut, such as software and hybrid devices. By understanding how to protect its assets early on, a company may confidently venture into convoluted niches, or even secure large portions of a new technological niche for itself.

Seeking IP support

Understanding the different mechanisms of IP protection that may encompass all the intricacies of a MedTech company’s products is a daunting task for businesses of all sizes. Challenges are as likely to appear at the start of a company’s journey – such as having to look through hundreds of patent claims, trying to identify those which could pose a threat to a newly-conceived idea at the center of their business – as they are to appear throughout the company’s expansion, with competitors looking to fill in the gaps of the company’s IP strategy.

With IP protection playing such a central role in MedTech, companies should look for professional counseling as soon as they can. Such early interface may help assess freedom to operate (FTO) and even prevent inventors from disclosing their inventions, a big pitfall for emerging businesses [Franz Möltgen, Annex II]. As importantly, companies should strive to familiarize their patent attorneys with their business strategy, as that will allow them to define optimal IP strategies to meet company goals [Iakovina Kindylidi, Annex II]. “*An attorney that works with limited knowledge about the company’s business model and technology will only be able to offer limited contribution*” [Robert Harrison, Annex II].

Working with an in-house patent attorney is very unlikely for smaller MedTech companies due to financial constraints, a limitation that also reduces the amount of involvement that an external attorney can have in their business strategy [Franz Möltgen, Annex II]. These companies should consider engaging with patent managers, which are certified, non-legal professionals that may offer great counseling on IP matters at much more affordable rates.

When seeking an IP professional, it is essential that MedTech companies engage with at least a few to determine which is most familiar with the technology at the company’s core (both in terms of technical aspects, and in regard to market and competition) [Iakovina Kindylidi, Annex II][Robert Harrison, Annex II]. “*Within a company, a patent attorney would be closer to the CTO than to the legal team*” [Franz Möltgen, Annex II].

A note on management involvement

In spite of what was previously said about the importance of counseling in IP matters, emerging MedTech companies should maintain a reasonable level of understanding on IP protection at the company management level. Especially in the conceptualization phase of a business, managers should be able to look for threats to their idea, as that will define the next steps their companies as a whole may take, including going back to the drawing board. “*I went over about 3,000 entries (patent claims) to ensure that what we wanted to bring to the market was patentable*” [Jeffery Ryan, Annex II].

For a comprehensive initial assessment of IP, early-stage businesses may consider using the World Intellectual Property Organization (WIPO)’s online IP Diagnostics Tool [129]. It consists of two-level questionnaires, the first of which is a “pre-assessment” used to identify relevant areas for the company (e.g., confidential information), while the second invites users to answer more detailed questions generated automatically based on their responses to the pre-assessment.

IP protection

MedTech falls between the Pharma (heavy focus on patent protection) and ICT (much more loose on patent application, focusing more on copyright) industries, though with increasing concern towards patent protection **[Robert Harrison, Annex II]**. More specific to MedTech, however, the combination of technologies used in innovative solutions often creates a complex scenario where a company's IP assets comprise hardware, proprietary algorithms, and even datasets, all of which may warrant different protection strategies **[João Claro, Annex II]** **[Robert Harrison, Annex II]**.

Regardless of the types of technology being used in their products, companies should define levels of IP protection based on their business strategy. For smaller MedTech businesses, that usually entails having one layer of protection for the core business, and one for complementary activities/tools surrounding the main device. Ideally, companies should also protect alternatives to their business model given the rapidly-changing landscape of MedTech, though it requires significant resource expenditure **[Robert Harrison, Annex II]**. A way of adjusting a company's IP strategy to variations in its business model is through the use of continuation (patent) applications, which allows applicants to pursue additional claims to an invention disclosed in an earlier application of the applicant that has not yet been issued or abandoned [130].

Companies with enough resources should also invest in a scope of protection, that is, having multiple active patent applications **[Franz Möltgen, Annex II]**. A scope of application can be achieved through divisional (patent) applications, in which “spin-off” patents are obtained from a parent application, constituting their own inventions. This allows a company to protect around its main invention, shrugging off competition. A patent scope may also be very valuable for companies that wish to be acquired, as they give acquiring companies a lot of flexibility in how they can expand their businesses by pursuing specific patent applications within the scope. On that note, by building a scope of protection and retaining the technology within (i.e., cutting licensing deals), a company may make itself more attractive to purchasers, not only for the portfolio they provide, but also for the exclusivity of the technology to be acquired **[Franz Möltgen, Annex II]**.

Software protection

The use of software as a central component in MedTech solutions has become the new standard, pushed by the desire of creating smart devices or platforms capable of collecting and processing, and analyzing data. There are some intricacies to the protection of software IP, however.

First, patenting software is possible, and quite simple to achieve in the US **[Iakovina Kindylidi, Annex II]** **[Franz Möltgen, Annex II]**. The scenario is a little more intricate in the EU, where a software patent claim must contain at least one technical feature; simply including the wording “computer-implemented method” is generally enough to make a software claim patent-eligible [118]. An important thing to keep in mind is that in the assessment of a claim's “inventive step”, only novel features that contribute to the solution of a technical problem are taken into account to determine non-obviousness (this restriction to the non-obvious assessment does not exist in the US). A company may find it hard to ascertain whether a software-based functionality is “technical”. Software embedded in a surgical robot to control its movements based on depth perception from sensor, or software embedded in insulin pumps to control the amount of insulin delivered to a patient in response to measured glucose levels, are examples of technical functionalities – though the treatment given to standalone SaMD (e.g., medical image analysis software) or other digital solutions is not clear-cut [118] [119].

Open source software (OSS) also includes a license, though it may be used for commercial purposes free of charge; only upon the distribution of the software or of its modified version do the effects of the license apply (which could incur a fee) [131].

The safeguarding of application programming interfaces (APIs) introduces another layer of complexity, with divergent copyright protection frameworks between the US and EU. In the US, APIs are eligible for copyright protection, leveraging "fair use" provisions for usage without compensation, whereas the EU mandates API licensing for innovative product development, underlining the practical necessity of established tools [Iakovina Kindylidi, Annex II]. Though APIs The safeguarding of application programming interfaces (APIs) introduces another layer of complexity, with divergent copyright protection frameworks between the US and EU. In the US, APIs are eligible for copyright protection, while in the EU they are not. Though APIs are seldom considered medical devices themselves, companies that intend to develop their own APIs to support their medical devices/software may choose to strategically protect APIs from being used by the competition in similar applications. It is important to note that if a MedTech company wishes to use well established, cross-industry APIs (such as Oracle's Java SE for general computing) they may leverage "fair use" provisions for usage without compensation, as such APIs are regarded as fundamental for the development of applications [Iakovina Kindylidi, Annex II] [132].

Freedom to operate: Copy-left licenses in open-source software

OSS is characterized by providing certain fundamental freedoms to the end user, including their ability to freely make copies, distribute them, and modify the software without needing authorization or paying royalties to the rightholder. The user of an OSS operates under a so-called copy-left license, which in spite of providing the aforementioned freedoms to the user, may impose restrictions to the commercialization of the OSS or its modified version [123] [124]. MedTech businesses centered around software should be attentive of using OSS libraries and other resources in the development of their products, as that may directly affect their freedom to operate. More specifically, they should be aware of OSS covered by strong copy-left licenses.

The impact of strong copyleft is that any modifications to an OSS component must be distributed under the same or a compatible strong copy-left license, with access to the source code. Importantly, if an OSS component under strong copy-left is integrated into a larger work with other software components, these other components must also be distributed under the same or a compatible strong copyleft license, ensuring full access to their source code [124] [125]. This phenomenon is often referred to as the "viral effect" of strong copyleft, as any linked or connected components are inevitably affected by the strong copyleft terms. With that in mind, it is essential that companies have clarity from the beginning about which OSS components will be used, their licenses, and how they will affect the distribution of the final product. The inclusion of a single strong copy-left OSS component can potentially prevent the entire product from being distributed under a proprietary license and may require providing full access to the product's source code [125].

A note on trade secrets and confidentiality

Companies that do not wish to rely on copyright or patenting for the protection of source codes or a specific hardware component may choose to keep them as trade secrets. The definition of the term "trade secret" as per the EU Directive [133] (very similar to that of the US) is any information which: is secret in the sense that it is not, as a body or in the precise configuration and assembly of its components, generally known among or readily accessible to persons within the circles that normally deal with the kind of information in question; has commercial value

because it is secret; and has been subject to reasonable steps under the circumstances, by the person lawfully in control of the information, to keep it secret.

MedTech holds a particularity in face of other industries in that regulations require that MedTech products be thoroughly examined for the assessment of their functionality and safety, which works against the exitance of trade secrets [Franz Möltgen, Annex II] [Robert Harrison, Annex II]. MedTech companies must thus not opt to keep trade secrets without prior deliberation. *“Many companies define things as trade secrets out of laziness; they do not want to put the effort to go through with a patent application process”* [Robert Harrison, Annex II]. If a company finds trade secrets to be the most strategically fit option, it must put stringent confidentiality measures put in place, such as presenting non-disclosure agreements (NDAs) to employees, restricting access to sensitive information (e.g., complete source code of a software), and clearly labeling confidential information [Franz Möltgen, Annex II].

Beyond IP: dealing with legal affairs

The technical and legal know-how required from companies navigating a complex sector like MedTech [Iakovina Kindylidi, Annex II] and the usual absence of the latter, especially in emerging businesses [Franz Möltgen, Annex II], evidences the need for legal counsel beyond IP matters.

While establishing a dedicated legal team may initially seem daunting, it proves invaluable in ensuring smoother negotiations for licensing, purchasing, or forming partnerships within the industry. Moreover, investing in the development of comprehensive templates, particularly licensing agreement templates, can expedite the overall licensing process by setting clear terms upfront. Early involvement of legal counsel to craft internal policies, term sheets, and templates lays a robust foundation for future operations, streamlining processes and minimizing potential legal pitfalls down the line [Iakovina Kindylidi, Annex II]. As companies grow, they should consider the relevance of having internal legal resources. Typically, this takes the form of an attorney who manages all legal operations and interfaces with external attorneys, such as external IP attorneys, when necessary [Franz Möltgen, Annex II].

Furthermore, companies should prioritize strategic planning and timely execution of legal strategies. Initiating the process with a broad legal consultation allows for the identification of key areas of concern, such as intellectual property rights and internal policy development. Subsequently, engaging specialized legal professionals aligned with the company's technological focus enables the refinement of an IP strategy tailored to their objectives, whether it be licensing innovations or positioning for acquisition [Iakovina Kindylidi, Annex II].

While it may be tempting to prioritize cost-cutting measures in the legal sector, particularly for MedTech startups that already need to deal with regulatory expenses, adopting a proactive mindset towards legal compliance from the outset enhances operational efficiency and, if applicable, augments a company's appeal to potential acquirers who may decrease purchasing offers or prolong the acquisition process if compliance shortcomings are detected.

III. Regulatory Affairs and Quality and Process Management

The regulatory landscape has undergone significant change with efforts to make it more supportive of innovation and, parallelly, to account for technological changes and their ramifications, including interoperability and data standardization concerns, artificial intelligence controls, software as a medical device (SaMD) evaluation, and cybersecurity. Here, current regulation surrounding digital or data-driven MedTech solutions are explored and considerations on ways to navigate it are made.

This section will focus on US regulation to stay in line with other sections of the framework. US regulations on medical affairs are update much more frequently than they are in the EU, with the US also having become *“an entry point for many global companies prior to obtaining regulatory approval in Europe due to the stringent nature of the European MDR”* [Marco Rafael, Annex II] [116].

The current regulatory landscape

The 21st Century Cures Act (Cures Act), enacted in December 2016, is a pivotal piece of legislation in the modernization of healthcare regulation. For medical devices, the Cures Act aims at streamlining regulatory pathways by introducing a more holistic and patient-centric approach to regulatory analysis, incentivizing the use of real-world evidence to support FDA applications. To keep up with newer technologies, the Cures Act also prompted the creation of specific regulation on software as a medical device (SaMD), as well as data use and cybersecurity matters. Addressing the complexities of modern medical devices in a more transparent way is a favorable step away from traditionally stiff, hard-to-navigate regulatory pathways [Pedro Costa, Annex II].

In that same vein, the FDA has also made efforts to align its requirements with that of well-established international standards, namely ISO 13485, and established an evolving list of recognized consensus standards that can be used to support regulatory applications.

The use of Artificial Intelligence (AI) in medical devices remains to be fully regulated. International legislation on the use of AI (not just in MedTech) is at its infancy, but existing guidance on the matter should be taken seriously.

General Strategies for Regulatory Compliance and Quality Assurance

FDA’s Quality System (QS) regulation outlines a framework for finished device manufacturers to develop and implement procedures appropriate to their devices based on current manufacturing standards. The regulation does not dictate specific manufacturing methods for each device given the diverse range of devices it encompasses, and manufacturers are advised to exercise discretion in applying relevant sections of the QS regulation to their products and operations. Within this flexibility, each manufacturer is accountable for establishing requirements ensuring the safety and effectiveness of their devices, as well as devising methods and procedures to meet quality system standards [74].

As explored in chapter 2.5.1.2, a new version of the QS regulation – referred to as Quality Management System Regulation (QMSR) – will take effect in February 2026. The new regulation is harmonized with the ISO 13485:2016 international standard for quality management system in medical devices. In that same view, the FDA has been incentivizing the use of consensus standards pertaining to medical devices and associated matters, and has built an FDA Recognized Consensus Standards Database for public consultation [85]. Declaring conformity with a consensus standard recognized by the FDA serves the purpose of fulfilling specific premarket requirements and minimizing the volume of supporting data and information submitted to the FDA. To certify conformance with a consensus standard, the submitter must submit a Declaration of Conformity [134].

Examples of subject areas with recognized consensus standards include neurology, radiology, biocompatibility, electromagnetic compatibility (EMC) and software/informatics. To ensure smooth navigation through regulatory matters, companies are advised to identify and seek conformity with standards relevant to their products and operations. For example, a company that manufactures smart medical implants for remote monitoring may want to look to EMC,

biocompatibility, software, and clinical (FDA-recognized) standards to signal to regulators that product development, testing and validation were properly performed.

Standards not only spell out the ways in which a company conforms to regulatory requirements, but are also very helpful in identifying risks in the development of a product. This allows for a company to refine its operations, allowing smooth passage through regulation and reducing the chances of issues in the post-market setting. On that note, CAPA processes and a Complaint Management System established by the ISO 13485:2016 Quality Management System are especially relevant for more deeply addressing development issues, and identifying risks that “slipped through” the premarket phase of a product, respectively [Jeffery Ryan, Annex II].

Standards also force the company to clearly establish a device’s intended use, must haves in the application of the product, and non-essential components [Jeffery Ryan, Annex II]. A great example of that is the Product Requirement Document (PRD), a requirement of the ISO 13485 standard: the PRD must encompass all explicit capabilities necessary for release of the device with detailed use cases and the expected user interactions with the device. Beyond functional specifications, the PRD should articulate any additional requirements, such as system or environmental prerequisites (e.g., compatibility with Windows 10 or later, or specific browser support), as well as usability criteria (e.g., one-handed navigation for mobile apps). After completing the PDR, a company should possess a collection of high-level documents outlining the market requirements within the PRD, alongside the design project schedule and budget [135] [136].

Real-World Example 2: Interventional Systems Using a multi-level technical file to demonstrate conformity

Interventional Systems (IS) is a medical device company best known for its Micromate™ robot for small medical interventions. Apart from the robot itself – capable of holding and guiding a variety of biopsy or ablation needles – Micromate™ also disposes of a proprietary planning and navigation software. IS licenses Micromate™ to a series of business partners, and their product – be it the robot or the software functionalities – can be adapted to fit the needs of each partner.

Extra steps were taken to ensure Security-by-Design during the development of Micromate™, and many industry standards were utilized to support regulatory pathways in Europe and in the US. The company also closely monitors the device’s post-market performance. All these measures greatly contributed to Micromate™ being accepted as a low-risk product, even granting it the lowest possible risk classification (Class I) under EU’s Medical Device Regulation. Given the possible variations that the device may have due to patient partnerships, IS implements yet another quality measure: a clever, multi-layered technical sheet for easy access of product features and indicators of regulatory conformity.

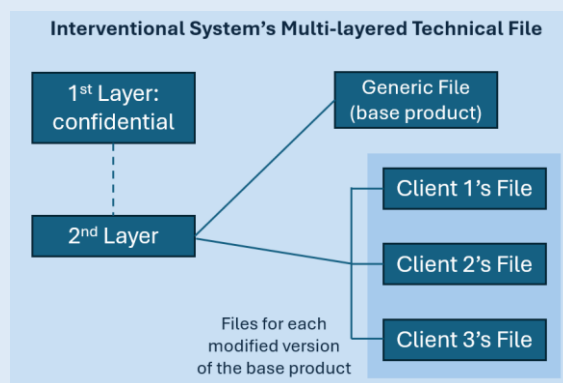


Figure 11. IS' multi-layer technical file.

The technical file is divided into two main layers: an inner layer, where the company stores confidential information, and a second layer with a detailed explanation of the product. That layer is further split into a “generic” file, which contains specifications of the base product, and many complementary files meant for IS’ partners, which include modifications made to the base product to suit a partner’s need. This mechanism ensures traceability in terms of what was changed from the base product, allowing easier identification of the root of problems that appear after modifications, and permits auditors from a client to work with IS in the evaluation of manufacturing, validation, and verification practices pertaining specifically to the clients product.

A note on management involvement

The regulatory environment is a complex one, and even with the current modernization initiatives of the FDA, MedTech companies may still find it challenging to fully conform with regulatory requirements. This is especially challenging for emerging MedTech businesses, as these do not have the field experience of major corporations. When building a MedTech company from the ground up, it is important that the managing team reads and informs themselves about regulatory requirements, including the requirements of each standard they may use. This will help avoid mistakes down the line, allow for the company to implement the best design and development practices right from the beginning, and give them agility in dealing with issues that may arise in the future **[Jeffery Ryan, Annex II]**.

Be it for businesses centered around more traditional medical devices or innovative, software-based solutions, the adoption of quality processes for regulatory conformity (and improved operability) is a necessity. *“Well, the quality process will not change. I suspect that quite a few of the software-developer and -planer will have to adapt their daily doing to the quality processes. This is foremost a psychological issue and challenge”* **[Anonymous, Annex II]**. These processes and standards, which at first may look complex, are in fact not particularly hard to follow – *“it merely requires the will to do so and some resources”* **[Anonymous, Annex II]**. Having a leadership that understands this and helps the rest of the team in implementation efforts is key to the successful implementation of standardized quality controls. *“The big hurdle [in implementing a QS], in my personal experience, is the mindset of R&D in general and the software developers in particular.”* **[Anonymous, Annex II]**.

Utilizing consultancy services for regulatory affairs are always an option – especially as a company grows and expands its portfolio – but should never replace internal knowledge on the matter; a company that has no understanding of regulatory requirements is at the mercy of consultants who may not have the best interests of the company as a priority, and thus may not provide the company all the relevant information to ensure success **[Jeffery Ryan, Annex II]** **[Pedro Costa, Annex II]**. That is not to say that a company should not look for ways to streamline its quality operations; eQMS software – such as Greenlight Guru [137] **[Jeffery Ryan, Annex II]** and Formwork [138] – is often used by companies large and small for CAPA/Risk management, document review, versioning and archiving, planning of trainings, and organization of technical documentation, being valuable tools for companies with a good initial understanding of regulatory affairs.

Strategies when Dealing with Innovative Devices

When a new medical device lacks substantial equivalence to existing ones, it cannot undergo clearance via the traditional 510(k) premarket notification process. In such cases, the manufacturer may opt to submit a De Novo application to the FDA. The evidentiary requirements for a De Novo submission vary based on the device's complexity and risk level. The FDA's review assesses the device's safety and effectiveness, considering factors like intended use, technology, and potential risks. Early attention to proof of concept and evidence generation processes is crucial, as the FDA may request clinical data, bench testing,

performance evaluations, and other pertinent information to establish the device's safety and efficacy.

A De Novo application, though laborious, often benefits from clearly stated general regulatory goals for the approval of a new technology. The types of evidence and the way it is collected are entirely defined by the sponsor – so long as it is deemed satisfactory by the FDA in the context of use for that device. In view of rapidly-evolving MedTech, a sponsor may thus take a strategic approach to their De Novo application, as they will be the ones to set special requirements and define the proper use of a whole new family of technologies. With all future sponsors having to abide by these indications when trying to get similar technology to the market (now via 510(k)), the original sponsor has the power to indirectly deter competition and/or facilitate the approval of their own future products, as they know exactly how to meet the requirements initially set by themselves [Jeffery Ryan, Annex II].

FDA's Breakthrough Devices Program

In 2016, the American Congress established the FDA's Breakthrough Device Program [139] through the 21st Century Cures Act. This program offers prioritized review for select medical devices meeting specific criteria, potentially expediting their development and FDA authorization. It thus constitutes a very attractive pathway for companies wishing to introduce unprecedented innovation into the market – a feat ever more common with the advancements of digital technology.

To qualify for the breakthrough device designation, a medical device must meet the following conditions:

- Provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; and
- Meet one of the following conditions:
 - Represent breakthrough technologies;
 - No approved or cleared alternatives exist;
 - Offer significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies; or
 - the availability of such medical devices is in the best interest of patients.

Apart from benefitting from a more streamlined and informed regulatory process, manufacturers of such breakthrough devices may be eligible for or have easier access to particular reimbursement avenues designed for new technology.

The example of RelieVRx®, the first VR-based therapeutic to receive FDA breakthrough designation and market authorization for treating chronic lower back pain (CLBP), is explored below as a prime example of a novel device setting a precedent for the use of a family of technologies. RelieVRx® is brought back in the “Reimbursement” section of this framework to discuss the unique reimbursement avenue it pursued, and how it ties back its regulatory pathway.

Real-World Example 3: RelieVRx® (part I)

Setting a regulatory precedent as an innovative virtual reality device [140]

RelieVRx® is a virtual reality device created by AppliedVR with an indication to reduce pain and pain interference in patients living with chronic lower back pain (CLBP). The RelieVRx® program was the first VR-based therapeutic to receive FDA breakthrough designation and market authorization for treating CLBP. While VR had been studied and used in various acute and chronic pain conditions for decades, headset technology has only recently become simple to use and broadly accessible, prompting the creation of the VR headset for RelieVRx®. The treatment program consists of a 56-session in-home course, incorporating modules based on cognitive behavioral therapy (CBT) principles and other evidence-based behavioral methods, including pain education, breathing techniques, pain distraction, and mindfulness.

Trial design

AppliedVR executed a fully decentralized, double-blind, parallel-arm, randomized, placebo-controlled trial of the 56-session self-administered behavioral skills RelieVRx® program for CLBP during the COVID-19 pandemic. This study's nationwide sample consisted of individuals with moderate to severe chronic non-malignant low back pain with a duration of three months or longer. The sample of 188 participants were enrolled and randomly assigned to either the RelieVRx® immersive VR pain relief skills program or the sham VR program, both delivered via the same model VR headset. The immersive RelieVRx® program delivered therapeutic VR experiences lasting 2 to 16 minutes, while the sham VR delivered 2D, non-immersive nature content with similar duration. The study's main goals were to assess differences between the RelieVRx® and sham VR groups and to measure changes in pain intensity and pain-related interference with activity, sleep, mood and stress from baseline to the end of the treatment, and ultimately to 24-months post-treatment.

Individual level study and Results

RelieVRx® led to clinically meaningful pain reductions at the group level, but it was important to determine whether they were also reflected at the individual participant level. To address this question, a responder analysis was performed to assess the percentage of RelieVRx® participants who met or exceeded a 2-point pain intensity or interference reduction. The results were clear at the end of treatment, with nearly 7 in 10 participants achieving a 2-point reduction in pain intensity, pain interference or both, with an average pain reduction of nearly 3.5 in this group. Results at 24-months post-treatment were very similar.

In November 2021, AppliedVR's RelieVRx® device received market authorization through the De Novo regulatory pathway, as no predicate device existed on the market. The FDA's approval of AppliedVR's De Novo submission was crucial in enabling the future marketing and distribution of the RelieVRx® program in the United States. This approval also established a new device classification, which other manufacturers can use as a predicate for future 510(k) submissions, highlighting how AppliedVR is paving the way for future VR therapeutic devices entering the field.

Real-World Data (RWD) to Support Regulatory Decision-Making

As discussed in “Real World Data”, the abundance of health data contained in EHRs, disease registries, medical device databases and more may be leveraged to support regulatory decision-making beyond traditional clinical trials, including the clearance of a new device, or the expansion in the indications for use of devices already on the market. Aggregation of real-world data may also prove useful as a post-market control suitable for providing ongoing device safety surveillance and additional evidence for effectiveness. Finally, in the context of current MedTech inventions revolving around digital health, software may be validated through the use of RWD, demonstrating its applicability in clinical practice.

A company that wishes to use real-world data to support the application of their devices may find a lot of use in FDA's 2017 guidance on the Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices [15]. The document stresses FDA's consideration of RWD only when accurately and reliably captured at clinically relevant time intervals throughout the device lifecycle. A company must ask itself the following questions when considering the use of RWD to support one of its devices:

- Does the RWD contain sufficient detail to capture the use of the device, exposures, and the outcomes of interest in the appropriate population?
- Are the data elements available for analysis capable of addressing the specified question when valid and appropriate analytical methods are applied?
- Are the RWD and the associated evidence interpretable using informed clinical/scientific judgement?
 - Is the use of the device in a real-world population representative as captured within the data source? Is it generalizable to the relevant population being evaluated?
 - Is the RWD source used regionally, nationally and/or internationally?

These questions are non-exhaustive, but intend to capture considerations about how relevant the RWD being collected actually is in the context of the device at hand – *“A software tool that detects melanoma from pictures of a patient's skin must use data from multiple skin tones in its development to prove its robustness”* [Célia Cruz, Annex II]. Beyond relevance, a company that wishes to employ the use of RWD in the regulatory pathway must also ensure that the data is properly collected (data accrual) and that quality control measures are put in place (data assurance).

Factors the FDA will consider when assessing proper data accrual include:

- the preparedness of individual sites for complete and accurate collection of RWD (e.g., whether there are defined processes, site training and support, and qualified personnel)
- whether a common data capture form was used
- whether a common definitional framework (i.e., data dictionary) was used
- whether patient selection and enrollment criteria minimize bias and ensure a representative real-world population (e.g., all-comer's design, consecutive patient enrollment)
- the timeliness of data entry, transmission, and availability; and whether necessary and adequate patient protections were in place

As for data quality control, RWD quality can generally be improved by following published recommendations concerning registries, such as those by the Agency for Health Care Quality, Patient-Centered Outcomes Research Institute, the National Medical Device Registry Task Force, and the Regulators Forum (IMDRF) Registry Working Group. However, certain sources of RWD, such as some administrative and healthcare claims databases or EHRs, may not have established data quality control processes and may not be capable of fully implementing or following the above recommendations. In those cases, important factors for consideration include:

- completeness (i.e., minimized missing or out of range values) of data necessary for specified analyses, including adjustment for confounding factors
- data consistency across sites and over time
- evaluation of on-going training programs for data collection and use of data dictionaries at participating sites
- the use of data quality audit programs

Using Patient-Reported Outcome Measures and Patient Preference Information

As discussed in chapter 2.2, Patient-Reported Outcome Measures (PROMs) and Patient Preference Information (PPI) have been gaining more relevance as evidence to support regulatory and even coverage decision-making. While PROMs may provide a snapshot of a patient's own assessment of various outcomes at a given point in time, they do not convey how much the patient values one specified outcome or therapy when compared to other potential outcomes and therapies, as is communicated by PPI.

MedTech companies wishing to incorporate PROMs into the evaluation of their products have to start by selecting PRO instruments. These instruments may be issued by a variety of entities, such as ICHOM – whose questionnaires are already used in major European hospitals [Dr. Lea Dijkman, Annex II] – and more field-specific organizations, or may be developed by companies themselves to support their own products. The FDA recognizes that well-designed PRO instruments facilitate incorporating patient perspectives as scientific evidence to support regulatory and healthcare decision-making, and has issued recommended best practices for developing relevant, reliable, and sufficiently robust PRO instruments for use in medical device evaluation [141], including leveraging existing PRO instruments. Companies may look at FDA's PRO Compendium for examples of PRO instruments that have been used and publicly reported in medical device premarket clinical investigations across a wide variety of devices and indications [142].

Real-World Example 4: PRO Instrument (from PRO Compendium Entry)

PRO Instrument used in the evaluation of a synthetic cartilage implant

Company: Cartiva Inc

Device Type: Prosthesis, Metatarsophalangeal Joint Cartilage Replacement

Device Indication for Use: The Cartiva Synthetic Cartilage Implant is intended for the use in the treatment of patients with painful degenerative or post-traumatic arthritis (hallux limitus or hallux rigidus) in the first metatarsophalangeal joint with or without the presence of mild hallux valgus.

PRO Name and Description: Visual Analog Scale for Pain Intensity (VAS) consists of a line of fixed length (usually 100 mm) with words that anchor the scale at the extreme ends and no words describing intermediate positions. Patients are instructed to indicate the place on the line corresponding to their perceived state. The mark's position is measured as the score.

PRO Appears in Labeling? Yes

As for PPI, though not as well-established as PROMs due to its often qualitative nature, companies may still want to pursue patient preference studies. Assessments of patient-centered variations in risk tolerance and perspectives on benefits may, in the aggregate, provide a population-level understanding of patient benefit-risk preferences for a device. This information may serve as valid scientific evidence and inform the FDA's benefit-risk evaluation for devices undergoing PMA, HDE application, or de novo request reviews. For straightforward decisions regarding risk tolerance and patient preference, qualitative input may be sufficient, though complex questions regarding such issues may warrant careful quantitative study design, and conduct. The FDA has issued guidance on the use of PPI, which include examples of PPI use in the support of applications [73].

Practical Examples of RWD use to Support Regulatory Decisions

The document “Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions” [14] also issued by the FDA constitutes another useful resource for companies that currently wish for further insights on the use of RWD. The document provides 90 examples of submissions that illustrate the broad spectrum of RWE, including, among others, 18 premarket (510(k)) notification submissions, 20 premarket approval (PMA) original applications and 14 De Novo classification requests.

Most relevant to emerging digital and/or data-driven MedTech businesses, the document includes a multiple examples of software-as-a-medical-device (SaMD) validation through RWD, and the utilization of patient- and device-generated data for pre- and post-market requirements.

Real-World Example 5: PeraServer/PeraTrend software validation using EMRs 510(k) – Software that computes patient status index (example 54 from [14])

Background: The Rothman Index is a single measure of a patient’s physiologic condition based on the aggregate statistical mortality risk associated with the values of the patient’s vital signs, nursing assessments, and selected lab values.

The Device: The PeraServer and PeraTrend System is for a software platform that computes a Rothman Index score from data extracted from patients’ electronic medical records, which can be associated with configurable warnings. PeraServer/PeraTrend is intended for the care of patients throughout the hospital setting (e.g., in the emergency department, on the wards, in intensive care units).

RWE Source and Use: EMRs were used for development and validation of the device, as well as for comparing performance of the Rothman Index to the predicate patient status index when both were calculated from hospitals’ electronic medical record systems. Over 170,000 adult patients and 105,470 pediatric patient visits were used in the validation of the device.

Real-World Example 6: ContaCT software validation using radiology reports De Novo – Computer-assisted triage and notification software (example 64 from [14])

The Device: ContaCT uses an artificial intelligence algorithm to analyze images for findings suggestive of a prespecified clinical condition and to notify an appropriate medical specialist of these findings in parallel to standard of care image interpretation. Specifically, the device analyzes CT angiogram images of the brain acquired in the acute setting, and sends notifications to a neurovascular specialist that a suspected large vessel occlusion has been identified and recommends review of those images.

RWE Source and Use: 300 CT angiogram images and corresponding radiology reports were obtained from two clinical sites in the U.S. The software was first tested for sensitivity and specificity on CT images against the expert-established ground truth. A secondary analysis compared the notification time of the device against a standard-of-care notification time extracted from corresponding standard-of-care radiologist reports.

The FDA also considered non real-world and real-world literature (e.g. from the STRATIS Registry) describing the potential patient benefit from earlier endovascular treatment, time from presentation to reperfusion and time to stroke center notification.

Strategic Insight: Adding Functionalities by Leveraging Medical Device Data Collection

As previously seen, RWD can be extracted from monitoring medical devices themselves. To “start with the low-hanging fruit” [Jos Hendrikx, Annex II] is a strategy often used by established MedTech companies – commonly with wearable technology [Jos Hendrikx, Annex II] – that consists in approaching regulation with a device with a simple function that can easily be validated through trials, and then once the device has reached the market, new parameters may start to be studied from collected real-world data (with the wearer’s consent). With that information, new features can be added to the device, or the information may be used to support the application of another device. The RWD collected either to expand the use of an existing device or support the classification of a new one must follow the same requirements as defined previously in terms of adequacy, bias and amount (e.g., if only a few devices were used to collect RWD data in the first place, that data may not be reliable enough to support a new function). Gradually building new features on top of another contribute to lessen the product’s perceived risk, making the regulatory pathway much smoother [Célia Cruz, Annex II].

Software

Learning whether a software constitutes a medical device or not

Regulations have evolved significantly to accompany the rise of software-as-a-medical-device (SaMD) among MedTech businesses. Perhaps most importantly, as described in chapter 2.5.1.2. in Software as a Medical Device (SaMD), many software functions that used to be considered SaMD have recently lost that status, namely software for administrative support of a healthcare facility, for maintaining or encouraging a healthy lifestyle, to serve as electronic patient records, and for transferring, storing, converting formats, displaying data and results. The following FDA guidance documents – all of which released within the last five years – are useful for companies to ascertain whether a software they have developed or plan to develop constitutes a medical device:

- **Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act**, which provides a comprehensive discussion on software function changes
- **Clinical Decision Support Software**, which interprets and explains the types of CDS software functions that are excluded from the definition of device on a risk-based approach
- **Multiple Function Device Products: Policy and Considerations**, which interprets and presents FDA’s approach to medical device data systems (MDDS), as well as medical image storage devices and medical image communications devices
- **Policy for Device Software Functions and Mobile Medical Applications**, which communicates how the FDA intends to apply its regulatory oversight to certain software, including device software functions and mobile medical applications (MMAs) intended for use on mobile platforms or on general-purpose computing platforms

Additionally, companies are advised to use FDA’s Digital Health Policy Navigator [143], an online tool intended to help product developers understand whether a software function is potentially subject to or the focus of the FDA’s regulatory oversight as a device, and if so, the considerations that may assist in determining the applicable FDA-specific legal and regulatory requirements and recommendations.

Software premarket submissions

Companies should refer to FDA’s 2023 guidance document “Content of Premarket Submissions for Device Software Functions” to understand what is the recommended documentation for

premarket submission for FDA’s evaluation of the safety and effectiveness of SaMD. The document goes into detail about the typical documentation generated during the software life cycle (development, verification, and validation), including a risk-based approach to determining a device’s Documentation level. Essentially, Enhanced Documentation is associated with software whose potential failure or flaw would probably lead to death or serious injury, either to a patient, user of the device, or others in the environment of use. These risks should be assessed prior to implementation of risk control measures. Basic Documentation is significantly less extensive, and applies to all other devices. Documentation Level examples are presented by the document. The following are the recommended software documentation elements – discussed in detail by the guidance document – each of which has an Enhanced and Basic Documentation level associated with it:

- Software Description
- Risk Management File
- Software Requirements Specification (SRS)
- System and Software Architecture Diagram
- Software Design Specification (SDS)
- Software Development, Configuration Management, and Maintenance Practices
- Software Testing as part of Verification and Validation
- Software Version History
- Unresolved Software Anomalies

The FDA also encourages the use of consensus standards related to software, which have helped improve the consistency and quality of software development and documentation, particularly with respect to activities such as risk assessment and management. A company may consult the FDA Recognized Consensus Standards Database [85] to find what standard is more adequate for itself. Examples of recognized software-related standards include:

- ANSI/AAMI/ISO 14971: Medical devices - Applications of risk management to medical devices
- ANSI/AAMI/IEC 62304: Medical Device Software - Software Life Cycle Processes
- ANSI/AAMI SW91: Classification of defects in health software

Determining whether a software change warrants a 510(k) submission

As per FDA’s Quality System (QS) regulation – now QMSR after its harmonization with the international standard ISO 13485:2016 – if a company makes a change in the design of a finished medical device, including software, they must demonstrate that the device still meets the original specification to avoid having to submit a new 510(k) for that change. Software modifications for addressing cybersecurity issues or performance enhancements are frequent within MedTech, and often don’t warrant the submission of a new 510(k). The flowchart and guiding principles presented in the guidance document “Deciding When to Submit a 510(k) for a Software Change to an Existing Device” [144] provide an easy way for developers to understand the regulatory implications of changes made to their approved software.

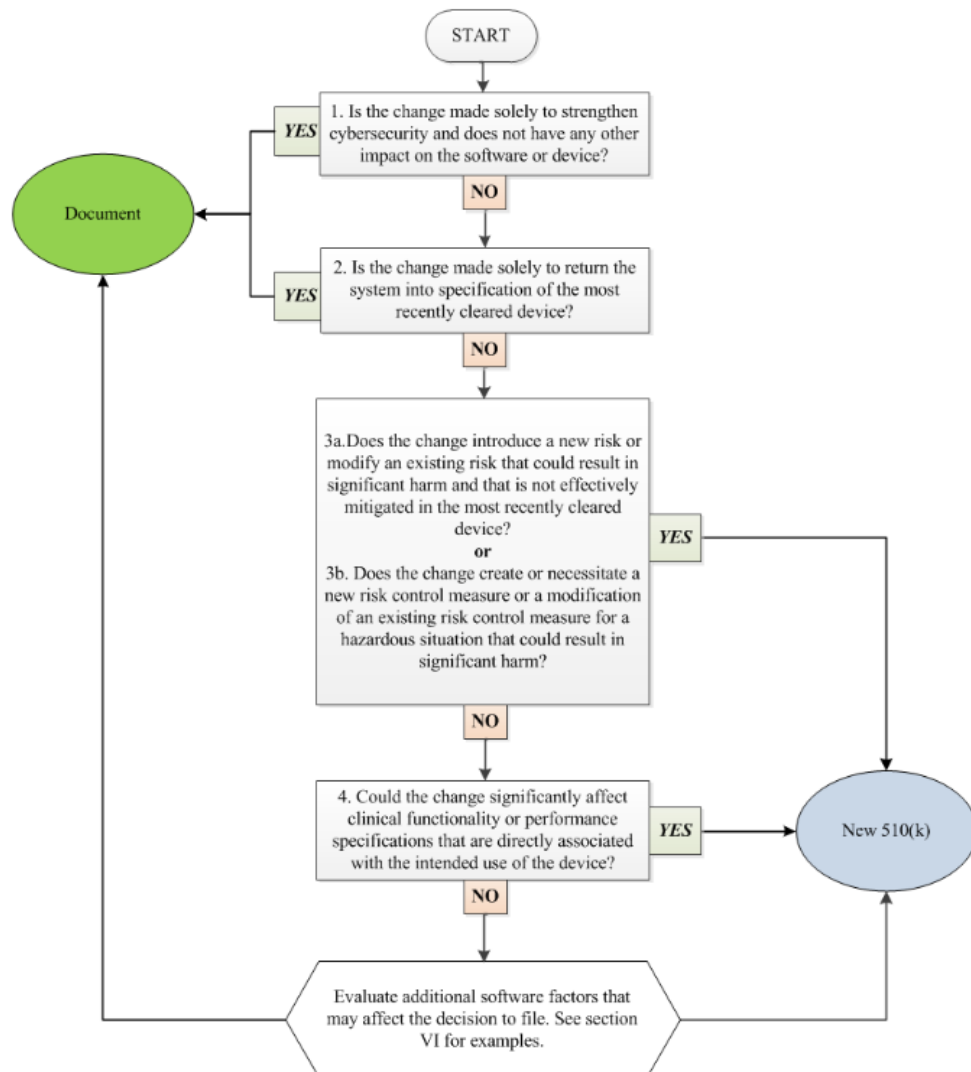


Figure 12. Flowchart from the guidance document “Deciding When to Submit a 510(k) for a Software Change to an Existing Device”.

Privacy

MedTech companies that wish to manipulate or extract insights from health data must invariably comply with privacy law. For a long time, the Health Information Portability and Accountability Act of 1996 (HIPAA) represented the main piece of legislation to ensure comprehensive protection of patient health information (PHI) in the US. However, as explored in chapter 2.5.1.2, the emergence of the European GDPR in 2018 greatly affected the treatment given to privacy around the world, as the GDPR requirements are extended to any entity that collects personal data from an EU citizen, be it for clinical studies, clinical trials planning, medical device model training, and other purposes. While HIPAA specifically addresses PHI, which includes data capable of identifying a patient, such as their name, address, social security number, and insurance details combined with health information, the GDPR establishes regulations for all sensitive personal data, or PII.

Organizations that are either HIPAA- or GDPR-compliant already have existing safeguards in place to protect data. Complying with one regulation may help in achieving compliance with the other, even though overlapping requirements are few [90]. Some of the common requirements for the two regulations are:

- Requirement for controlled access to sensitive data
- Requirement for methods for detecting unauthorized changes to PHI
- Requirement for PHI encryption at rest and in transit
- Requirement for an appointed data protection officer (DPO)

MedTech companies that wish to leverage the abundance of patient data must be aware of the extensive requirements on the safeguard of privacy [Jeffery Ryan, Annex II][Pedro Costa, Annex II], especially when operating under the GDPR. *“An example of measure taken by our company was to automatically anonymize data (medical images) when it comes from the hospital system to within our device – a type of entry control”* [Pedro Costa, Annex II].

Nevertheless, by focusing on a few general guidelines, companies may be able to navigate privacy concerns somewhat easily. A company working with patient data must be able to answer the three following questions [João Ribeiro, Annex II]:

- **What data do I have access to?** (What kind of patient data is being used (e.g., medical imaging results, demographic information))
- **What do I do with that data?** (Why that data is necessary, and how it is used)
- **Am I able to eliminate patient data in my possession?** (Elimination of all patient information, both physical and digital)

As defined by the GDPR, there is no forbiddance in the use of patient data, though patients must be informed of and consent to the use of their data. If a medical device is intended to be used directly by a patient, then the company should be able to request for their consent directly; conversely, if a provider is the end-user of a data collection device, normally the request of consent for patients comes from the provider. *“I don’t see a problem in the treatment of patient data itself, but rather some doubt in regard to what can be done with that data. When that is clear, it becomes quite simple”* [João Ribeiro, Annex II].

Cybersecurity

As explored in Barriers to digitalization and data use in MedTech, opportunities brought by the interconnectivity of devices and the sharing of health data came accompanied by serious cybersecurity concerns. Due to the risks cyberattacks pose to proper medical device functioning and sensitive patient data, the subject of cybersecurity has quickly been moved to the center of regulatory concerns.

Given the relatively recent efforts of regulators to address cybersecurity concerns, new information on the matter is published with frequency. MedTech companies should frequently refer to FDA’s Digital Health Center of Excellence (DHCoE), namely its webpage on Cybersecurity [92], to stay up to date on the Agency’s takes on the matter. Currently, the main source of guidance for the industry on cybersecurity regulatory requirements is the document “Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions” released in September 2023 [78]. It has been well received by industry stakeholders, such as the Advanced Medical Technology Association (AdvaMed) [145].

As presented by the document, companies should adopt a Secure Product Development Framework (SPDF) for risk management across the total product lifecycle (TPLC). According to the FDA, the use of a SPDF helps ensure that the QS regulation is met (see “General Strategies for Regulatory Compliance and Quality Assurance” at page 73). An SPDF should address the following security objectives:

- Authenticity, which includes integrity;
- Authorization;

- Availability;
- Confidentiality; and
- Secure and timely updatability and patchability

Premarket submissions of devices containing artificial intelligence, machine learning (AI/ML) and cloud-based services, or any device that stores sensitive health information [Célia Cruz, Annex II], should include information that describes how the above security objectives are addressed by and integrated into the device design. The extent to which security requirements, architecture, supply chain, and implementation are needed to meet these objectives will depend on a series of matters, including the device's intended and actual environment of use, the presence and functionality of its electronic data interfaces, and the risk of patient harm due to the exploitation of cybersecurity vulnerabilities.

Moreover, to effectively address cybersecurity concerns, it's crucial that companies allow the users of their devices to access comprehensive information regarding the device's cybersecurity measures, potential risks to the medical system, and other pertinent details. Failure to disclose all of the communication interfaces or third-party software, for example, could fail to convey potential sources of risks for users of a given device.

Cybersecurity requires extensive steps to be followed – way beyond the guiding principles provided in this section of the framework. Apart from regulatory guidance, companies may also look at emerging cybersecurity standards [Pedro Costa, Annex II] for cross-industry best-practices.

Cybersecurity groups

Another way for MedTech companies to stay up-to-date with cybersecurity concerns is to join a cybersecurity group – organizations dedicated to sharing concerns and occurrences in cybersecurity, including updates on regulation. *“The participation of a company in such groups may show a company's commitment to cybersecurity concerns, which may favor them in the eyes of regulators”* [Célia Cruz, Annex II]. A company may consider engaging with one or more of the following organizations:

- **Medical Device Manufacturers Association (MDMA) – cybersecurity working group:** MDMA's cybersecurity working group [146] serves as a key channel to disseminate timely and relevant information to medical technology innovators. Working with federal partners, MDMA helps members navigate vulnerability disclosures, threats and ransomware activity targeting the health care and public health sector. MDMA collaborates with the Healthcare & Public Health Sector Coordinating Council (HSCC) Cyber Working Group in the development of outputs for risk mitigation, recommendations, best practices and guidance for enterprise cybersecurity improvements.
- **Health Information Sharing & Analysis Centre Europe (Health-ISAC Europe):** Health-ISAC [147] is a community of healthcare organizations with headquarters in 15 European countries and members with operations in every country in Europe and in the US. Health-ISAC collaborated to strengthen critical infrastructure resilience by creating a dedicated ISAC-to-ISAC automated sharing capability, and conducts numerous workshops, exercises, annual summits, webinars, and other events in the region. Health-ISAC Europe develops monthly threat briefs and other guidance with a focus on regional issues.

FDA's eSTAR Program: Cybersecurity Implications

The electronic Submission Template And Resource (eSTAR) is an interactive PDF form that guides applicants through the process of preparing a comprehensive medical device submission.

eSTAR is required for all medical device 510(k) submissions, and is voluntary for De Novo and PMA submissions [148]. Companies whose businesses revolve around SaMD or devices embedding software must be aware of the cybersecurity requirements of eSTAR's latest version (STAR v5.0) [149]. These include, amongst many others, risk management assessment and report, cybersecurity testing, and Software Bill of Materials – a list of all the open source and third-party components present in a codebase, as well as the licenses that govern those components, the versions of the components used in the codebase, and their patch status [150].

Artificial Intelligence

The exponential growth of AI-based devices in MedTech raises the question of whether the particularities of AI warrant any specific regulatory treatment. As explored in chapter 2.5.1.2, broader legislation such as the EU's AI Act and President Biden's Executive Order on Safe, Secure, and Trustworthy Artificial Intelligence (US) aim at setting expectations and some limitations to the use of AI by different sectors of the society and industry. For (US) regulatory purposes, however, the FDA is yet to establish a clear pathway for the evaluation of AI in medical devices, though many efforts are being put in that front.

The FDA is working on finalizing a guidance tentatively titled "Marketing Submission Recommendations for A Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions" (AI/ML-PCCP draft guidance) [151] and drafting a guidance tentatively titled "Artificial Intelligence/Machine Learning (AI/ML)-enabled Device Software Functions: Lifecycle Management Considerations and Premarket Submission Recommendations." While in draft, and therefore not for implementation, the AI/ML-PCCP draft guidance may be of interest to MedTech companies to review FDA's current thinking on the types of information the Agency would like to review in a predetermined change control plan – that is, the documentation describing what modifications will be made to a ML-based software and how the modifications will be assessed – which can be used to support iterative improvement of devices containing AI. Specifically, Appendix A of the AI/ML-PCCP draft guidance includes questions on how developers manage data, re-train the model, and evaluate model performance. Many of the recommendations regarding the use of data for AI share similarities to that of using RWE to support regulatory decision-making (see section "Real-World Data (RWD) to Support Regulatory Decision-Making" above) in terms of its adequacy and the reliability of its sources.

Companies may also find it useful to search through FDA's list of artificial intelligence/machine learning (AI/ML)-enabled devices [152]. By reviewing submission summaries provided in the FDA's public databases, a developer can review the intended use and indications for use statements, performance testing, and standards that were implemented and presented for the premarket review. As an example of a submission summary found in that list, companies may look at the summary for the AVIEW CAC (K233211) [153] – a SaMD that provides quantitative analysis of calcified plaques in the coronary arteries using non-contrast/non-gated Chest CT scans.

Finally, to try to preemptively adopt good practices in the use of AI/ML to avoid future regulatory hurdles, MedTech companies may look at the Good Machine Learning Practice (GMLP) Principles jointly defined and published by the FDA, Health Canada, and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) in 2021 [82].

IV. Reimbursement

The constant stream of new MedTech technology reaching the market is unprecedented, especially in the way digital health and SaMD can be used to enhance existing procedures and medical device performance. This section focuses on the payment infrastructure to accommodate such new technologies, most of which find no match among existing products.

A company should be strategically aware of reimbursement when designing a new product and developing its business plan [**Jeffery Ryan, Annex II**]. Evaluating reimbursement possibilities helps a company gauge customer purchasing power and more effectively communicate fees, and aids customers in understanding the potential return on investment achievable by using the company's new technology, encouraging provider adoption and boosting investment prospects. National medical coding is used to describe clinical conditions or procedures, and the location of care, primarily for payment purposes. Briefly, the following three types of coding are the most often used in the coverage of MedTech and procedures:

- ICD-10 codes for hospital inpatient claims
- HCPCS Level I (CPT) codes for hospital outpatient and physician claims
- HCPCS Level II codes for products, supplies, and services that are not included in the HCPCS Level I (CPT) codes, including durable medical equipment, prosthetics, orthotics, and supplies.

An innovative solution might not, however, be associated with any kind of code. At that point, the company responsible for that solution will either file for a new code, or find alternative ways to pay for its product. Pursuing the former option – an often complex and slow process [**Pedro Costa, Annex II**] – is not uncommon, and may open avenues of coverage for groups of new technologies.

For more information on Medicare's payment system, companies may refer to the "CMS Guide for Medical Technology Companies and Other Interested Parties" [154] for a summary of Medicare's processes for determining coding, coverage, payment, and other important considerations, and MedPAC's "Payment Basics" series [155] [**Susan Janeczko, Annex II**] that provides brief overviews of how Medicare's payment systems function (e.g., Durable medical equipment payment system and Hospital acute inpatient services payment system). Both resources are available online and are free of charge. [130]

Reimbursement Strategy

Evidence and technology assessment

When pursuing reimbursement from CMS or other payors for a new medical device, evidence plays a critical role. The quality and quantity of evidence furnished can significantly influence CMS's decision-making process regarding reimbursement approval and its terms. Manufacturers must build a comprehensive case showcasing the device's clinical benefits, comparative effectiveness, safety, economic value, and impact on patient outcomes. Robust clinical evidence, reflecting the patient population's characteristics, is essential and typically includes data from clinical trials, studies, and real-world evidence. Manufacturers should anticipate discussions with CMS by considering the demographics of patients in clinical studies, ensuring alignment with the age, gender, and diversity of Medicare beneficiaries. It's crucial to note that FDA authorization is a prerequisite for reimbursement eligibility.

One aspect of note is that in countries like the United Kingdom and Germany (and most of Europe), drug pricing is determined through a health technology assessment (HTA). The goal of an HTA is to evaluate the effectiveness of newly approved MedTech to existing treatment options for a specific condition or disease and guide reimbursement decisions. These

assessments are carried out by independent third parties, often non-governmental agencies, ensuring impartiality. However, in the United States, there is no centralized organization empowered to conduct HTAs or set reimbursement thresholds; the CMS relies solely on assessments from the FDA and its own internal team to evaluate health technology [Susan Janeczko, Annex II].

Real-World Example 7: RelieVRx® (part II)

Leveraging regulatory decisions for obtaining reimbursement as an innovative device [140]

RelieVRx® is a VR-based immersive therapeutic device with an indication to reduce pain and pain interference in patients living with chronic lower back pain (CLBP). The RelieVRx® program was the first VR-based therapeutic to receive FDA breakthrough designation and market authorization for treating CLBP.

AppliedVR, the developers of RelieVRx®, achieved a remarkable feat, working with the CMS to include RelieVRx® in the existing benefit category for durable medical equipment (DME), the first immersive VR therapeutic to follow this strategy to tap into existing payment authority. CMS granted a unique HCPCS Level II code for AppliedVR's RelieVRx® device and published a purchase price, paving the way for reimbursement and adoption of this novel approach to CLBP management. This decision by CMS holds the potential to influence coverage policy with commercial health plans, self-insured employers, and other payors.

The strategy behind including RelieVRx® in DME

The RelieVRx® device is intended for use in the home independent of direct clinician involvement. This is similar to items of durable medical equipment (DME), and this is the existing benefit category AppliedVR pursued. Through the statutory definition of DME, only software IN a medical device (SiMD) but not software AS a medical device (SaMD) would qualify for this benefit category. However, as shown by the assignment of code A9291 and code A9292 (*"Prescription digital visual therapy, software-only, FDA cleared, per course of treatment"*), not meeting the requirements for the DME benefit category does not preclude HCPCS code assignment, though there is not a statutorily defined way for Medicare to pay for items that fall outside this benefit.

This new coding decision positions the RelieVRx® program as the first digital therapeutic to be integrated into an existing benefit category. Fulfilling all five of CMS' requirements for DME categorization allows a clearer path to Medicare coverage eligibility, thereby influencing wider commercial coverage. The official DME determination from CMS clarified their reasoning: *"The medical software and the device on which it is housed are so integral to each other that we consider them to be one whole device, not software and a separate device."*

The regulatory decision that made this possible (see *Real-World Example 3*)

A VR headset is essentially a head mounted computer system that displays visual data in an immersive 360-degree format. It was critical that the RelieVRx® device be configured and tested to meet the requirements for a medical device used in the home and the definition of DME. This included modification of the operating system to be gaze-based instead of controller operated, the addition of a patented shield to capture breath and incorporate it into the patient experience, and testing to ISO 60601 electrical standards for medical equipment in the home. Additionally, the FDA authorization included special controls specific to its use as a medical device.

Identifying existing payment pathways within CMS

Companies should ask themselves the following questions to ensure that they understand how best to tap into existing payment pathways within CMS [140]:

1. What is the location of care, and what is the predominant payment type in this setting?
2. What products are similar in nature and how have they been treated by CMS?
3. What are the statutory requirements for this benefit category, and does the company's product meet them? If not, can a product modification or regulatory approach remedy this?
4. What is the application process and timeline for the code application?
5. What are the evidence requirements for the application?
6. How will pricing be determined in this pathway?

MedTech companies should consider performing a market study at the start of product development. By talking to potential users of the new technology (e.g., providers) across geographical regions of interest, a company may assess how their solution is to be used and how receptive to the new product these different geographies are. Based on that expected use and receptiveness, a company is able to assess whether or not reimbursement is possible. This will allow the company to build a strategy around receiving reimbursement, and in the case that reimbursement is not possible, find alternative ways to sell the product or even pivot the initial idea [Jeffery Ryan, Annex II].

Obtaining reimbursement for innovative technology

The digitalization of MedTech has brought to the market a variety of software and data-centric medical devices. As is the case with regulation, payors have put mechanisms in place to evaluate emerging technology, though at a slower pace than the former. The CMS has been working with Software in Medical Devices (SiMD) for a while now, but some confusion still arises from SaMD standalone coverage due to its lack of “tangibility” – it seems to harder to justify coverage of a product that has not undergone manufacturing, and that is a product of R&D and Intellectual Property alone [Susan Janeczko, Annex II].

For practical examples on the most current rulings on innovative medical device coverage, companies should refer to Inpatient Prospective Payment System (IPPS) Final Ruling [156] and Outpatient Prospective Payment System (OPPS) Final Ruling [157] documentation [Susan Janeczko, Annex II]. These documents provide the most current information on matters such as New Technology Add-on Payment (within IPPS) and New Technology Ambulatory Payment Classification (within OPPS), as well as rulings on more traditional reimbursement matters.

New Technology Add-on Payment

In general, to qualify for New Technology Add-on Payment, a new technology or medical service must demonstrate that it is a substantial clinical improvement over technologies or services otherwise available, and that, absent an add-on payment, it would be inadequately paid under the regular diagnosis-related group (DRG) payment. In addition, certain transformative new devices may qualify under an alternative inpatient new technology add-on payment pathway by demonstrating that, absent an add-on payment, they would be inadequately paid under the regular DRG payment [156]. A medical device designated under FDA's Breakthrough Devices Program that has received marketing authorization as a Breakthrough Device, for the indication covered by the Breakthrough Device designation, may qualify for the new technology add-on payment, as was the case with the following examples.

Real-World Example 8: Coverage for the Canary Tibial Extension (CTE) With Canary Health Implanted Reporting Processor (CHIRP) System
A system for data collection in the implant to support TKA post-surgical care [156]

The Device: CTE with CHIRP System is a tibial extension implant containing electronics and software. The CTE with CHIRP System collects kinematic data pertaining to a patient's gait and activity level following total knee arthroplasty (TKA) surgery using internal motion sensors (3-D accelerometers and 3-D gyroscopes).

Regulatory Background: CTE with CHIRP System received Breakthrough Device designation from FDA. The Agency granted De Novo classification to the CTE with CHIRP System for the following indication: to provide objective kinematic data from the implanted medical device during a patient's TKA post-surgical care. The kinematic data is an adjunct to other physiological parameter measurement tools applied or utilized by the physician during the course of patient monitoring and treatment post-surgery.

Add-on payment decision: The total cost of the CTE with CHIRP System to the hospital is approximately \$1,654 per knee, which includes \$1,309 for the CTE and \$345 for the Canary Medical Home Base Station. Since the Home Base Station System is intended for use in the patient's home environment and is used to query the CTE while the patient is asleep, the CMS determined that the relevant inpatient costs for the add-on payment would include only the cost of the CTE. The CMS then proposed that the maximum new technology add-on payment for a case involving the use of the CTE with CHIRP System would be \$850.85 for one knee (that is, 65% of the cost of CTE, which is percentual limit for new technology add-on payments).

New code for the add-on payment: Cases involving the use of the CTE with CHIRP System that are eligible for new technology add-on payments will be identified by ICD-10-PCS procedure codes XNHG0D9 (Insertion of tibial extension with motion sensors into right tibia, open approach, new technology group 9) or XNHH0D9 (Insertion of tibial extension with motion sensors into left tibia, open approach, new technology group 9).

Real-World Example 9: Coverage for the EchoGo Heart Failure 1.0 Software Machine learning diagnostic aid software [156]

The Device: EchoGo Heart Failure 1.0 is an automated machine learning-based decision support system for functional cardiovascular assessment using echocardiography, used in the detection of heart failure.

Regulatory Background: EchoGo Heart Failure 1.0 received Breakthrough Device designation and 510 (k) clearance from the FDA with an indication to be used as a diagnostic aid for patients undergoing routine functional cardiovascular assessment using echocardiography. When utilized by an interpreting clinician, this device provides information that may be useful in detecting heart failure with preserved ejection fraction (HFpEF). EchoGo Heart Failure 1.0 takes as input an apical 4-chamber view of the heart that has been captured and assessed to have an ejection fraction ≥ 50 percent.

Add-on payment decision: The applicant provided multiple analyses to demonstrate that it meets the cost criterion for a new technology add-on payment. For each analysis, the applicant searched the MedPAR file – which contains information about inpatient hospital and skilled nursing facility stays that were covered by Medicare – using a combination of Medicare Severity-DRGs and medical diagnosis codes (ICD-10-CM codes) to identify potential cases representing patients who may be eligible for EchoGo Heart Failure 1.0. Based on the analyses, the anticipated cost per patient for EchoGo Heart Failure 1.0 was \$1,575. According to the applicant, the EchoGo Heart Failure 1.0 is charged on a per patient basis with no monthly subscription to the hospital. The CMS then proposed that the maximum new technology add-on payment for a case involving the use of EchoGo Heart Failure 1.0 would be \$1,023.75 (that is, 65% of the average cost, which is percentual limit for new technology add-on payments).

New code for the add-on payment: Cases involving the use of EchoGo Heart Failure 1.0 that are eligible for new technology add-on payments will be identified by ICD-10-PCS procedure code XXE2X19 (Measurement of cardiac output, computer-aided assessment, new technology group 9).

New Technology Ambulatory Payment Classification

New Technology APCs are reserved for comprehensive services or procedures that are truly new and significant enough to warrant having a unique code under the Healthcare Common Procedure Coding System (HCPCS). The most important criterion in determining whether a technology is “truly new” is the inability to describe appropriately the complete service with a current individual HCPCS code or combination of codes. A service that qualifies for a New Technology APC may be a complete, separate, stand-alone, or it may be a service that would always be billed in combination with other services [158].

It is relevant to note that the OPPS ruling gives special treatment to software as a service (SaaS) procedures. Essentially, the CMS always assigns add-on codes to SaaS procedures, which are then included in payment packages (bundles) for add-on services. That would thus prevent a SaaS from qualifying for a New Technology APC. However, in its latest ruling, CMS has decided to except certain SaaS add-on codes from their general policy of packaging add-on services – namely ones involving SaaS for autonomously analyzing medical images – and describe them as standalone services [159], making them eligible for a New Technology APC. The CMS deemed this appropriate because such SaaS procedures are the same and require the same resources regardless of whether it is furnished with or without the imaging service (i.e., they may analyze a medical image even if it was not examined by a clinician or other agent beforehand). The following is one of these examples.

Real-World Example 10: Coverage for Optellum Lung Cancer Prediction Software Machine learning diagnostic aid software [157]

The Device: The Optellum Lung Cancer Prediction (LCP) applies an algorithm to a patient's CT scan to produce a raw risk score for a patient's pulmonary nodule. The physician uses the risk score to quantify the risk of lung cancer and to determine what the next management step should be for the patient (for example, CT surveillance versus invasive procedure).

Codes associated with the Optellum LCP technology

CMS assigned CPT codes 0721T and 0722T to APC New Technology 1508 (New Technology—Level 8 (\$601-\$700)) corresponding to Optellum LCP.

- *Code 0721T:* Quantitative computed tomography (CT) tissue characterization, including interpretation and report, obtained without concurrent CT examination of any structure contained in previously acquired diagnostic imaging
- *Code 0722T:* Same wording, but “...obtained with concurrent CT examination...” rather than “...obtained without concurrent CT examination...”

Being independent from a concurrent CT examination validates Optellum LCP as a standalone service, allowing for it to be paid as so.

FDA’s Early Payor Feedback Program (EPFP) and Parallel Review with the CMS

The FDA’s Center for Devices and Radiological Health (CDRH) established the Payor Communication Task Force to facilitate communication between device manufacturers and insurers to potentially shorten the time between FDA marketing authorization and coverage decisions, which may expedite patient access. For that purpose, Payor Communication Task

Force implemented the Early Payor Feedback Program (EPFP) and Parallel Review activities [160].

The EPFP allows medical device manufacturers to obtain payor input on clinical trial design or other plans for gathering clinical evidence needed to support coverage decisions, especially for novel devices that do not have clear coverage pathways. Manufacturers who are developing devices which may be first-of-a-kind PMAs, or De Novos, including Breakthrough designated devices (see section III of this framework), are encouraged to contact the EPFP, as their devices may benefit the most from the program. The CDRH recommends manufacturers contact the EPFP when they are planning their pivotal clinical trial, or even sooner. Coverage organizations willing to meet with manufacturers include major private insurers such as Aetna, BlueCross BlueShield Association, and United Healthcare.

Interactions supported by EPFP have either validated the manufacturer's initial approach or prompted adjustments to study designs. These adjustments may involve incorporating additional endpoints, modifying patient inclusion/exclusion criteria, expanding clinical trial sites, collecting health economic data, and capturing real-world data, among other modifications [160].

The Parallel Review activity builds on top of the EPFP. After a manufacturer goes through the EPFP and incorporates regulator and payor feedback, the FDA and CMS will concurrently review (“in parallel”) their submitted clinical trial results in Premarket Approval application (PMA) or De Novo classification request. Preference for enrollment in Parallel Review is given, among other factors, to devices that addresses the public health needs of the Medicare population (and the request for Parallel Review includes an explanation of how).

V. Business Model and Strategy

As explored in chapter 2.5.1.4, the MedTech industry's business models are influenced by healthcare sector dynamics and accelerated by digitalization. To address challenges such as care shortages and system inefficiencies, MedTech companies have devised monetization strategies like pay-per-procedure, leasing, and subscription models, empowering providers to control costs. Some also offer refunds for unmet objectives or reduced prices tied to successful outcomes. In addition, by combining devices, data, and software into end-to-end solutions, MedTech firms are able to address clinical and economic needs across the continuum of care, fostering enduring relationships with consumers and creating mutual benefits. Leaning more into the digitalization of the sector, digital business models, focusing on technology-driven products and services to engage patients and inform providers, are gaining traction within the MedTech industry.

Setting expectations about business and investment as a small business

Recent studies show that of the 15,500+ MedTech companies that are actively operating in the US, over 90% are either pre-revenue or have no revenue at all. Close to 80% of MedTech companies have fewer than 20 employees, with a mere 130 companies reporting revenues of \$100M or more [4]. Given the preponderance of small, early-stage MedTech businesses across the industry, it is important to go over some important business and investment considerations particular to that group.

Amongst emerging MedTech companies, perhaps the biggest cause of failure lies in not setting proper expectations when it comes to resource expenditure [Jeffery Ryan, Annex II]. From its inception, a company must evaluate all relevant dimensions of its business (IP, Research, Regulation, etc.) that will require the use of resources. Hiring an IP specialist, conducting clinical trials, implementing QS systems – these are all examples of activities related to putting

a new product into the market that require financial resources. “It always ties back to money” [Jeffery Ryan, Annex II]. Concurrently to defining and (roughly) quantifying potential sources of expenditure, MedTech companies must build their business models and strategies around the financial sustainability of their businesses. On that note, obtaining initial funding constitutes the first step in bringing a business to life.

When looking at the initial stages of a business, venture capital is still the best way for a company to obtain funding. However, the past years have seen considerable hesitation among investors driven by the uncertainty of whether new technologies will be approved, paid for, and/or adopted [4]. *“In the past, investors would ask for upwards of 80-90% of a company which had a promising product still in its very early stages. The funny thing is that investors are now applying a similar valuation to companies with somewhat well-established products”*

[Jeffery Ryan, Annex II]. Companies targeting new markets or with unconventional technologies outside existing coverage policies often need to demonstrate product adoption before reimbursement has been approved, then apply for a new code, and then hope for payer coverage. This process prolongs the path to commercial success and delays exit opportunities for investors [4]. MedTech businesses must be strategically aware of regulatory and reimbursement pathways – explored in the “Regulatory Affairs and Quality and Process Management” and “Reimbursement” sections of this framework – early on, as that will help them define how they should approach investors.

While engaging with potential investors, MedTech businesses should look for a strategic fit with venture capitalists (VCs). Companies interested in expanding their business, for example, should be wary of VCs solely motivated by economic return, especially those with no in-depth knowledge of the MedTech landscape [Jeffery Ryan, Annex II]. An investor with limited understanding of the field may steer a business the wrong way if given enough power in exchange for larger initial funding – which might not be an issue for companies wishing to be sold as soon as possible. Apart from venture capital, alternative modes of financing have been gaining more notoriety amongst MedTech businesses [4], some of which are presented below:

- **Access to public markets via IPOs/SPACs:** Nontraditional IPOs and Special Purpose Acquisition Companies (SPACs) can be used as vehicles for accessing public markets to secure capital at an earlier stage. While not an easy route, IPOs and/or SPACs can give entrepreneurs an opportunity to access a much broader investor pool and generate broader interest – even in the pre-revenue stage.
- **Build-to-buy:** In the build-to-buy model, a strategic investor identifies an early-stage company with a promising product and negotiates investment terms. This involves evaluating the startup's business plan, assisting in product development, and possibly taking an ownership stake in exchange for support and guidance. The strategic retains the option to acquire the company if specific milestones are achieved. Startups may accept lower valuations in exchange for financing and developmental assistance. This model offers strategic investment security and reduces competition for the product. While gaining traction, engaging strategically in negotiations requires effort and coordination, though equity investments from venture funds often play a role in this approach.
- **Family offices:** Family office investment groups tend to be less formal than VC funds, are often mission driven, and are usually run by independent families. Furthermore, they may not be limited to exit timelines like traditional venture capital funds. Family offices usually have specific interests in certain therapeutic areas and can often offer functional expertise to the entrepreneur – sometimes by taking a controlling stake and/or board seats.

Creating value-based partnerships

As discussed in chapters 2.2.2 “Value partnerships between providers and industry” and 2.5.1.4 “Business Model and Business Strategy”, the optimal solution a MedTech company can offer is able to both alleviate financial struggles within the system and offer improvements in the quality of care – be it directly, via more specialized products, or indirectly by optimizing existing procedures. These two dimensions can be referred to as Monetization and Offering [109]. Companies that succeed in addressing such dimensions benefit from a continuous revenue stream, long-term partnership and cross-selling opportunities irrespective of the provider budget situation. Leveraging Monetization and Offering may be of especial interest for companies whose solutions are not reimbursable, as providers and clients under budgetary constraints may be less willing to adopt such solutions in “standard” dealings (see *Real-World Example 11*).

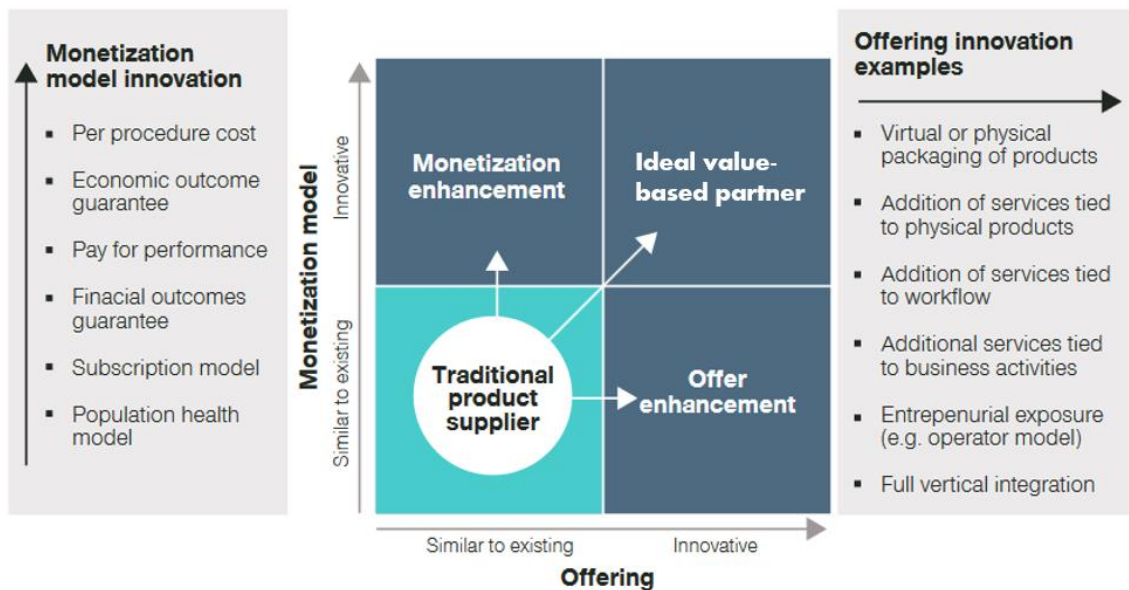


Figure 13. Using Monetization and Offering to build Value-based partnerships with providers.

Monetization models can be used to allow providers to more closely monitor their expenses and/or help reduce provider hesitancy in the use of a new solution by sharing some of the financial risk. The following are some of the most popular monetization models being used in the industry:

- **Medical device leasing:** leasing medical equipment is gaining popularity as a way to reduce the upfront cost of buying equipment outright. Some leasing agreements support ongoing maintenance and upgrade costs. Lease agreements may also assist with equipment return at the end of the lease term, making upgrading fast and easy.
- **Subscription:** also applicable to physical devices, subscription-based models are popular among SaMD developers. Providers are able to access digital services (e.g., a nodule detection software tool for chest CT analysis) and pay for them on a monthly basis.
- **Pay-per-procedure:** a simple yet effective model in which a provider only pays for the uses of a device (e.g., the laser for laser vision correction procedures) or service (e.g., number of medical images analyzed by a SaMD).
- **Pay-for-performance:** in these kinds of deals, companies may offer refunds to providers when the use of their product does not meet specific clinical or economic objectives, or may agree to reduce price point in exchange for a financial upside when

providers achieve a successful outcome using their product, taking some of the financial risk upon themselves.

Pay-per-procedure and pay-for-performance models and their variations are becoming increasingly popular within the industry as capital sales become rarer and providers are expected to improve their outcomes to satisfy mounting patient needs and payer requirements [Pedro Costa, Annex II]. Companies should expect a rise in value-based contracting, as it is already seen in other sectors. For example, the EY Health Outcomes Platform is a tool designed to facilitate value-based contracting at scale in the pharmaceutical industry by helping stakeholders simplify and streamline data capture and management whilst providing organizations the flexibility to create their own contracts and determine the requirements for measuring success.

Real-World Example 11: Interventional Systems' Crawl, Walk, and Run approach Incorporating client input and promoting flexibility in initial deals

As discussed in **Real-World Example 2**, Interventional Systems (IS) is best known for its flagship product Micromate™, a robot for small medical interventions that disposes of proprietary planning and navigation software. Most of IS' partners are strategics, which purchase licenses for the use of Micromate™. Through those licenses, strategics are able to address gaps in their portfolio without having to invest in technical know-how and manufacturing facilities.

IS' business model is based upon the Crawl, Walk, and Run approach, which has allowed the company to create long-standing relationships with many of its clients in spite of its product not being reimbursable. The approach – namely the Crawl and Walk steps – incorporates important value-based elements, including addressing clients through modifications to the base Micromate™ product and allowing clients to test the solution “with no strings attached”.

1. Crawl – Clinical Testing

Prospective partners reach out to IS with interest in Micromate™. IS discusses features of interest with the prospective partner and starts a co-development process. New features to be added to the base Micromate™ product (be it on the hardware or software) are analyzed for the value they may bring and subject to regulatory scrutiny.

2. Walk – Early Commercialization

During this phase, prospective partners can test the solution in a real-world scenario to ascertain its impact on cost-savings (or other metrics of interest), as studied in the Clinical Testing phase. Prospective partners pay a fee on a periodic basis and are free to drop out at any time. They may also provide IS with feedback on the functionality of the product, leading to adjustments.

3. Run – Close Deal

Once the test period is over and the prospective partner is satisfied, a partnership is solidified, and the now partner buys a license for using the solution (which entails more requirements, such as minimum investment according to the partner's size).

Complementary to Monetization, companies should strive to provide more holistic solutions to the needs of patients and healthcare providers. To achieve greater success, a company's Offering should go beyond the selling of a product and include services and accessory tools to address a medical condition or clinical gap as a whole. These can be as simple as providing users of a device with questionnaires to monitor their satisfaction levels, prompting changes to the original device based on their outputs, or as complex as extending the functionalities of a software tool to evaluate more aspects of a disease based on the same input. In view of the lack of digital

resources within healthcare institutions, which look at the industry for solutions [Markus Neuer, Annex II], companies should leverage emerging technologies to create integrated solutions, coupling hardware and software, data analytics, remote connectivity and more. *“The digital transformation must be understood as a far-reaching change, as core medical/nursing processes are being changed. This requires constant support for digital projects with medical/nursing expertise”* [Markus Neuer, Annex II]. The following examples illustrate how real-world companies have implemented tools to facilitate provider workflows and improve patient outcomes.

Real-World Example 12: Medtronic’s UNiD™ ePRO service and UNiD™ ASI platform Supporting spinal surgery through pre-, intra- and post-op services [161] [162]

On March 2024, Medtronic announced the launch of its UNiD™ ePRO service in the US. The service provides spine surgeons with an electronic Patient Reported Outcomes (ePRO) system. The UNiD™ service integrates with a customer’s existing Electronic Medical Record (EMR) system in the hospital and clinic and the UNiD™ Adaptive Spine Intelligence (ASI) platform to provide an unparalleled, seamless experience.

The creation of UNiD™ ePRO service was made possible by Medtronic’s partnership with OBERD, a leading practice intelligence data collection company. According to the company, PROs are an increasingly important part of the perioperative process, providing insights from patients about their health, quality of life, or functional statuses associated with the treatment they received (see chapter 2.2.1.1 for more information). However, achieving top compliance from patients in the filling of PRO questionnaires is extremely difficult without an automated ePRO service like OBERD. The OBERD platform offers improved data collection methods both pre-operatively and post-operatively through integration into the EMR system, increasing patient response rates by 40-60% on average.

Amongst the benefits of the UNiD™ ePRO service, Medtronic mentions enhancing patient experience by engaging them through various channels (e-mail, text, web portal, app) and delivering patient-specific educational materials throughout their care journey. From a provider standpoint, the service promotes the gaining of influence with payers by sharing reports and PRO data on demand.

Medtronic’s UNiD™ Adaptive Spine Intelligence (ASI) platform

UNiD™ ePRO service is only the latest addition to Medtronic’s UNiD™ ASI, a copybook example of integrated solution. The UNiD™ ASI platform leverages data aggregation of thousands of spinal procedures, to plan, execute and analyze processes, creating an iterative virtuous cycle that improves with each procedure. UNiD™ offers:



Figure 14. Medtronic's UNiD™ ASI cycle of services for spinal surgery

- **Plan – Pre-operative services**
 - **Imaging Analysis** of spinopelvic parameters from medical images. UNiD™ is integrated with PACS to streamline workflows.
 - **Case Simulation** using proprietary software to determine optimal surgical strategies based on medical images and surgeon preferences. Each simulation uses artificial intelligence to generate predictive models allowing the surgeon to visualize the postoperative compensatory mechanisms most likely to occur following surgery. The proprietary algorithms also include the latest scientific literature to support decision-making.
- **Execute – Intra-operative services**
 - **Patient-Specific** rods are manufactured based on the case simulation approved by the surgeon.
 - **Case Support** in which rods are aligned with the preoperative surgical plan, eliminating the manual rod bending process and simplifying the rod insertion process — saving valuable time in the operating room.
- **Analyze – Post-operative services**
 - **Data Collection** combined with advanced analytics and visual aids to organize and facilitate access to surgical cases. Multiple output options are available for use in presentations, reports, and clinical studies.
 - **Machine Learning** used to identify correlations and tendencies within the aggregated set of de-identified data. The growing pool of UNiD™ data increases the power of this cognitive insight.
 - **Predictive Modeling** models leveraging machine learning to estimate compensatory mechanisms and to provide decision making support in surgical strategy. The entire UNiD™ ASI system is strengthened with every surgery and iteration.

The newly implemented UNiD™ ePRO builds upon this cycle of services by addressing both pre- and post-operative concerns about a patient's condition and helping inform therapy decisions. Designed to improve the patient experience from intake through recovery, the UNiD™ ePRO may enable patients to recover more quickly, leaving the hospital sooner by minimizing the effects of stress on the body after surgery.

Defining a value-based plan

Borrowing Medtronic's seven step VBHC framework presented in "Medtronic's VBHC framework", companies that wish to pursue value-based partnerships with providers should follow a plan that will allow them to clearly define the condition and patient group they wish to tackle, relevant outcomes to address, time-frame for the evaluation of the product, and the determination of baseline and target outcomes, prior to proposing a value-based contract. Companies should work with providers in the definition of patient groups and target outcomes (both clinical and financial) to ensure that patient's and provider's needs are properly addressed. The plan has especial value for companies that have recently introduced a new product to the market and are looking for ways to build trust with providers.

A Company's Implementation Plan for a Value-Based deal (Product example: antibacterial envelop for pacemaker implants)

1. <i>Selection of a disease or condition</i>	The company chooses a broad condition based on its product portfolio. <i>Example: Cardiac arrhythmia</i>
2. <i>Development of patient cohorts based on risk and protocols</i>	The company narrows down the condition to a significant cohort of patients. Keeping the scope too broad will demand too many metrics to be analyzed, while keeping it too narrow may not be attractive to providers due to overall less significant economic or clinical impact. <i>Example: Patients undergoing a cardiac electronic device implant at high risk of infection.</i>
3. <i>Definition of outcome measures meaningful to patients</i>	The company should discuss this with providers and patients themselves. Apart from clinical outcomes, PROMs could also be considered depending on the condition. <i>Example: Reduction in device-related infections</i>
4. <i>Definition of a time frame required to achieve optimal outcomes</i>	The company should look at its previous clinical testing of the product to establish a realistic time frame for obtaining improved outcomes. Providers should also be consulted as they might require or expect shorter time frames. <i>Example: 6 months, post device implantation</i>
5. <i>Quantification of baseline outcomes and cost for each patient cohort</i>	The company should work with the provider in establishing a realistic baseline. Relevant data should be provided by the provider for that purpose. Failing to set proper baseline values might impact the provider's perception of improvement in outcomes. <i>Example: 3.6% infection rate in high risk patients. Average of \$50,000 per infection.</i>

6. *Determination of prospective performance and cost objectives*

Again, the company should take into account previous clinical experience and cost projections. Failing to establish realistic values (i.e., overshooting) will likely lead to goals not being met, weakening the relationship with the provider. Conversely, setting overly conservative goals may signal a lack of confidence from the company's part.

Example: 0.4% infection rate with the product utilized.

***Settling on a value-based deal
(Pay-for-performance)***

Figure 15. Proposed implementation plan for a Value-Based deal.

A note on public tenders

Although price-based procurement remains the norm at many organizations, others are adopting a value-based approach – often through tenders – that incorporates total costs and outcomes into the procurement process. “The procurement of surgical tools and disposables seems to be slowly migrating towards the widespread use of tenders” [Jeffery Ryan, Annex II]. MedTech companies should be aware of such procurement modalities, as they may become more frequent in the near future.

An example of tender-based procurement was seen in UniHA's call for tender focusing on peri-operative warming devices in 2019 [163]. The French procurement cooperative comprising 870 public hospitals ultimately selected 3M's proposal, establishing a 4-year contract with an outcome target of maintaining normothermic temperature in 80% of post-surgery patients. 3M faced penalties if its device failed to achieve this specified outcome [19]. Another more recent initiative is RITMOCORE [164], a Public Procurement of Innovation (PPI) project funded by the European Union, addressing the evolution in the treatment of patients using or in need of an implantable pacemaker (PM). The initiative connects medical device manufacturers with public purchases to allow for the exchange of information and co-creation. Solutions that are best able to address the clinical need by leveraging remote monitoring are incorporated by the public sector, regardless of the manufacture's size – a great opportunity for small and medium-sized enterprises (SMEs).

Leveraging new technology

The emergence of new technologies has created opportunities for companies to develop new and effective business models. Artificial intelligence, digital health and robotics are some of the fields that have seen exponential growth in investment over the past years [4]. The Artificial Intelligence healthcare market leads the way, having being valued at \$11 billion in 2021, and being projected to reach upwards of \$187 billion in 2030 [165]. As for the digital health market, the compound annual growth rate from 2020 to 2027 is expected to be an astonishing 28.5% [111]. A niche of digital technology that has also gained prominence comes in the form of wearable devices to gather health data. Alongside telemedicine, these wearables are seen as the two most important trends in digital technologies by many providers [166]. The wearable medical device market is expected to reach \$62.82 billion by 2025, growing at a compound annual growth rate of 18.3% from 2020 to 2025 [111].

Many of the models previously discussed in “Creating value-based partnerships” have risen in response for these new technology trends. With many medical devices reliant on software and artificial intelligence to provide high-value services to healthcare institutions and patients, licensing as a model for SaMD has been gaining traction in the MedTech industry [Robert

Harrison, Annex II] [Franz Möltgen, Annex II]. Such model is extremely scalable and relatively low-cost: expenses mainly come in the form of expanding the company’s cloud infrastructure (as explored in “Marketing and Stakeholder Strategy”) and dedicating personnel to deal with licensing deals and monitoring (as explored in “Intellectual Property”). The following example of the PeekMed company illustrates some of the benefits of adopting a license-based business model for SaMD products.

Real-World Example 13: PeekMed’s Licensing of SaMD
A sustainable, scalable business model

As discussed in ***Real-World Example 1***, PeekMed provides a software for orthopedic surgery pre-planning. It allows surgeons to study avenues of intervention, and to determine the adequate and best fit implants to be used in the surgery, according to their own measures made on 2D and 3D models of the patient’s imaging exams. Medical implant manufacturers are informed of the specific implant that will need to be manufactured, reducing the need for stock.

PeekMed’s sales are based on licensing either directly to providers (hospitals or individual physicians) or to intermediary companies. Regardless of the stakeholders to which they sell, the business model remains the same, as it is based on the licensing of their platform to be used in a customer’s computer(s) or mobile device(s). As PeekMed’s CEO João Ribeiro puts it “*more clients just means more licensing deals*”, with PeekMed’s software being deployed through the cloud in the same way as it was with fewer clients – granted, the cloud capacity must be increased. This flexibility greatly increases the range of clients they may have, and allows the company to leverage the sales forces of intermediary companies to reach healthcare providers, potentially capturing new clients.

6. Case Study: Adapttech Prosthetics LTD

This chapter aims to analyze Adapttech, a young MedTech company whose business is heavily based on innovative, data-centric solutions, through the lens of the framework presented in chapter 5. The insights gleaned from this assessment are meant not only to highlight Adapttech's current standing on industry best-practices but also offer strategic recommendations for future growth and development. The company is well acquainted with the Stanford Biodesign framework and adopts many of its recommendations; thus, in this chapter's assessment one can see where, in practice, the original Biodesign framework falls short within the modern MedTech context, and how incorporating the Updated Framework addresses (or could address) such shortcomings.

All the information below that pertains to Adapttech has been discussed with either the company's CEO or other employees at management positions.

6.1. The company

Adapttech is a UK-based MedTech company with solutions revolving around medical devices and data analytics, with its focus being to generate data-based actionable outcomes for the O&P sector. The company comprises 15 employees distributed across the functions of CEO, CTO, CDO, Clinical Manager, QA & RA manager, Engineering Manager, Operation Manager, Marketing Manager, HR Business Partner, Full-stack/Software Developer, Biomedical Engineer, and Admin Support/Office Manager. As is typically the case with smaller companies, multiple functions may be performed by a given individual within the company.

Adapttech has a well-established Product Lifecycle Development plan which lays out the expected activities to be performed throughout different "Stages". Such Stages range from product conceptualization to product development, and post-market surveillance. The Adapttech Product Lifecycle Development plan incorporates features of the original Biodesign framework.

Adapttech's Motio StepWatch™

Adapttech's flagship product in the Motio StepWatch™, a remote monitoring device designed for lower-limb prosthetic users that analyses patients' real-world daily activities, providing insightful reports, and supporting clinicians in the functional level (K-level) decision process.

Motio's hardware is built upon the clinically approved and FDA-listed Modus Health StepWatch 4 (hardware and firmware), which has been validated in a broad range of research activities as being able to accurately measure the event of a step. In addition to the hardware, Motio StepWatch™ is powered by the Motio App, a web application accessible in the clinician's PC or mobile device.

The device tracks patients' daily activities for periods of time and, upon visiting a clinician's office, the monitoring information pertaining to the last period of measurements is sent via Bluetooth to the clinician's PC or mobile device where the MotioApp is opened. MotioApp then combines the data collected by the Motio device with answers from a questionnaire to access the etiology of limb difference, including information about a patient's sex and age, to perform an analysis of a patient's activity level. The clinician is then able to download a report detailing the patient's activity level and other measurements (e.g., energy expenditure during gait). The report assigns each patient an activity score between 0.5 to 4.9, which is used to indicate whether a patient should be assigned a new K-level. K-levels are a rating system from 0 through 4 (at integer steps) that indicates a person's potential to use a prosthetic device if they had a

device that worked well for them, being used as the main piece of information to guide reimbursement decisions for lower-limb prostheses.

In addition to generating reports based on off-clinic activity, MotioApp also displays instructions for clinicians and patients on how to perform in-clinic activity tests traditionally used for assessing K-levels.

6.2. Concept Generation and Screening

The three initial stages of Adapttech's Product Lifecycle Development – Idea and Research (Stage 1), Concept Stage and Review (Stage 2), and Design Input (Stage 3) – pertain to the conceptualization of a new solution and the definition of its features.

Adapttech already implements many of the practices discussed in section I of the proposed framework. At the very beginning of its Idea and Research Stage, Adapttech conducts semi-structured interviews with relevant stakeholders identified through preliminary market, technology and economic research to establish a Feasibility plan. These interviews serve a very similar purpose to the “market studies” discussed in the framework, as they help determine the interest and potential applicability of a newly-conceived product amongst end user stakeholders. Adapttech also implements similar interviews further along the conceptualization phase of the product to define or modify design requirements based on stakeholder inputs, helping ensure that stakeholder needs are addressed. As the company grows, performing more structured and overarching market studies – ideally through a third party – would be advisable, as these tend to reduce bias towards pre-conceived ideas, and even garner preferences not observable in smaller stakeholder groups.

More specifically on matters concerning data, the company is aligned with some of the best practices defined in the proposed framework. When defining a project scope, Adapttech sets high-level requirements for the sources and format of data they intend to work with, as well as the necessary infrastructure to support its processing. As Adapttech's Motio StepWatch™ currently stands, the data used by Adapttech in the creation of the reports comes from two sources: questionnaires to assess the etiology of limb difference in patients and monitoring data (step events across periods of time). If Adapttech thinks of including new sources of data in the analysis of a patient – for example, data collected from the Limb Loss and Preservation Registry – it must first evaluate the feasibility of converting that new data into a format that can be processed alongside data formats that are already utilized by the company. Moreover, if Adapttech intends to implement more complex ML tools into its solutions, the company must ensure that there are enough and reliable sources of data for the training, testing and validation of models beforehand, as to avoid investing in features that will not be able to provide relevant or trustworthy results.

Another important matter for Adapttech to consider at concept screening as per the proposed framework, is how scalable their infrastructure to support the digital solution at hand can be. Adapttech's current cloud infrastructure is based on Microsoft's Azure (public cloud). The company should do a preliminary evaluation of whether such infrastructure could support an increase in traffic, and how burdensome the transition to another infrastructure (either to a private cloud or another more appropriate public platform) would be, as a way of avoiding problems or unexpected spending down the line. These concerns become more intricate if Adapttech opts to implement complex ML tools, requiring more potent cloud infrastructure for training models (see section I of the proposed framework for considerations about cloud).

Finally, Adapttech's current effort to integrate results from Motio into OPIE – a leading platform in providing electronic health records, workflow, billing, and practice management solutions to O&P facilities worldwide – is a prime example on how to address convenience, a

key point of interest for providers concerning digital solutions (as seen in section I of the proposed framework). Interoperability and integration concerns such as this one should always be implemented at concept generation by Adapttech, as that will guide their development process towards more convenient, appealing solutions.

6.3. Intellectual Property and Legal Affairs

Adapttech's practices in regard to IP are well aligned with those in the proposed framework. Firstly, Adapttech's management has a good understanding of IP affairs, being involved in the search of claims and assessment of FTO at the initial stages of concept generation (IP registration is explicitly cited in their Product Lifecycle Development plan already at Stage 3, right after more detailed product requirements are defined). In accordance with section II of the proposed framework, the company's management views their involvement with IP matters as way of improving process efficiency (operations and cost). Adapttech also periodically interfaces with a major IP firm to validate its own IP strategy.

Adapttech's Motio StepWatch™ hardware/firmware are already protected (patented) by another company, Modus Health, which conceded an exclusive worldwide license to Adapttech in the use of their StepWatch hardware and firmware for prosthetics. As for proprietary algorithms used in the processing of data and generation of reports, Adapttech keeps them as trade secrets. Amongst the confidentiality measures used by Adapttech, the company shares some of what is presented in the proposed framework (section II): the software is cloud-based, meaning that the source code is not fully available on-site; all employees must sign NDAs; and access to more sensitive information is kept under restricted access (i.e., especial credentials are required).

Adapttech's current handling of IP is satisfactory in view of what is presented in the proposed framework, but may warrant some changes as the company grows. As Adapttech considers exploring new products and business avenues, it is crucial to have support from specialized IP professionals at the early stages of product conceptualization. This counseling, which can come from a less costly patent manager, rather than an attorney (as discussed in section II of the proposed framework) will help the company identify opportunities and address challenges in matters such as the combination of Adapttech's products into more powerful devices – an interest that has been expressed by the company – and even a potential departure from the Modus Health hardware as new technologies reach the market. Moreover, as the company gains more visibility and the number of employees increase, new avenues of protection for software should be explored as alternatives to trade secrets.

6.4. Regulatory Affairs and Quality and Process Management

The proposed framework recommends the use of standards – especially the ones recognized by the FDA – to ensure regulatory compliance and smooth operations. Adapttech is aligned with the framework, being compliant with a couple different standards, from generally applicable (e.g., ISO 13485 Quality management systems and ISO 14971 Risk Management) to more specific to their product (e.g., IEC 62304 medical Device software and EN 60601-1 Safety and performance of medical electrical performance), all of which can be found in the FDA Recognized Consensus Standards database. Another point of alignment between Adapttech and the framework is the involvement of the company's management in regulatory matters, actively monitoring product development to ensure compliance and mitigate risks. A Risk Management plan is established right at the beginning of the company's Product Lifecycle Development plan, being updated as product requirements are defined; beyond that, each stage of the Product Lifecycle Development plan has one or more risk and/or safety assessments.

The pitfall in Adapttech’s regulatory strategy as per the proposed framework is the company’s lack of formal measures concerning cybersecurity. The company does not follow any type of cybersecurity standard, and is yet to understand the FDA’s most recent requirements pertaining to cybersecurity. Adapttech’s main source of cybersecurity guidance comes from security updates on (code) external dependencies, which are displayed in IDEs used by the company’s software developers, or highlighted in GitHub. Apart from that, software developers apply “common sense” rules based on their previous experiences. The company has mentioned cybersecurity as one of the factors justifying the use of their current cloud infrastructure (namely, Microsoft’s Azure good level of protection against DDoS attacks and other threats), and has participated in a recent cybersecurity webinar.

As a business focused on data analytics and interconnectivity, having robust cybersecurity strategy – and explicit mention of it in the Product Lifecycle Development plan, as is the case with the “EMC & Electrical safety testing” step – is key to ensuring regulatory compliance for future products and establishing trust with product users. Following some of the suggestions presented in the proposed framework, Adapttech should start by going over FDA guidance documentation on cybersecurity matters discussed in section III of the framework, including the cybersecurity requirements of the eSTAR Program for the submission of 510(k) applications. They should also consider looking through the FDA Recognized Consensus Standards Database for specific cybersecurity standards. To stay up-to-date with trending cybersecurity matters in the industry, it would be advisable for Adapttech to interface with organizations such as MDMA – cybersecurity group or ISAC-Health, both of which are discussed in section III of the framework.

On a future perspective, if Adapttech intends to implement more complex AI/ML functionalities for the processing of data into their products, it is important – as per the proposed framework – that they monitor the latest advancements in AI regulation (e.g., the EU’s AI Act). More specifically, the company should go over the draft regulations presented at the end of section III of the proposed framework, as they present matters likely to be considered by the FDA in the evaluation of future AI-based MedTech. For tangible examples on how FDA currently evaluates AI-enabled MDs, the company should go through submitted applications for these types of devices, as discussed in section III of the framework.

6.5. Reimbursement

Adapttech’s Motio StepWatch™ is not reimbursable, as there are no reimbursement codes for monitoring devices in O&P. The company considers filing for a new code not worth it, seeing the process as too long and complex. Rather, they have been thinking of alternatives such as integrating the monitoring functionality into a reimbursable device (e.g., Adapttech’s Motio Vacuum Pump) or trying to associate the product with other fields of use, e.g., monitoring in rehabilitation, for which there are reimbursement codes.

The most important aspect of the proposed framework concerning reimbursement that applies to Adapttech is that the company must define a reimbursement strategy from the outset (see section IV of the framework). There is no explicit mention of a reimbursement strategy in Adapttech’s Product Lifecycle Development plan, even though a Regulatory Strategy – also extremely important for early consideration, as seen in chapter 6.4 – is mentioned at one of the earliest stages of the plan (Stage 2 – Concept Stage and Review). Failing to determine a reimbursement strategy early on – or avenues to compensate for the lack of reimbursement – may severely impact the company’s long-term financial sustainability and discourage early investments from VCs.

In the development of future products, Adapttech could leverage their concept validation interviews – similar in purpose to market studies mentioned in “*Identifying existing payment pathways within CMS*” in section IV of the proposed framework – to more explicitly inform them of reimbursement avenues, including non-obvious ones (see the RelieVRx® example in section IV of the framework; a software-based device that managed to obtain coverage as durable medical equipment). Adapttech should also be aware of FDA’s Early Payor Feedback Program (EPFP) and Parallel Review described in the proposed framework if the company comes up with a particularly innovative solution for which there are no clear coverage pathways in O&P.

6.6. Business Model and Strategy

Adapttech’s current business model is based on B2B sales of reports to clinics, which are generated using the data collected by Motio StepWatch™ hardware. A clinic may purchase a starter pack with 6 reports and a Motio StepWatch™ device, which remains in the clinic’s possession for 1 year. A clinic may extend their access to the Motio StepWatch™ device for another year by purchasing any number of reports, and can request another Motio StepWatch™ device by purchasing a 6-report package. Adapttech deploys its MotioApp application via Web, while the hardware is delivered through a partner in the US. Adapttech aims to integrate the current functionality of the Motio StepWatch™ and report generation into other relevant O&P componentry, selling them to clinics which would in turn sell them to patients (B2B2C model).

Adapttech’s business model has many aspects of the Monetization models presented in section V of the proposed framework. Clinics do not have to commit to the purchase of the Motio StepWatch™ device and have the freedom to either increase or decrease the amount of reports they wish to generate, making them more likely to accept Adapttech’s solution. In terms of Offer models (presented as the “sister” dimension to Monetization in section V), consisting in addressing multiple matters along the care pathway, Adapttech’s plan to integrate current solutions into O&P componentry is on the right tracks – having a functional component (e.g., vacuum pump) also able to measure activity levels and inform report generation will certainly bring more value to clinicians and patients alike.

Adapttech explores another aspect of value-based partnerships that, similarly to some Monetization models, uses product performance to build trust with end-user stakeholders. At the earliest stages of product roll-out, Adapttech reached out to clinicians to test their product, allowing the company to build a database based on Motio data collected from wearers of the device. With a more robust database, Adapttech was able to deliver better performance and demonstrate the validity of their solution to clinicians. The company is currently employing a similar strategy as it considers an expansion to France, Belgium and Australia: The Motio device and the report generation functionality are given for free for clinics of those countries during a trial period – if they are satisfied, they may commit to the purchase of report packages. In addition, trial participants are required to report on the device (ease of use) and on the generated reports (relevant fields and information), as well as provide suggestions on how to introduce the product into the local market.

The aforementioned strategy addresses the rise of performance-based deals discussed in section V of the proposed framework, but it also brings up another important point of value relationships: the incorporation of customer inputs into the products improvement cycles and leveraging product performance to establish trust relationships. Outside of trial periods, Adapttech has asked for users of their reports (clinicians) to evaluate the information and structure of the generated reports, both for a generic report and for reports pertaining to their patients (for the identification of use cases). The inputs of those clinicians were then used to change the kind of information displayed in the report. For determining further functionalities to

be added into their solution, Adapttech consistently asks for clinician input on outcome measures of interest (e.g., walking stability, number of falls) through structured questionnaires and interviews. Patient preference is also included in product improvement cycles, with actual wearers of the Motio device answering questions on whether they understand the purpose of the device or whether they have any complaints regarding the device's bulk or aesthetics.

By including customer inputs on improvement cycles, Adapttech is able to increase its Offer (see section V of the framework) by adding functionalities able to address multiple customer pain points, and to build value partnerships with its clients. The combination of co-creation and performance-based trials used by Adapttech is similar to the business strategy used by Interventional Systems in Real-World Example 11, albeit in that case solutions were much more customizable depending on the client.

In spite of Adapttech's overall alignment with the proposed framework's Business Model and Strategy considerations, recommendations for the future are still applicable. As Adapttech acquires more data, incorporates more customer inputs, and gains more confidence in its product, the company should consider approaching more conservative stakeholders with a value-based plan similar to the 6-step plan presented in section V of the proposed framework. Even though both the plan and "simple" trial periods relieve the end-user stakeholder of financial burdens (as they will incur no expenses if they are not satisfied with the product) a structured plan explicitly sets out the target outcomes for the trial, showing more commitment and confidence on Adapttech's part, and creates the commitment for a deal at the end of the trial if target outcomes are reached, thus allowing Adapttech to secure a client early on (assuming that the company is certain that the target outcomes can be met to begin with).

7. Conclusions and Future Improvements

The aim of this dissertation was to develop an effective framework to support medical technology innovation and objective data usage in healthcare, serving as a practical guide for businesses in the current MedTech landscape.

“What aspects of the Stanford Biodesign framework may warrant additions to better support current MedTech businesses?” was the main research question underlying this Master thesis. A first set of five unstructured interviews was conducted to validate the different dimensions of the Stanford Biodesign framework most significantly impacted by changes in the healthcare sector over the past years, followed by a set of ten semi-structured interviews to further explore such dimensions. In total, fifteen interviews contemplating the dimensions of “Concept Generation and Screening”, “Intellectual Property and Legal Affairs”, “Regulatory Affairs and Quality and Process Management”, “Reimbursement”, and “Business Model and Strategy” – each of which pertain to one or more steps of the original Biodesign framework – were conducted.

The data analysis and findings expanded upon some aspects of the original Biodesign framework still relevant to the current state of MedTech while introducing new considerations for MedTech businesses, culminating in the creation of An Updated Framework for MedTech Businesses. The proposed framework brought insights into many dimensions of modern MedTech, including: The importance of identifying potential data sources and defining a data standardization strategy at the product conception stage (namely for digitally-enabled devices or SaMD); discussion of avenues of protection for software-based products, including copyright and patenting, as well as the impact of open-source software licenses on businesses’ FTO; identification of relevant regulation on real-world data use to support regulatory claims, SaMD regulation, and prospective AI regulation (including how to handle data fed into ML algorithms), as well as ways to facilitate compliance; avenues for obtaining coverage for innovative technologies in the inpatient and outpatient settings, including SaMD and digital tools; and highlighting the importance of Monetization models and the offer of integrated solutions to address multiple steps of an episode of care (e.g., through hardware, monitorization and data analytics) to secure value partnerships with providers as part of a company’s business strategy, just to name a few.

To corroborate the practicality of the Updated Framework for MedTech Businesses, a case study using the proposed framework is presented in this dissertation. In it, the MedTech company Adapttech is analyzed in terms of its alignment with the proposed framework across all its dimensions, with targeted recommendations backed by the framework being addressed to the company.

In this dissertation, findings and recommendations confer limitations pertaining to its qualitative exploratory character, the reduced sample of interviewees and research period. In addition, the last phase of this study would ideally include a feedback round [113, p. 114], where interviewees would be contacted again and presented with the finalized proposed framework. Feedback could further validate the framework as a practical, useful tool in view of stakeholders inserted in the current landscape of healthcare, or potentially address any misinterpretations of their self-reported behaviors and views, leading to corrections and/or refinements. It would also be highly desirable to discuss the Updated Framework for MedTech Businesses with the creators of the original Stanford Biodesign framework – which inspired this thesis in the first place – and current members of the Stanford Biodesign Center (both contacts were attempted). Their input could validate or shed new light on aspects of the original framework that have been updated in the Updated Framework for MedTech Businesses, leveraging, for example, the

knowledge spread across the different programs and courses offered by the Stanford Biodesign Center.

On that note, this study acknowledges the existence of updates to the Stanford Biodesign framework presented in the 2015 book “*Biodesign: The Process of Innovating Medical Technologies 2nd Edition*” by Yock *et al.*, which was the basis of this dissertation. More recent courses and programs at the Stanford Biodesign Center, such as the Digital Health Course, have taken the framework in new directions to address current technological and socio-economic trends. Although these alternatives were not known prior to or during the creation of this dissertation, their existence does not invalidate the framework proposed in this thesis; rather, much of what is discussed in those courses and programs [68] – as per their syllabi, e.g., [167] – validates aspects of the Updated Framework for MedTech Businesses (e.g., the emphasis on real-world, measurable health outcomes, the discussion of emerging digital and information technologies and their reimbursement and regulatory implications, and the handling of data generated by these and other sources). Moreover, since the release of the aforementioned book by Yock *et al.* in 2015, there has not been a piece of widely available literature (i.e., not restricted to courses and programs) to compile and comprehensively frame the Biodesign framework in the current state of MedTech, and thus to provide worldwide guidance on the development of current innovative MedTech solutions, which is the purpose of the Updated Framework for MedTech Businesses.

Future studies could include the perspectives or more diverse stakeholders to derive new insights on the dimensions of the original Biodesign framework explored in this framework, or find relevant best practices pertaining to other dimensions not included in this work. On the general side of innovation, it would be interesting to engage with private payers to better understand the rise of value-based deals, such as pay-for-performance. Leaning into data-centric and digital solutions, engaging with more MedTech companies at the edge of technological innovation, as well as big tech corporations venturing into healthcare, could provide more insights on the optimal infrastructure to support emerging technology, shed light on rising data-centric business models and strategies, and even discuss further challenges in regulation and IP pertaining to new technology (e.g., generative AI).

As a final note, it is relevant to mention that many of the subjects explored in this thesis are extremely new, with some of referenced reports, studies, and documents having been published only a few months to a few weeks prior to the conclusion of this study. This was to be expected given the rapidly changing dynamics of the healthcare sector and the MedTech industry, and was accounted for in limited fashion through the discussion of future trends and relevant resources in the literature review, interview outputs and discussion, and in the Updated Framework for MedTech Businesses itself. Nevertheless, as was the initial inspiration for this dissertation, future studies are encouraged to take a fresh look at the MedTech landscape and to layer upon the considerations presented in this study and in the Biodesign framework, in a continual effort to provide guidance to businesses in the critical industry that is MedTech. Through the updated framework presented in this thesis, I hope to better equip innovators to be successful in the implementation of digital and data-centric solutions, and to show how to leverage the current abundance of data and emerging technologies in the delivery of value to healthcare providers and, ultimately, to patients.

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Annex I: The Future of MedTech – 5G Connectivity

Communication networks provide the infrastructure to facilitate advances in many aspects of digitalization, as it allows data to go where it is intended at the speed at which it is required. 5G constitutes the cornerstone of modern communication technology, not only helping create solutions nowadays, but also offering many possibilities for the future. In an increasingly interconnected medium such as healthcare – where medical devices monitor and act upon patients in remote or ambulatory setting, or exchange information with EHRs and provider electronic systems – rapid, reliable communication technologies such as 5G are a must. Robotics, mobile units, remote care, extended reality – these are all examples of MedTech innovations leveraged by the power of interconnectivity.

5G expands the frequency bands commonly used by cellular networks (typically below 6 GHz) to include high band frequencies between 24 GHz—52 GHz that are collectively referred to as the millimeter-wave [mmWave] spectrum. The addition of the mmWave spectrum allows 5G to accommodate communication channels with significantly larger bandwidths, thus considerably increasing connection throughput. 5G has three distinct use cases which are discussed below [1]:

- **Enhanced Mobile Broadband (eMBB)** provides greater data bandwidth and is intended for cases requiring high data rates across a high coverage area. eMBB improvements help enable applications with intense data transmission demands like 360° video streaming and immersive virtual reality (VR) and augmented reality (AR) applications.
- **Ultra-Reliable Low Latency Communications (URLLC)** has strict requirements on latency and reliability to support mission critical communications, such as remote control of medical devices, industrial automation, and autonomous vehicles. Low latency allows a network to be optimized for processing large amounts of data with minimal delay.
- **Massive MachineType Communications (mMTC)** supports a very large number of devices with reduced data transmission volumes in a small service area, such as Internet of Things (IoT) applications for sensing, metering, and monitoring devices. mMTC is closely linked to the IoT concept and connected wearables

It is important to note that different use cases have distinct quality of service (QoS) features, meaning that 5G-enabled MedTech applications must be designed with a clear purpose in mind. For example, a certain application may necessitate the transmission of large volumes of data, being limited to a single device, while another requires connecting many devices in a certain area at the expense of volume.

Deployment

5G permits flexible network deployment options by facilitating the introduction of 5G features while continuing to leverage existing 4G network infrastructure, which can be achieved by using 5G modules for integration. These modules are provided by several vendors, and enable communication over diverse spectrum bands, and using software to customize the functions of network equipment and dynamically control those functions. 5G standalone (SA) deployments are also a possibility, which means that only 5G network elements are used (e.g., 5G modems). By detaching the network from older 4G infrastructure, the user potentializes 5G features (e.g., lower latency and higher number of devices) but may incur significant costs for establishing a wholly new network.

Private 5G deployments can be done in tandem with other existing wireless technologies. For example, Bluetooth can be used to connect medical devices to patients' and caregivers' smartphones, which in turn connect to the cloud through the private 5G network. A private 5G network or an existing Wi-Fi network can be used to provide connectivity for devices within a hospital, while 5G is used to maintain connectivity when the device is taken away from the hospital. The flexibility of 5G deployment options can help organizations use the wireless connectivity that best fits their needs and the communication requirements of the devices they use while managing the performance and cybersecurity aspects of the chosen scenario.

5G deployments use edge computing to improve connectivity performance for end users, such as reduced latency. This means that data storage and processing unit are placed closer to the "edges", that is, where data is generated and processed. A network-based deployment involves placing computing in cell tower shelters, central offices, or commercial data centers that connect the network equipment and network users. Alternatively, users may prefer a premise-based deployment, where hardware solutions can be installed on a customer's premise and are designed for integration with 5G edge nodes offered by the cellular network provider. This model allows the cellular network to be used like Wi-Fi and is characterized by extremely low latency.

Challenges in the implementation of 5G

There are practical considerations to be kept in mind when deploying or making use of a 5G networks. These are relevant for MedTech companies that wish to implement 5G in their own premises, or that expect providers/clients to dispose of a well-established 5G network for the proper functioning of their solutions.

Supply Chain and Cost

The limited supply options for 5G modules for integration in existing infrastructure compared to common wireless technology can significantly raise the cost of using 5G [1] [2]. Alternatively, companies might consider the direct implementation of 5G modems into their devices. However, that option can incur increased design and development costs. Additional costs are associated with certification tests to deploy devices on a 5G network, costs of deploying 5G networks by service providers, and the actual cost of obtaining 5G service by users. The rising adoption of 5G across industries may lower the costs of 5G integration in medical devices.

Finally, the rapid evolution of 5G technology may outpace medical device lifecycles, meaning that continuous effort and resources may have to be put in the modification of medical devices to accommodate for newer communication technology.

Network Coverage

Depending on the geography whereupon a 5G-device is to be deployed, there may be limitations in the available 5G spectrum. Applications requiring a densely populated radio access network, such as those requiring extremely low latency and high reliability (e.g., remote surgery robotics), may be initially restricted to urban areas where small-wave-length cells can be deployed economically [1][3]. Similarly, solutions meant to be deployed in hospital campuses need to account for the complexity of such environments, securing connectivity in a variety of indoor and outdoor settings ranging across multiple buildings, and rooms with shielded walls.

Evaluation Methods for 5G-Enabled Device Functions

5G-enabled medical devices, like all devices connecting to a 5G network, must obtain a series of approvals prior to being allowed connection. In the US, all 5G user equipment (UE) need market grants from the Federal Communications Commission (FCC) in addition to certification testing [1]. UE is also subject to testing from mobile network operators.

Though 5G UE certification provides evidence supporting that a 5G-enabled medical device can operate on a 5G network, the existing testing methods are not designed to address the safety and effectiveness concerns for 5G-enabled medical device functions regarding network-specific risks such as packet loss, communication delay, and link disruption, especially considering some of medical devices' unique data patterns. This could mean that even 5G-enabled medical devices that have gone through the certification process may be taken with caution by consumers (e.g., providers), mainly when dealing with higher risk class devices.

To add to that, there is considerable delay in the creation of certification tests for new features introduced into 5G UE solutions, which could leave early technology adopters with an unclear path to certification in the first place.

Impact on cellular device performance

One drawback of 5G technology is its impact on cellular devices, as it accelerates battery depletion and shortens their lifespan. The high-speed 5G connection on mobile devices leads to substantial power consumption, resulting in reduced battery life – a considerable problem for remote monitoring devices. To mitigate these challenges and safeguard battery performance, manufacturers are compelled to invest in advanced battery technologies [2][3].

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Annex II: Interviews

Table II-1. Unstructured interviews: interviewees' profiles, key lessons learned and recommendations. shared in the interviews.

Category	Contact Person Position, Institution	Main Takeaways
General	João Claro Chairman and CEO, INESC-TEC	Driving forces of MedTech - The driving forces of the MedTech industry are many, and may vary greatly geographically. Generally, there have been a series of technological waves that create opportunities for innovation: blockchain, cloud, data analytics. Factors external to technology include economics to support innovation (e.g., venture capital investment). Barriers to digitalization - There seems to be a traditional distance between health sciences and the digital medium, with the two starting to get closer to one another, especially after the COVID-19 pandemic. - The economic organization of healthcare is based on older interactions. There is considerable inertia in the change of the economic landscape with digitalization. The Biodesign framework - The original Biodesign framework is still far from obsolete; in fact, few organizations follow it to a satisfactory/efficient extent. Products with simpler digital components are easily framed within the original model (MedTech products usually have some kind of digital component to them). - However, emerging technologies, their associated risks and their capacity of growing rapidly in unregulated environments are matters that, in conjunction, warrant a revision from the original Biodesign. Namely, data- and AI-driven solutions have very particular characteristics, and should require additional instructions complementary to the original framework. Concerns about the interpretability of such tools and associated provider adoption, as well as data collection concerns, are some of the factors to be considered. - In terms of IP, software-based, digital and hybrid MedTech products may be generally harder to protect. Nevertheless, There are many avenues of protection, and one must choose an adequate one. Infrastructure and associated new players - Cloud technology in an absolute necessity in all sectors to support digital innovation, including in healthcare. Public clouds are almost unparalleled in the compliance of their services with requirements of particular industries, including MedTech. - All players involved in the deployment of necessary infrastructure for digitalization in other industries will become relevant players in MedTech. Cloud providers, application gathering platform's (such as Apple's AppStore), and telecom companies (wireless technology providers) are examples of such new players that must be interacted with.

Concept Generation (Provider Insights)	Dr. Lea M. Dijkman Epidemiologist and Senior Advisor/Researcher at the department of Value-Based Healthcare, St. Antonius Hospital (part of the Santeon network)	About Santeon - St. Antonius hospital is part of the Santeon network, consisting of 7 independent hospitals working together to improve patient outcomes and achieve economic efficiency. Santeon corresponds to 11% of Dutch hospital care in volume. It is one of the most experienced organizations in health data sharing worldwide. VBHC and the use of data within Santeon - Providers universally suffer with a lack of money. Often, prior to looking to a new solution, it may be more intelligent to analyze data and find ways to optimize the cycle of care by removing unnecessary (and costly) steps. - Within its network, Santeon benchmarks 30+ conditions. It uses real-world data collected from procedures across the different hospitals (e.g., rate of post-surgical infection) in improvement cycles (i.e., define optimal procedures and medical equipment to use). - Clinician- and Patient-Reported Outcome Measures (CROMs and PROMs) as well as Patient-Reported Experience Measures (PREMs) are extremely relevant to the evaluation of procedures and medical equipment performance. Their choices of CROMs, PROMs and PREMs are based on ICHOM sets. For patient-reported measures, questionnaires are mostly delivered digitally to facilitate adhesion. Requirements and Challenges for using data to support clinical decisions - Data must be clean and complete. Doctors must trust the data; if the methods of data collection are not clear and the data robust, doctors tend to question what the data tells them. - The case-mix must be considered. In the Santeon network, variables are presented as collected, and so is the case-mix of each institution. An analysis is then performed to correlate outcomes with case-mix. - Data needs to be mapped to common standards, as hospitals have different electronic systems. - Perhaps the biggest hurdle: data security. The collection of data must account for privacy concerns. Only the strictly necessary patient data must be used and shared (data minimization), and the anonymization/pseudonymization of patient must be performed. Acceptability of data-centric and digital solutions - The collection of data by healthcare workers should not be extensive, as it becomes dull/overwhelming and eventually leads to data collection being neglected. For example, in St. Antonius they do not cover all measures established in ICHOM sets due to their sheer volume, opting to focus on the most relevant ones. - Devices, apps or platforms meant to interact with patient information must be integrated into the hospital's electronic system. If integration is not possible, accessing an external platform from the hospital system should be a seamless transition, otherwise doctors will likely dismiss it.
Concept Generation (Provider Insights)	Dr. Jos Hendriks Clinical Data Analyst and Epidemiologist, Santeon Ex- Clinical and Scientific	Provider's lack of in-house digital solutions - Hospitals are severely discouraged to develop digital solutions due to high costs with personnel and regulatory pathways. They look at external solutions to cover their needs. Primary and secondary use of data - Data for primary use pertains to health data used in the clinical setting itself. Regulations and standards tend to work faster and have less requirements, as information needs to flow quicker to produce changes in operations

	Affairs Manager, Philips	• Data for secondary use pertains to research (e.g., including the validation of AI models). Secondary use often require Metadata catalogs, which make the health data used traceable • Real-world data is highly valued for both primary and secondary uses Requirements and Challenges for using data to support clinical decisions • Data must be very well structured, and responsible personnel for each phase of data collection, processing and sharing need to be defined; otherwise, it's very easy for doctors to dismiss the data that should actually be used in improvement cycles. • Data standards are necessary for data transfer. FHIR is the most widely format for data transfer, being compulsory in the US and largely adopted in Europe. Terminology standards may also be relevant when working with reimbursement claims, with SNOMED CT being by far the most popular in the hospital setting. Acceptability of data-centric and digital solutions • Educating healthcare professionals of the value of a digital solution is key to its adoption and use. When implementing its digital platform for cross-hospital data sharing, HIPS, Santeon opted for a bottom-up approach, as a top-down strategy (engaging hospital managers first, and then healthcare workers) led to poor acceptance. • Providers are interested in digital solutions with actionable outputs, and that have some degree of explainability – enough to grant them regulatory approval. So long as these conditions are met, MedTech companies can refrain from sharing the raw medical data they collect if that gives them competitive advantage over the competition. Monitoring medical devices (based on his experience at Philips) • Monitoring medical devices require a lot of data. In introducing such devices to the market, it is wise to “start with the low-hanging fruit”: a device with only a simple measure must be validated through trials, and once that product has entered the market, then new parameters may start to be studied from the collected real-world data, and new features may be added.
Regulatory and Quality Assurance	Célia Cruz Chief Regulatory Affairs Officer, Comlear Health	About Comlear Health • Provides regulatory support to MedTech companies whose products have a large software component (either purely digital or hybrid). Comlear is EU-based but uses the FDA as the gold standard, as the Agency more frequently updates its regulation to reflect advancements in the industry. General considerations on data-centric MedTech • EHRs gather increasingly more information, and many companies' solutions revolve around the processing of EHRs. • MedTech companies often have to deal with a lack of data format standardization. Data generated by devices from major companies (e.g., image format generated by a MRI machine) may have unique formats that hamper interoperability – it is a strategy to maintain customers tied to their devices/systems. Cybersecurity • Any kind of product that stores sensitive information must, by regulatory authority, have cybersecurity measures. • There are groups of organizations (cybersecurity groups) created to share concerns and occurrences in cybersecurity. By engaging with such groups, MedTech companies may indicate their commitment to cybersecurity to regulators, and help make their products more robust against cyberattacks. Data considerations for ML/AI-based devices • Data is needed for training, testing and validation of ML/AI-models.

		• Data must be as complete as possible. • Depending on the application of the technology, varying amounts of data may be needed (i.e., more critical applications may require large volumes of data to ensure robustness). • Data must be as close to unbiased as possible (data adequacy). Whenever possible, companies must collect demographic data alongside main data; this information needs to be disclosed in order to prove data variability. For example, a software tool that detects melanoma from pictures of a patient's skin must use data from multiple skin tones in its development to prove its robustness. • Data adequacy may also have an impact in reimbursement: for example, if a ML/AI-based software was trained with data from only one geographical area, payers may require that it also be trained with data in the region at which the developer seeks reimbursement. General considerations on real-world data • There is a strong emphasis on the post-market collection of data from FDA's part. • Registries are very important for post-market studies, and the data provided by them may help identify problems with devices even if their manufacturers provide poor post-market data. Registries are also useful in pre-market, as a means of conducting comparative analysis. Outside of regulatory affairs, registry may help companies identify actionable niches within a certain condition. • Real-world data is often associated with retrospective observations (that is, no controlled, prospective clinical trial). That type of data essential for developing AI MedTech tools. Companies must take extra steps to ensure that the data collected in such cases is unbiased. Leveraging data collection to improve devices already in the market • It is very common to introduce a product in the market with a basic functionality that can easily be approved from a regulatory standpoint. Said device may collect data beyond what it uses for its current functionality (with the user's knowledge) and then be used to add new functionalities to the product. When this is done, the product must undergo another regulatory process, but does not need to start from the very beginning as seen in its first iteration. Real-world data collected by a device in the market can also be used to support the approval of another unrelated product. In any case, the data collected must follow the same requirements as defined previously in terms of adequacy, bias and quantity. • Gradually building new features on top of each other contribute to lessen the product's perceived risk, making the regulatory pathway much smoother.
Business Models and Strategies	Pedro Costa CEO, Interventional Systems (IS)	Driving forces of MedTech • The entry of tech giants in the MedTech sector due to its "endless market" that pertains to all people. This shift causes Medical device companies, which were initially very focused on hardware, to pursue digitalization and invest in software; this is often achieved by partnering with or using resources from major tech companies that have ventured into MedTech. • Other driving forces include the emergence of new market niches and conditions within healthcare, and investor behavior (namely venture capital). IS' Micromate™ robot: use of data • Micromate™'s software uses ML to combine TAC and fluoroscopy images (DICOM standard) and the robot's position to define the optimal angle and location of intervention. • Data for model development may be obtained from public databases, obtained from hospitals through deals, or collected by devices themselves.

		Interventional System’s business model • Partnering with strategics that do not to invest in knowhow and specialized robotics manufacturing infrastructure. • The Crawl, Walk and Run approach: co-development with prospective partners (modification to IS’ base product according to client needs), offer of a trial period where they can ascertain the performance of the product, and finally the closing of a licensing deal. Regulatory considerations • For many years, regulators have failed to evaluate applications in a more holistic way, making it complicated for companies to strictly conform to all requirements. Navigating the regulatory landscape is especially hard for newer companies due to their lack of experience. A company should hire and train personnel to deal with regulatory matters, building know-how within the company. External counseling is an option, but should be complimentary. • Interventional Systems took extra steps in its quality system to ensure Security-by -Design. The company also uses many industry standards and keeps close post-market surveillance of its products. In terms of cybersecurity, there are extensive steps to be followed – an example of measure taken by IS is to automatically anonymize data when it comes from the hospital system to within their own (entry control). There is a rise in cybersecurity standards to support compliance. • Interventional Systems uses a multi-layer technical file to support regulatory compliance, consisting of a first confidential layer and a second layer split into a technical file for the base product, and technical files for each modified version of the base product requested by IS’ partners, which can easily be audited by them. Reimbursement considerations • The creation of new reimbursement codes is a complex process. IS did not pursue the creation of a new code, though surgical robots are not reimbursable. • There is a rise in pay-per-procedure models (big capital sales are becoming rarer) accompanied by a pay-per-performance trend. This generates a chain of responsibility: payers set performance expectations for providers, and providers transmit these expectations to MedTech manufacturers. Providers often want proof that a new product is able to improve outcomes in clinical application prior to committing to a full deal. The inherent problem of this is that somewhat long time intervals are required to measure performance, which may delay payments.
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Table II-2. Semi-structured interviews: interviewees’ profiles, key lessons learned and recommendations shared in the interviews.

Category	Contact Person Position, Institution	Main Takeaways
Regulatory and Quality Assurance	NA Digital Health Center of Excellence	Important Considerations for Emerging MedTech • FDA has published several guidances for digital health technologies, which provide more specific recommendations for developers of digital health devices, which include SaMD, SiMD, and AI-enabled devices. For these devices, often, the FDA recommends reviewing the “Content of Premarket Submission for Device Software Functions” guidance, as

	(DHCoE), Food and Drug Administration (FDA)	it provides information regarding the recommended documentation for premarket submissions for FDA's evaluation of the safety and effectiveness of device software functions. - FDA is available to discuss specific questions with developers through the Q-Submission Program. Types of interactions range from clinical study assessment in a study risk determination and clinical study design questions in a Pre-Submission. They encourage reviewing FDA's guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program". FDA's treatment of AI medical devices - The 2023 Executive Order on Safe, Secure, and Trustworthy Artificial Intelligence is very much in alignment with the current mission and vision of FDA and DHCoE, including focusing on key points including, but not limited to: Develop standards, tools, and tests to help ensure that AI systems are safe, secure, and trustworthy; Address algorithmic discrimination; and Advance the responsible use of AI in healthcare. - FDA is working on finalizing a guidance tentatively titled "Marketing Submission Recommendations for A Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions" (AI/ML-PCCP draft guidance) and drafting a guidance tentatively titled "Artificial Intelligence/Machine Learning (AI/ML)-enabled Device Software Functions: Lifecycle Management Considerations and Premarket Submission Recommendations." While in draft, the AI/ML-PCCP draft guidance may be of interest to you to review FDA's current thinking on the types of information the Agency would like to review in a predetermined change control plan, which can be used to support iterative improvement of devices containing AI. Specifically, Appendix A of the AI/ML-PCCP draft guidance includes questions on how developers manage data, re-train the model, and evaluate model performance. - For an AI-enabled device, it may be helpful to search through their list of artificial intelligence/machine learning (AI/ML)-enabled devices. By reviewing submission summaries provided in the FDA's public databases, a developer can review the intended use and indications for use statements, performance testing, and standards that were implemented and presented for the premarket review.
Regulatory and Quality Assurance	<i>Anonymous</i> Former Head of Quality Management, Schiller	- Within a company, the quality process should not change substantially when working with software; rather, software developers and planners have to adapt their daily doing to the quality process. - There are specific quality standards for software upkeep – Software Lifecycle Management standards – which are not particularly hard to follow. It merely requires the will to do so and some resources. - When working with multiple interconnected devices (from multiple stakeholders), looking at the different health information system communication protocols may help find sources of risk and error in data transfer. - The biggest hurdle in the implementation of a quality process is the mindset of R&D in general and software developers specifically.
Regulatory and Quality Assurance	Marco Rafael Regulatory Policy Lead, Roche	Driving forces behind digitalization in healthcare Rapid advancement of technologies that are "bleeding into" healthcare. These advancements and large quantities of data to be processed (e.g., genomics) push the need for digital analytical tools. The general state of regulation

		• Different sectors of healthcare are already well covered by legislation if considered in isolation. The problem arises at the interplay of sectors: a product that encompasses many different technologies (medical device hardware, AI, drug delivery) must comply with many different regulations. Oftentimes, regulations require similar things in different ways, leading to inefficiencies (“duplicate” activities). Moreover, there is often conflict in the form of timeframes and standards to follow. • Products are changing in such a way that soon there won’t be a regulatory basis to support innovation. Regulation and competitiveness: the US vs. Europe • US regulation is updated much more quickly, allowing innovation to be incorporated into the regulatory framework and avoiding hold-ups. • The European regulatory framework is much more complex due to the number of member states (there are many levels of regulation). Moreover, there is often separation of relevant regulations that should be considered in tandem (e.g., industry regulations separated from tech regulations). • Europe suffers from the “Brussels Effect”, with regulations being very strict and requiring that any company that operates in the EU conform with European regulations, extending to the company’s whole operation (as seen with the GDPR). That combined with venture capital being much less abundant in Europe due to risk-aversion results in the US pushing ahead in competition, attracting research, intellectual power and qualified professionals. The future • Companies should push to establish digitalization tools that can be accepted on an industry-wide level, instead of always relying on decades-old tools. For example, for evaluating a patient’s motor function, instead of using a chronometer and counting the number of steps an afflicted person takes, one may develop a digital tool capable of measuring movement. • Regulatory sandboxes are a way of addressing current pitfalls in regulation; they are complementary to standard regulation, and are meant to cover exceptions. Regulatory sandboxes are already widely used in the financial sector, and are seeing growth in healthcare (though limited).
Reimbursement	Susan Janeczko Acting Deputy Director at the Hospital and Ambulatory Group, Centers for Medicare & Medicaid Services (CMS)	General remarks • Newer companies are advised to check MedPAC Payment Basic’s series and the “CMS Guide for Medical Technology Companies and Other Interested Parties” for an overview on how Medicare’s payment system functions. SaMD coverage (general) • The CMS has been working with Software in Medical Devices (SiMD) for a while now. Some confusion arises from SaMD, however, as it is harder to justify coverage for R&D and IP alone, without the tangibility of traditional MDs. SaMD coverage (inpatient) • In the inpatient setting, SaMD is rarely covered as a standalone device, but may be covered as part of a procedure. Companies are recommended to go through the latest “Inpatient Prospective Payment System Final Ruling” document, which provides a list of practical examples of coverage decisions, including attributing New Technology Add-on Payment (NTAP) to some SaMD.

		SaMD coverage (outpatient) • In the outpatient setting, SaMD and innovative digital MedTech solutions usually qualify for New Technology Ambulatory Payment Classification (New Tech APC), allowing them to be paid for as standalone services. Medical software may also be included in service bundle codes, depending on its complexity/innovation, which generally reduces the payment amount. • In the outpatient setting, coverage is often requested by the device's manufacturer. Some are interested in having a SaMD be considered an accessory service (part of a procedure), while others want for it to be covered separately. • Companies are recommended to go through the latest "Outpatient Prospective Payment System Final Ruling" document, which provides a lot of examples of coverage decisions (including software in New Tech APC) and Q&A from the industry. Health technology assessment • The CMS relies solely on assessments from the FDA and its own internal team to evaluate health technology; there are no relevant external actors. The FDA and the CMS often collaborate in the evaluation of new technology, and companies may be interested in their program of parallel review.
Business Models and Strategies (General)	Jeffery Ryan CEO, Interscope Ex-Area Sales Manager (Great Boston), Medtronic	Strategically setting expectations • Not setting proper expectations when it comes to resource expenditure is the biggest cause of failure in emerging MedTech businesses. A company must evaluate all relevant dimensions (IP, Reimbursement, Regulations, etc.) that will require resource expenditure. Hiring an IP specialist, conducting clinical trials, implementing QS systems – these are all examples of activities related to putting a new product into the market, and all of them require, in the end, financial resources. MedTech market • The MedTech sector, namely for medical instruments/tools, seems to be migrating towards the widespread use of tenders. This may be an avenue for procurement cooperatives/hospitals to obtain the most efficient solutions for the best value. Investment in MedTech • MedTech investors expect high returns and have become more demanding, usually asking for "fully baked" solutions before committing to an investment. High percentages may be asked of a company even if they already have somewhat well-established products. • Between the US and Europe, the latter remains considerably more risk-averse. Venture capital is much more abundant in the US. • Companies must look for a strategic fit when dealing with VCs. This process must be exhaustive. Beware that most VCs may have experience due to multiple investments, but they rarely have the in-depth knowledge of the MedTech landscape. This is especially relevant at the current rate of advancements in MedTech. Intellectual Property • Defining an IP strategy right from the beginning is an absolute requirement for all MedTech companies. For newer companies, it is important that the company management does their job in looking for threats to the IP they wish to develop. Professional legal advisory is important as the company grows.

		• A “true” FTO is exceedingly rare, and happens when products are innovative enough to completely avoid competition altogether. It took Interscope about 4 years to build a robust enough patent portfolio to gain “actual” FTO. Continuing patent applications play a big role in expanding patent claims and context for initial, central patents. Regulatory pathway considerations • There has been a shift in the global regulatory panorama, with the US now being the entry point for many global companies prior to obtaining regulatory approval in Europe. The FDA currently provides a less stringent approach to lower-risk medical devices when compared to the European MDR. US regulation is updated frequently, and FDA guidance documents are a good way of staying up to date with such changes. • Companies should build regulatory know-how within them. External consultants on regulatory matters are also a valid option, and may be used to leverage the knowledge of the company’s internal team. • FDA’s 510(k) process can be very burdensome in the way a company has to prove that its device relates to existing technology in the market. De Novo classification can take a lot of work, but is generally more transparent than 510(k). • A De Novo classification can be used as a defensive tactic against competition. The first to sponsor a De Novo Classification provides guidance on the uses of a new device or technology, and may “impose special requirements” for “proper use”. If these requirements are sufficiently complicated (e.g., laborious testing), they may deter other companies from going forward with similar products under the 510(k) pathway. • Interscope has tried to use RWD in its regulatory process with the FDA few years back, but it was given little consideration: RWD from 200 patients were barely acknowledged by the FDA, which instead focused on the data collected from 30 patients through an IDE (clinical study). However, the current state of regulation seems to favor the use of RWD. FDA’s consideration of RWD may vary according to the purpose of the product, and its intended uses. Moreover, sponsors for De Novo devices could justify the use of RWD as there is no predicate. • The FDA has made it easier to submit and monitor application through online portals. Quality assurance considerations • The knowledge of relevant standards and regulations must be within the company. When building a MedTech company from the ground up, it is important that the managing team reads and informs themselves about regulatory requirements, including the requirements of each standard. That will help avoid mistakes down the line, allow for the company to implement the best design and development practices right from the beginning and give them agility in dealing with issues that may arise. A company that has no understanding of regulatory requirements is at the mercy of consultants who may not provide them with all the relevant information to ensure success. • There are a variety of international standards to be followed, many of which are absolute requirements from a regulatory standpoint. The FDA is making changes to its regulations in order to incorporate those standards. Standards not only spell out the ways in which a company may conform to regulatory requirements, but are also very helpful in identifying risks in the development of a product, which may lead to
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		pivoting. Standards also force the company to clearly establish a device's intended use, must have in the application of the product, and non-essential components. The Product Requirements Document (PRD) from the 13485 ISO standard is an example of this right in the initial phase of product design planning. - Companies are advised to follow Corrective and Preventive Action (CAPA) processes, an important part of the ISO 13485:2016 Quality Management System. They help more deeply address issues in the development chain. The implementation of a Complaint Management System (as part of the ISO 13485 QMS) is also advisable, as it allows for the company to readily identify problems with the product that couldn't be found in the development and premarket phases. - There are software tools to support quality management in a company, such as Greenlight Guru. They streamline the handling of complaints, keep design QS up to date, etc. Using software in MedTech - There are specific requirements for software, namely about where and how data used by the software is stored. - Handling patient data can be challenging due to the extensive regulations relating to privacy. However hospitals appreciate solutions that incorporate patient data, as they can be integrated in their own systems and help in tasks such as patient monitoring.
Business Models and Strategies	João Ribeiro CEO, PeekMed	SaMD licensing as a scalable Business Model - PeekMed's sales are based on licensing their software either directly to providers or to intermediary companies. - The model has proven itself extremely scalable and work with any type of client: more clients just means more licensing, with the software being deployed through the cloud to computers or mobile devices in the same way it was with fewer clients (granted, the cloud capacity must be increased). By selling licenses to intermediaries, PeekMed can take advantage of their sales forces and reach new potential clients. Reimbursement considerations - PeekMed was aware that its software was not eligible for reimbursement, building its business model around that. They chose not to pursue a new reimbursement code, as that did not align with their business model. Using data in the development of SaMD - For privacy concerns, working with patient data comes down to asking the following questions: <i>"What data do I have access to?"</i>, <i>"What do I do with that data?"</i>, and <i>"Am I able to eliminate patient data in my possession?"</i>. As defined by the GDPR, there is no forbiddance in the use of patient data, though patients must be informed of and consent to the use of their data. In PeekMed's case, it is the provider which requests permission for treating patient information (which includes sending medical images to PeekMed). - Data standardization is one of the cornerstones of data-driven digital companies. They need to focus on a type of uniform data to work with, and then work on how to convert other types of data into the desired format. A company should ask itself early on <i>"What kinds of data do I expect to receive, and from whom?"</i>, <i>"How to store that data?"</i>, and <i>"How to convert that data into a unified format for processing?"</i> - PeekMed had a good idea of what the different entities handling patient data in their business model would be. In their case, a provider or associate clinic directly uploads a medical image to their cloud, and

		PeekMed sends already anonymized data to implant manufacturers (also through cloud). Infrastructure • PeekMed uses a private cloud developed in-house. Their choice of using a private cloud is mainly focused on being able to control who accesses their information. They initially used public clouds as they provided ready-to-use functionalities and reduced the need of investment in IT infrastructure. • Private clouds can be more cost-efficient for testing software/AI-models, but may generate a bottleneck in the deployment of software in the long term as the number of clients grow. SaMD regulation and quality assurance • Regulation has become much clearer on how to ensure safety in SaMD. The FDA regulatory process is much better structured, organized and responsive than before. • Fundamentally, in the same way you need to have quality systems in place for physical MDs to trace back any faults in the development, there is the same requirement for SaMD at the code level: one must be able to trace back bugs and errors in the development of the code. Successfully implementing a SaMD essentially comes down to thinking of quality controls since the get-go: following ISO directives is a way of ensuring process robustness and safety.
Intellectual Property	Robert Harrison German and European Patent Attorney European Trademark and Design attorney, Sonnenberg Harrison	IP in MedTech • MedTech falls between Pharma (heavy focus on patent protection) and ICT (much more loose on patent application, focusing more on copyright). There seems to be a rising concern towards patent protection. • Within MedTech, there seems to be an overall problem in coupling knowledge about the hardware (mechanics, biomechanics) and software (information systems, computer science). Software and digital asset IP protection • The presence of software in itself hasn't changed the approach to IP in a substantial way: IP still pertains to the specific value added by a company to its medium. Patents should be placed in order to protect a company's position in the value chain, including intellectual contributions (e.g., services provided through software). • There are many new tools for software protection, which may not be easy to account for. Even open-source software may be subject to licensing if it's used for commercial purposes, or if it is altered in any way in the creation of a new solution. • In terms of software copyright, the US requires copyright to be registered. A copyright protects the source code of a given software, but it is still possible to deliver a similar functionality by engineering around it. This is no easy task, however. Copyright licensing allows for immediate revenue. • Trade secrets are an option of protection, but in practice many companies follow that avenue due to not wanting to go through the effort of filling a patent application. The great amount of explanation of an invention that goes into the MedTech regulatory process works against trade secrets. Very strict confidentiality measures (beyond simple NDAs) must be put in place to safeguard trade secrets, especially when partnering with other companies. Licensing of innovative technology

		- Technology licensing seems to be gaining popularity, especially amongst smaller businesses. However, it may become hard to administer licensing deals for many licensees, requiring resources such as a dedicated team. Companies are advised to start with few licensing deals, or even exclusive deals with a larger corporation. Involvement of a patent attorney - Companies should involve the attorney in the company's business decision-making; an attorney that works with limited knowledge about the company's business model and technology will only be able to offer limited contribution. - When looking for an attorney, make sure to talk to a couple of them to determine which is most familiar with the technology at the company's core (market and competitive environment are associated with the technology). Levels of protection - Smaller companies usually have 2 levels of IP protection: one for its core business, and one for complementary activities. - If a company has the resources, they should protect alternatives to their main business model. Having a good understanding of its position in the value chain from the beginning will reduce a company's chances of having to turn to alternative models down the road. - Continuing patent applications (US) play a big role in expanding patent claims and context for initial, central patents. They offer a good way of reflecting changes in a company's priorities. Standard Essential Patents (SEPs) - SEPs should become more common in all fields of technology as they become more complex. In MedTech, SEPs may appear in the near future for companies that connect to/rely on mobile devices. MedTech companies often purchase pre-made communication/interface modules, meaning that they usually don't need to worry about SEPs.
Intellectual Property	Franz Möltgen German and European Patent Attorney European Trademark and Design attorney, Keller Schneider	Software and digital asset IP protection - Patenting is a common way of protecting software. "Pure software" patenting is often done in the US, as in the EU a software must have a "technical effect" to be patentable. - Software copyright is also very popular, as it is automatic upon the creation of the source code (though it must be registered in the US). Copyright protection is not as overarching as a patent protection. - Trade secrets may be used to protect proprietary software. In MedTech, regulatory requirements may work against trade secrets, though the biggest threat to trade secrets is the lack of measures to ensure confidentiality within a company. Licensing of innovative technology - Licensing has been gaining popularity. Patents are becoming increasingly hard to get, and the process of obtaining patents (e.g., by having a patent department) incurs costs; licensing is a way to capitalize on the patent, paying back the investment. - A company that wishes to be acquired should make their patents as valuable as possible by not licensing them at all (exclusivity of the innovation). Scope of protection - Having a scope of protection, that is having multiple active patent applications, can be achieved through divisional applications: a "spin-off" is separated from the original patent application, and the spin-off

		becomes a patent by itself. It is a good way to protect around the company's business model and shrug off competition. • A scope of protection is also relevant for companies that wish to be acquired by larger corporations: that increases the value of the company as the buyer can choose in which active patent applications to invest according to their preferences. Involvement of a patent attorney • Patent attorneys should be involved right from the get-go; counseling may help assess FTO and even prevent inventors from disclosing their invention, which is a big pitfall often seen. • Within a company, a patent attorney will be closer to the CTO than to the legal department, as technical knowledge is required. • External attorneys rarely have the same penetration in a company's business strategy that an internal attorney would have. It's not a matter of distrust, but rather that external attorneys are expensive, and for that reason relegated only to the essential IP protection functions. Even larger companies often do not have an internal attorney; usually they hire an attorney that is not IP-focused, but that manages all legal operations and interfaces with external attorneys (e.g., external IP attorneys). • For small companies patent managers may be a good alternative to attorneys when it comes to IP counseling; these are not legal professionals and are often cheaper. Standard Essential Patents (SEPs) and cross-licensing • SEPs are rare outside of ICT, but there is potential for them to appear in other industries, such as MedTech, that incorporate communications tools. • Cross-licensing is a somewhat common practice in which (usually) two companies share patents between each other, thus promoting innovation in the two parties. These deals are common when one company would need to license another's technology to develop their products, and vice-versa.
Intellectual Property	Iakovina Kindylidi Senior International Adviser, VdA	Software and digital asset IP protection • The rise of digital innovations has not made it particularly harder to protect IP. A company should define the purpose of their product early on, and that will guide its IP strategy. • Software may be patented or protected under copyright. Both are common avenues, with the former being harder to obtain but covering the functionality of the software, and the latter being easier to get, but only protecting the source code. In the EU, software is often coupled with hardware for patenting due to standalone software not usually being patentable. • Software-based companies may consider the protection of APIs. APIs fall into a grey zone of things that could either fill a functional necessity within a software, or constitute actual innovation. APIs are eligible for copyright protection in the US, but not in the EU. Fundamental APIs (e.g., Java SE APIs) can be freely used in the development of digital solutions in the US through "fair use" provisions. Strategic IP considerations • A copyright owner may opt to license its software or to make it available as open source. Licensing allows for the initial control of who has access to the software and imposes deals (SaaS deals) on the number of uses, available features, etc. It also allows for immediate

		capitalization. With Open Source licenses it is very hard to control who has access to the software. Such licenses often allow for capitalization if the software is used for business purposes, but due to the difficulty of monitoring who uses the software for what, this capitalization may come very late. • Licensing becomes more complex the more clients a company has, and the more geographies are involved; for example, the functionality of a software to access EHRs from one given country may not be applicable to another. Monitoring licensing deals also requires personnel. Legal team and legal counsel • Having big clients (e.g., hospitals, which have their own information systems) and working on highly regulated industries (e.g., healthcare) require both technical and legal know-how. A legal team, be it internal or external to the company, is necessary. Oftentimes it is the commercial team which deals with legal matters, and due to their lack of experience in that regard, it makes legal affairs drag for much longer. • A legal team is also very relevant in the creation of templates. Licensing agreement templates, when offered by a small company to a potential licensee, help set the tone of the deal and streamline the licensing process by clearly spelling out the licensor's conditions from the get-go. • The sooner a legal strategy is defined, the better. In the beginning, it may be useful to consult an attorney with a more general background in order to assess areas of concern (IP, internal policy, etc.). Later, a professional dedicated to IP may work together with the company's management to define an IP strategy according to the company's objectives. There are highly specialized legal professionals in the market (e.g., attorneys specialized in software copyright), and choosing one that is aligned with the company's technology is a priority. • Ensuring legal compliance also benefits smaller companies with plans of being acquired by larger corporations. The buyer company performs due diligence and legal compliance assessments of the company to be purchased; if the latter has faults in its compliance, the buying company may reduce the offer of purchase (due to incurring higher risks and having to invest in compliance measures), or even demand the smaller company to implement compliance measures as a condition of purchase, thus delaying the acquisition process. (Regulation) Regulatory sandboxes • The European AI Act establishes that each member state (or clusters) are required to implement regulatory sandboxes for the testing of AI, with small and medium MedTech businesses being given priority (as part of a critical sector). • The European "Brussels Effect" points to the AI Act having worldwide influence, prompting the US to follow the sandbox example.
Concept Generation	Markus Neuer Project Manager Digital Health, Medical Valley cluster Nürnberg	Hurdles in the implementation of digital tools in hospitals • Lack of human resources in the IT area (quantitative and qualitative) to carry out complex projects. Hospitals do not have the financial resources to invest in well-qualified specialists. Hospitals look at the MedTech industry for digital solutions. • Communication problems during the introduction of IT projects. IT does not understand medicine/nursing and vice versa. Users of digital

	Ex-Digitalization Project Specialist, Rottal-Inn Clinics	solutions (medicine/nursing/etc.) are not involved in their development. • Digital transformation is not focused on by management, which leads to a lack of digital strategy; hospital IT infrastructure is often not up to date. • False promises made to users on the functionality of digital tools and not kept, which leads to a loss of acceptance. • Lack of compatibility with the hospital information system. Compatible solutions are desired by hospitals, as they allow access to patient information and promote optimal use of medical data.
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