

Harmonised approach to **Early Feasibility Studies** for Medical Devices in the **European Union (HEU-EFS)**

WP 2 Research and analysis on regulatory framework and institutional and organization characteristics of EU competent authorities

DELIVERABLE 2.4

Research report summarizing the current EU
regulatory framework for clinical evidence generation
for MDs and DHTs and relations with the future EU
EFS Program (Part 2 - Focus on DHTs)

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ABBREVIATIONS

Abbreviation	Definitions
ADA	American Diabetes Association
AI	Artificial Intelligence
AIeMD	AI-enabled Medical Devices
CE	Conformité Européenne
CI	Clinical Investigation
CONSORT-AI	CONSORT-AI Consolidated Standards of Reporting Trials extension for Artificial Intelligence interventions
CROs	Clinical Research Organizations
DHCoE	Digital Health Center of Excellence (FDA)
DHTs	Digital Health Technologies
DiGA	Digitale Gesundheitsanwendungen (Digital Health Applications)
EASD	European Association for the Study of Diabetes
EFS	Early Feasibility Study
EMA	European Medicines Agency
EU	European Union
FIH	First in Human
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
HEU-EFS	Harmonised approach to Early Feasibility Studies for Medical Devices in the European Union
HTA	Health technology assessments
IHI	Innovative Health Initiative
IMDRF	International Medical Device Regulators Forum
IVDR	In-Vitro Diagnostic Device Regulation
IRB	Institutional Review Boards
ISO	International Standards Organization
ML	Machine Learning
MDCG	Medical Device Coordination Group
MDD	Medical Device Directive
MDR	Medical Device Regulation (EU) 2017/745
NBs	Notified Bodies

Abbreviation	Definitions
PCCP	Predetermined Change Control Plan
PMAP	Pre-market Approval Pathways
PMCF	Post-Market Clinical Follow-Up
PRIME	PRiority MEdicines
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
RCT	Randomized Clinical Trial
RWE	Real Work Evidence
SaMD	Software as a Medical Device
SiMD	Software in a Medical Device
SMEs	Small and medium-sized enterprises
US	United States
WP	Work Package

EXECUTIVE SUMMARY

The rapid emergence of Digital Health Technologies (DHTs) and Artificial Intelligence-enabled Medical Devices (AIeMDs) is reshaping healthcare by enhancing diagnostics, personalizing treatments, and streamlining clinical workflows. However, regulatory complexity, clinical validation challenges, and uncertainties regarding compliance with both the EU Medical Device Regulation (MDR) and the EU AI Act create significant barriers. These challenges delay market entry and hinder the adoption of innovative technologies. The Harmonised Approach to Early Feasibility Studies for Medical Devices in the European Union (HEU-EFS) project mission is to create a standardized, harmonized, and widely applicable framework for EFS that aligns with EU regulations, including DHTs.

To gain deeper insight, several DHT-specific activities were conducted in work package 2 (WP2) and are reported in this deliverable, complementing the previous D2.1 report (Research report summarizing the current EU regulatory framework for clinical evidence generation for MDs and DHTs and relations with the future EU EFS Program):

1. **Scoping Literature Review:** Analysis of regulatory challenges for DHTs.
2. **Focused Review on EU AI Act – MDR interplay:** Examination of the relationship between the AI Act and MDR, focusing on early clinical evidence and Early feasibility studies (EFS).
3. **Stakeholder Interviews:** Insights from DHT companies and Contract Research Organizations (CROs) on regulatory frameworks, clinical evidence needs, and EFS barriers.

These analyses revealed both the potential benefits of EFS in advancing DHT innovation and the regulatory challenges that must be addressed to facilitate early-stage clinical validation. The high degree of design iterations and software updates intrinsic to most DHTs strains regulatory pathways originally designed for hardware-based medical devices (MDs). The AI Act introduces an additional layer of scrutiny for MDs with AI-driven functionalities, yet its interplay with the MDR remains only partially defined.

The underutilization of EFS in DHTs

EFS are underutilized in the development of DHTs, despite their recognized value in early-stage device assessment. Many developers avoid EFS (or similar early Clinical Investigation (CI) measures) due to regulatory uncertainties, relying instead on simulation, *in silico* analysis, or less formalized pilot studies. This reluctance often means missing critical opportunities to refine user interfaces, test algorithmic performance in clinical settings, and detect unforeseen safety issues arising from human-DHT interaction.

Regulatory complexity and fragmentation

While MDR applies to a broad range of MDs, including DHTs, many of its clinical evaluation requirements reflect frameworks designed for hardware. Regulatory fragmentation across EU Member States further complicates matters. Diverging interpretations of MDR's software classification rules, inconsistent documentation demands, and varying expertise among regulators and ethics committees for DHTs add costs and prolong development timelines. These hurdles hinder EU competitiveness, prompting some companies to adopt a "US-first" strategy. Moreover, meeting MDR risk management standards, particularly regarding AI model updates, can be unpredictable, slowing the iterative improvements that define DHT innovation. The EU AI Act, intended to mitigate risks specific to high-risk AI systems, introduces an additional compliance burden that remains only partly defined.

Need for an EU EFS program reflecting DHT-specific aspects

Both the literature and stakeholder interviews affirm the need for a harmonized EFS framework tailored to DHTs. While certain hurdles such as complex evidence requirements and multi-country fragmentation are shared with non-digital MDs, DHTs face unique challenges. Interviewees cited the FDA's Digital Health Center of Excellence, the Danish "umbrella protocol" approach allowing multiple iterations within a single study, and Germany's guidance on digital health applications as promising blueprints. Stakeholders suggest that adapting these best practices to align with EU mandates and the FDA's EFS program core elements could create a cohesive, innovation-friendly environment that benefits both DHTs and traditional MDs.

Implications for policy and practice

First, regulatory guidance addressing EFS and early clinical evidence generation for DHTs and AIeMDs is needed, describing proportionate requirements for different software risk classes. Second, the phased introduction of the AI Act offers a key opportunity to align with MDR rules on clinical evaluation, reducing duplication. Finally, financial challenges must be addressed, particularly for small and medium-sized enterprise (SMEs), potentially through targeted funding or incentives that offset the costs of EFS.

In conclusion, these findings emphasize the urgent need for greater clarity, harmonization, and stakeholder collaboration to unlock EFS's potential in accelerating innovation while safeguarding patient safety and device performance in DHTs. These insights will directly inform HEU-EFS's subsequent work packages, including the development of standardized processes (WP3), protocol design (WP4), and ethical and legal considerations (WP6). A coordinated effort among regulators, industry, and researchers is vital to fostering a framework that encourages agile innovation and maintains robust safety standards.

1. Introduction

Digital health is the field of knowledge and practice associated with the development and use of digital technologies to improve health. Digital health technologies (DHTs) are systems that use computing platforms, connectivity, software, and/or sensors for healthcare and related uses (World Health Organization, 2021). DHTs encompass wellness apps, lifestyle apps, bioinformatics software and software that qualifies as a ‘medical device’ (MD) in regulatory frameworks. As such, a subset of DHTs qualifies as ‘MDs’ and is therefore subject to the requirements of the Medical Device Regulation (MDR) (Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices, Amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and Repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA Relevance.), 2017).

Different terms are used in the EU and the US for medical device software; in the US, the terms ‘software as a medical device’ (SaMD) and ‘software in a medical device’ (SiMD) are used, whereas in the EU, the term ‘medical device software’ (MDSW) is used (Fraser et al., 2023). The determination as to whether a DHT is a ‘medical device’ in the US, or the EU is managed differently. In the US, developers can refer to examples of previous decisions in the product classification database, and the 510(k) Premarket Notification Device software function example page (Food and Drug Administration, 2025b, 2025a). The EU framework places a greater emphasis on the application of generic definitions to individual technologies. In the EU, developers are required to consider the definition of a ‘medical device’ in MDR (Article 2(1)), and the definitions of ‘software’ and ‘medical device software’ provided in MDCG guidance (Medical Device Coordination Group, 2019). If the device qualifies as a MD, it is then necessary to determine the appropriate risk classification rule that applies. The software classification rule is provided in MDR, Annex VIII, Rule 11, which provides generic rules based upon the function of the technology (for example, monitoring or therapeutic functions) and health risks (for example a risk of death or irreversible harm).

MDR does not refer to artificial intelligence. The Artificial Intelligence Act, Regulation (EU) 2024/1689 (‘AI Act’) provides a definition of an ‘AI system’ and ‘general purpose AI model’. The International Medical Device Regulators Forum (IMDRF) have also developed terminology relating to subtypes of artificial intelligence and machine learning (ML) (IMDRF, 2022). For the purpose of this report, we use the term AI-enabled MDs (AIeMD) to refer to those technologies that qualify as both ‘MDs’ for the purpose of MDR and an AI system or general-purpose AI model for the purpose of the AI Act.

The rapid advancement of DHTs that qualify as MD, including AIeMD, has ushered in transformative changes within the field of medicine. These technologies hold immense promise to revolutionize healthcare by improving diagnostic accuracy, personalizing treatment, enhancing remote patient

monitoring, and streamlining clinical workflows. AI-driven tools, particularly AleMDs are becoming increasingly integral to clinical decision-making, enabling early interventions and more effective patient care. However, the emergence of DHTs and AleMD comes with unique challenges, particularly in the realms of clinical validation, evidence generation, and regulatory alignment. Ensuring that the introduction of innovative technologies is supported, and that those technologies are safe and effective remains a fundamental goal. Achieving this goal requires robust, efficient frameworks for early clinical research and regulatory oversight to support these innovative medical solutions.

The MDR applies to a significant number of DHTs and all AleMDs. AI-enabled In-Vitro Diagnostics are subject to separate legislation, the In-Vitro Diagnostic Device Regulation (IVDR, 2017/746) and this was not subject to analysis, as the focus of the HEU-EFS project is related to MDs. The overarching goal of MDR is to facilitate timely access to innovative technologies while ensuring their safety and performance, however, the regulatory approval process significantly impacts how MDs are developed, how clinical evidence to support their use is generated, and how safety is validated. These processes influence exchanges among key stakeholders, including regulatory bodies, health technology assessment (HTA) bodies, clinicians, patients, healthcare payers, and technology producers. For DHTs and AleMD, the dynamic and iterative nature of these technologies may generate challenges in meeting MDR requirements, particularly during early stages of feasibility and validation.

The total number of DHTs that qualify as a MD is unknown and there are likely a significant number of MDs marketed as DHT applications that do not have a CE-mark (Sadare et al., 2023).

For DHTs that qualify as MDs, the MDCG has produced guidance describing principles of clinical evaluation for MDSW (Medical Device Coordination Group, 2020). This guidance describes three components of clinical evidence:

1. **Scientific validity or a valid clinical association:** This represents the extent to which the output of the software is associated with a targeted physiological state or clinical condition.
2. **Technical or analytical performance:** This relates to the ability to accurately, reliably and precisely generate the intended output, from the input data. This is undertaken as part of the design verification and validation of the software and may use retrospective or curated data.
3. **Clinical performance:** This is the demonstration that the software is able to yield clinically relevant output in accordance with the intended purpose. This may be demonstrated by pre-clinical testing, a CI or a clinical performance study.

These three components are documented in a clinical evaluation report, which identifies, appraises and analyses the data. The clinical evaluation, and the clinical data, on which it is based, form the clinical evidence to support the MDSW in a regulatory sense.

The regulation of DHTs and AleMD remains a work in progress, marked by ongoing challenges and evolving frameworks. While the EU MDR lays a foundation, additional complexities arise with the EU AI Act, which governs AI-based technologies, including their safety, transparency, and ethical considerations. The interplay between the MDR and the AI Act introduces a dual compliance burden, which must be carefully navigated to support the safe development of these technologies.

EFS are limited CI of a device early in development, typically before the device design has been finalized, for a specific indication (e.g. innovative device for a new or established intended use, marketed device for a novel clinical application) (FDA Center for Devices and Radiological Health, 2022). It can be used to evaluate the device design concept with respect to initial clinical safety and performance in a small number of subjects when this information cannot practically be provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable. Information obtained from an early feasibility CI can guide device modifications. An early feasibility CI does not necessarily involve the first clinical use of a device. In the context of clinical evaluation, EFS are relevant to the demonstration of clinical performance, and in some cases an EFS may be relevant to the technical or analytical performance when retrospective or curated data is unavailable (European Committee for Standardization, 2020). Despite the critical role EFS can play in assessing early safety and performance and facilitating iterative innovation, they have historically been underutilized in DHTs. However, this reluctance might represent a missed opportunity to refine technologies in real-world settings as part of the development lifecycle.

The Harmonised Approach to Early Feasibility Studies for Medical Devices in the European Union (HEU-EFS) project mission is to create a standardized, harmonized, and widely applicable framework for EFS that aligns with EU regulations, including DHTs. To gain more insight into the DHT-specific aspects, several research activities have been conducted as part of work package (WP) 2. In the previous Deliverable 2.1, we analysed EU regulations, international standards, and guidelines to identify gaps relevant to a potential future EU Early Feasibility Studies Program, conducted two scoping literature reviews including an interim literature review for DHTs, and performed a targeted analysis of research projects and regulatory considerations specific to DHTs.

Since then, the following three research activities were completed and are reported in this deliverable:

- **Scoping Literature Reviews on DHTs and Regulation:** DHT-relevant findings are thematically described and contextualized to the two previous scoping reviews.
- **Focused Review of the EU AI Act and its interplay with MDR:** This review explored the relationship between the EU AI Act and the MDR, with a focus on implications for early clinical evidence generation and EFS.
- **Stakeholder Interviews on DHTs in the context of early clinical evidence generation:** Interviews with DHT companies and contract research organization (CROs) gathered insights

on clinical evidence requirements for market access, experiences with EFS, perceptions of the EU regulatory framework, expectations regarding the EU AI Act's impact, and recommendations for a harmonized EFS program tailored to DHT companies.

The findings from these activities inform ongoing activities of WP 1 & 2 as well as the subsequent work packages:

- WP3: Rationale, processes, and procedures to develop and validate a sound, widely applicable, and harmonized EU EFS Program, compliant with EU regulations.
- WP4: Evidence requirements, data, and statistical tools to develop a standard protocol for conducting EFS studies in the EU.
- WP6: Ethical and legal aspects in support of the EFS Program.

2. Methods

The methodology of this report comprises three interconnected research components aimed at exploring the intersection of DHTs, regulatory frameworks, and early clinical evidence generation. These include:

- Scoping Literature Review on DHTs
- Focused Review of the EU AI Act and its interplay with MDR
- Stakeholder interviews on DHTs in the context of early clinical evidence generation

2.1. Scoping Literature Review on DHTs

The scoping literature reviews on DHT-specific aspects were conducted between January and December 2024. These reviews were a joint effort between WP1 and WP2, supporting both the Pre-Market Approval Pathways (PMAP) analysis and the regulatory environment analysis. Preliminary findings from the PMAP- and EFS-focused reviews (Search 1 and Search 2) were first presented in WP1 Deliverable D1.1 (Characteristics, Gaps, and Best Practices of Pre-Market Programs) and WP2 Deliverable D2.1 (EU Regulatory Framework and International Standards). Since then, an additional scoping review focusing on DHTs and regulation (Search 3) has been completed. This report presents the results and contextualizes them in relation to the two previous scoping reviews.

Searches were conducted using Web of Science, Scopus, and PubMed. Search strategy details (keywords, data ranges and language restrictions) and eligibility criteria (inclusion/exclusion) are described in detail in [Appendix 1](#). The search results were managed using Zotero for reference management and Rayyan.ai for screening. The screening process followed Preferred Reporting Items for Scoping Reviews and Meta-Analyses (PRISMA) guidelines and included:

1. Two-staged Title/Abstract screening (general & DHT-specific eligibility)
2. Full text/content screening.
3. Further in-depth screening using snowballing methods and consulting colleagues.
4. Data analysis and synthesis.

A total of 4,719 records were identified primarily. After a 2-staged eligibility screening 106 were identified for full publication screening by two independent experienced researchers. At the conclusion of full text screening, 26 publications were included in the scoping review. An additional 9 publications were identified by other means (snowballing, identified by colleagues/researchers)

resulting in a total of 35 publications on DHTs included in this review. A detailed description of the methods and the PRISMA flow diagrams of search 3 are described in [Appendix 2](#).

A standardised data extraction table was established to harmonise information gathering. The themes relevant to our task included:

- regulatory hurdles,
- quality and risk management,
- economic sustainability,
- eligibility criteria for EFS,
- evidence of early dialogue, and
- the roles of stakeholders before, during and after an EFS.

In this deliverable, we report on the DHT-specific analysis, synthesizing key findings.

2.2. Focused Review of the EU AI Act and its interplay with MDR

This focused review aims to explore the interplay between the EU AI Act and the MDR in the context of DHTs. A semantic search method was used, which involves using advanced language models to understand and retrieve relevant information from sources, focusing on the meaning and context of search terms rather than just keyword matching. Elicit served as a primary tool for identifying and organizing relevant publications with the final search conducted on Dec 1st, 2024. Its database aggregates sources from Semantic Scholar, CrossRef, PubMed, and arXiv, providing a robust foundation for finding peer-reviewed literature and grey literature.

The search strategy focused on uncovering cross-over and gaps between the AI Act and MDR. The research questions were:

- "How do the EU AI Act and the existing MDR interplay in the context of Digital Health Technologies?" and
- "What implications arise on early clinical evidence generation / EFS?"

Inclusion and exclusion criteria were applied to ensure the quality and relevance of the reviewed materials:

Inclusion Criteria:

- Articles and documents explicitly addressing both regulations (MDR and EU AI Act).

- Publications from January 1, 2023, to November 30, 2024.
- Sources available in English or with certified translations.

Exclusion Criteria:

- General discussions of AI or DHTs without reference to both regulation or non-EU regulatory frameworks
- Materials focusing on only one of the two (MDR, EU AI Act)

The top 200 search results were screened for inclusion. Relevant documents were imported into a reference management tool (Zotero) for systematic organization and analysis. Eleven publications were identified to fulfil the inclusion criteria, which underwent analysis. A standardised data extraction table was established to harmonise information gathering. Categories included: Interplay of MDR and EU AI Act, Key Challenges Identified, Regulatory Malalignment, Gaps, Implications and Recommendations, Reference to EFS or early clinical evidence generation, Harmonization and Solutions.

2.3. Interviews on DHT in the context of early clinical evidence generation / EFS

DHT companies, frequently supported by CROs, are the key drivers of innovation in digital solutions, including SaMD and AleMD. Their insights are vital for understanding the challenges and opportunities in EFS / early clinical evidence generation. The interview study focused on diverse DHT developers, ranging from startups to large enterprises and the CROs supporting them, with products from all risk classes.

Potential interview partners were identified by all research team members of WP2. These included individuals from HEU-EFS consortium companies as well as from other DHT companies. Additional interview partners were recruited through a survey (a WP1 activity) in which participants indicated their willingness to be interviewed.

Semi-structured interviews were conducted using a tailored interview guide designed for the study's objectives and based on findings from literature and pre-existing experience of the WP2 study team (see [Appendix 2](#)). Questions were designed to allow for open-ended responses, ensuring in-depth exploration of experiences and insights. The interview guide was piloted within the research team before data collection to ensure clarity and relevance.

The interviews were designed as a semi-structured conversation organized into five key topic areas:

1. Understanding the clinical evidence required for market access of their products.

2. Experiences with EFS and early clinical evidence generation for DHTs.
3. Perceptions of the EU regulatory framework, particularly the practical application of MDR, guidance, International Standards Organization (ISO) standards, and how these standards impact early clinical evidence generation.
4. Anticipations around the impact of the EU AI Act on regulatory requirements for DHTs.
5. Expectations and recommendations for a future EU harmonized EFS program, specifically tailored to the needs of DHT companies.

A total of 15 interviews were carried out via Microsoft Teams, recorded with participants' consent, and transcribed for analysis. Three researchers independently analysed the transcripts and their individual notes using thematic analysis. Transcriptions were clustered to identify recurring themes, patterns, and divergences across responses and documented in an Excel sheet. Main themes from the interview guide served as the basis for the first structure of a category system with additional categories created deductively. Discrepancies were resolved through discussion and a summary created.

The study protocol was approved by the Bocconi University Ethics Committee (approval EA000846 on Nov 11th, 2024) and adhered to the ethical principles of the Declaration of Helsinki. Participants provided written informed consent, which included details on the data management plan, before participation, and all data were pseudonymized in compliance with the EU General Data Protection Regulation (GDPR). Transcriptions and recordings were securely stored, ensuring confidentiality.

3. Results

3.1. Scoping Literature Review on DHTs

3.1.1. Characteristics and features of pre-market programs in DHTs

Several publications analyzed market approval pathways, highlighting regulatory mechanisms across different jurisdictions. Regulatory frameworks like the Food and Drug Administration (FDA) De Novo pathway and the 510(k) process are noted for their role in assessing novel and moderate risk (Class II) devices, respectively (Haig et al., 2023; Wichmann et al., 2020). Exemptions from regulatory requirements for certain low-risk AI-driven software devices in the US exemplify streamlined oversight, facilitating rapid market entry (Fraser et al., 2023). Programs such as the US Breakthrough Devices Program, while not specifically designed for DHTs, are still crucial for facilitating timely access to innovative technologies (Angehrn et al., 2020).

Risk classification features prominently across several publications, particularly the tiered categorization systems used in Europe and the US, which adopt different classification approaches—for instance, the EU distinguishes between Class IIa and IIb devices, whereas the US system does not make this subdivision. Devices are typically divided into Class I (low risk), Class II (moderate risk), and Class III (high risk), with higher-risk devices requiring more stringent evaluation (Angehrn et al., 2020; Wichmann et al., 2020). In Europe, MDR 2017/745 determines risk classes based on intended use, while the US employs pathways like De Novo for moderate-risk devices and PMA for high-risk products (Angehrn et al., 2020; Fraser et al., 2023). Notably, some publications emphasize the reclassification of medical device software in the EU, such as those progressing from Class I to Class IIa, driven by their intended use and clinical findings (Jeary et al., 2019; Svempe, 2024).

The FDA's regulatory policy for DHTs evolved from a traditional regulatory approach into a more flexible, innovation-enabling framework. This includes risk-based regulatory adjustments tailored to the unique nature of DHT, such as focusing on functionality over platform or traditional classification (Lievevrouw et al., 2022). The FDA's attempts to standardize DHT led to internal organizational changes, reconfiguring its role from a "safety watchdog" to an "innovation enabler" (Lievevrouw et al., 2022). Initiatives like the Pre-Certification Pilot Program shifted the focus of regulatory assessment from product-specific approval to a more company-based or organisational assessment (Lievevrouw et al., 2022).

The length of the application process in the context of EFS in DHTs was highlighted in only a few studies and is identical to MDs, since the US EFS program does not have a specific focus on DHTs (Lottes et al., 2022; Rêgo et al., 2023).

3.1.2. Compliance Hurdles

Regulatory challenges are a significant barrier to the development and deployment of DHTs. MDR reclassification for devices under Rule 11 significantly impacts SaMD (Jeary et al., 2019; Py et al., 2021; Torous et al., 2022). This has increased documentation requirements, and the detail needed for clinical evaluations, resulting in particular burdens for smaller enterprises. The increased complexity and financial burdens disproportionately affect SMEs, leading some to discontinue products, postpone launches, or exit the EU market entirely, favoring less stringent regions like the US (Svempe, 2024). Slow research ethics committees review processes and restrictive technology transfer policies delay pre-market research, making it difficult for innovators to navigate regulatory pathways efficiently (Ford et al., 2021). While the MDR aims to enhance patient safety, the delays and financial hurdles may paradoxically harm patient access to innovative technologies and reduce the availability of critical MDs (Svempe, 2024). Additionally, the extensive external validation required for regulatory approval, especially for AI/ML-based tools, creates significant delays. These requirements often vary by jurisdiction, further complicating cross-border deployment of innovations (Angehrn et al., 2020). The lack of harmonized global standards creates inefficiencies, leaving developers to navigate inconsistent requirements across regions (Aisu et al., 2022; Fraser et al., 2023; Hedderich et al., 2023). The traditional frameworks of randomized controlled trials (RCTs) are not well-suited for the dynamic nature of DHTs. This gap in alignment complicates the integration of these technologies into healthcare systems, as existing regulatory mechanisms lack the flexibility to evaluate DHT-specific needs (Haig et al., 2023).

The European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) highlight that the lack of regulation for digital health apps leaves safety and efficacy unverified, posing risks to patient care (Fleming et al., 2020). These organizations emphasize that the high costs and limited commercial value of conducting rigorous clinical trials deter long-term investment in app validation. Furthermore, issues such as poor interoperability, insufficient data security, and limited collaboration among stakeholders hinder the widespread adoption and trust in digital health interventions.

According to the consensus report by the EASD and ADA, regulatory agencies should establish updated standards for app development, while researchers and manufacturers must collaborate to generate robust clinical evidence through long-term studies. Developers are urged to integrate strong data security protocols, user-friendly interfaces, and platform interoperability, ensuring accessibility for diverse populations. The report advocates for a collective effort among healthcare professionals, regulators, and patients to enhance innovation while ensuring safety and efficacy in diabetes digital health solutions (Fleming et al., 2020).

3.1.3. Quality and risk management

The rapid evolution of DHTs has introduced new challenges in ensuring product quality and patient safety. For example, AI/ML tools, while offering unprecedented capabilities, present a "black box" problem, where their decision-making processes are not always transparent. This opacity undermines trust and raises concerns about potential biases in the underlying models, particularly when training data are incomplete or unrepresentative of populations or minority groups with relevant impact on health inequities. (Fraser et al., 2023; Hedderich et al., 2023; Hernandez-Boussard et al., 2021).

Risk management frameworks must also address the dynamic nature of self-learning systems, where algorithms evolve post-deployment. Ensuring the safety and efficacy of these systems requires ongoing monitoring and validation, supported by a total product lifecycle approach (Ho, 2023; Lottes et al., 2022). This includes addressing cybersecurity vulnerabilities and implementing innovative regulatory paradigms. Furthermore, collaboration between regulators and industry, as well as upskilling of regulatory authorities, is essential to adapt to the rapid evolution of these technologies and aspects. Current regulatory approaches are insufficient to meet these challenges (Awad et al., 2023; Hernandez-Boussard et al., 2021).

Data quality issues, including accuracy, reliability, and usability, compound these challenges. Privacy risks and cybersecurity threats are particularly prominent in connected health technologies, where sensitive patient data is often exchanged across digital platforms (Woodford et al., 2021). Finally, there is scepticism in the healthcare community regarding claims made by developers of AI tools. This stems from a lack of high-quality clinical evidence demonstrating real-world utility, as well as the absence of standardized metrics for assessing safety and performance (Fraser et al., 2023; Wichmann et al., 2020).

3.1.4. Economic challenges

Economic sustainability is a recurring concern, as the high costs of regulatory compliance, validation studies, and clinical trials place a disproportionate burden on smaller developers (Angehrn et al., 2020; Ford et al., 2021; Hedderich et al., 2023). Traditional funding mechanisms, such as grants, are often insufficient to meet the resource-intensive demands of DHT development, creating reliance on venture capital funding (Ford et al., 2021). However, this reliance on private funding can introduce commercial pressures that conflict with broader public health objectives (Ford et al., 2021).

In many countries, the lack of formal reimbursement pathways for DHTs prevents widespread adoption. For instance, while Germany's DiGA process provides a model for reimbursing certain digital health applications, such frameworks are rare globally, leaving most developers without clear financial incentives to scale their solutions (Haig et al., 2023).

The labor-intensive nature of regulatory compliance, coupled with the fragmented global regulatory landscape, exacerbates these economic pressures. Small enterprises often face the dual challenge

of navigating these complex systems while managing limited resources, highlighting the need for more cost-effective and streamlined regulatory models (Angehrn et al., 2020; Hedderich et al., 2023).

3.1.5. Solutions to overcome gaps, barriers, and challenges in pre-market clinical research in DHTs

The need for specific guidance on clinical evidence generation in DHTs is a recurring theme. Creating clear regulatory frameworks and updating pre-market approval pathways to accommodate rapid innovation cycles are also recommended (Izmailova et al., 2023). Addressing data privacy, security, and ownership issues, as well as facilitating the use of real-world evidence (RWE), are key steps toward improving regulatory alignment (Hernandez-Boussard et al., 2021).

3.1.6. Improving Data Accessibility and Quality

Access to large, high-quality datasets is essential for overcoming barriers in pre-market clinical research. Solutions include ensuring compliance with data protection laws, improving data quality for ML algorithm development, and conducting thorough validation of these algorithms (Angehrn et al., 2020). Data interoperability, usability, and integrity metrics are critical to ensuring successful integration into healthcare systems (Wichmann et al., 2020). Standardizing data collection methodologies and leveraging international collaborations can further enhance data quality and availability (Weirauch et al., 2024). RWE plays a central role in accelerating innovation in DHTs. Supporting advancements in data acquisition methods and addressing barriers to data sharing between stakeholders can foster faster adoption (Haig et al., 2023). Incorporating real-world data into evidence generation processes provides more dynamic and practical insights for pre-market evaluation (Silberman, 2023).

3.1.7. Enhancing collaboration and structured dialogue

Effective collaboration and communication among stakeholders—regulators, HTA agencies/units, technology developers, healthcare providers, ethicists and patient organizations—are critical to overcoming these challenges. For example, strong project management and shared goals among stakeholders can help align priorities and ensure the efficient execution of clinical studies (Ford et al., 2021). However, there is often a disconnection between technical and clinical teams, as well as between regulators and innovators, leading to inefficiencies and misaligned expectations (Hernandez-Boussard et al., 2021; Woodford et al., 2021).

Jeary et al. propose a regulatory framework emphasizing closer collaboration between competent authorities and developers, including mechanisms for identifying acceptable changes, periodic software update reporting, and stakeholder engagement to monitor developments (Jeary et al., 2019). The framework highlights the importance of partnerships between technology companies and healthcare entities to facilitate dialogue and align innovations with clinical needs. This approach aims

to balance technological advancements with robust oversight, ensuring safety and efficacy in digital healthcare tools.

Jiang et al. highlight the critical role of notified bodies in assessing the conformity of wearable DHTs to ensure safety, accuracy, and regulatory compliance. Fostering dialogue between them is highlighted as pivotal (Jiang et al., 2020).

Olaye & Seixas underscore the importance of stakeholder engagement through initiatives like focus group workshops. These gatherings synthesize recommendations to overcome integration barriers in early-stage digital health technologies development. The emphasis is on fostering relationships among startups, healthcare providers, and regulatory boards to facilitate the adoption of novel solutions. Barriers such as complex validation requirements and limited procurement knowledge can be addressed through structured roadmaps (Olaye & Seixas, 2023).

Colloud et al. emphasize the importance of fostering collaboration among stakeholders to streamline the development and approval of DHTs (Colloud et al., 2023). They highlight multi-stakeholder platforms as a means to enhance pre-competitive collaborations and recommend joint advice from regulatory bodies to address the complexities of overlapping regulatory frameworks. Furthermore, the involvement of software validation experts and the development of formal strategies for integration are seen as crucial for ensuring that digital methodologies meet the necessary qualification standards. This integrated approach, combining technical and regulatory expertise, aims to facilitate a more efficient path to implementation.

In 2017 the FDA has piloted the Software Precertification (Pre-Cert) Pilot Program to foster collaboration with industry players, but these efforts need broader and permanent adoption and clearer guidelines to be truly effective (King et al., 2019; Watson et al., 2023). In the EU structured dialogue is evident in initiatives like the European Medicines Agency's (EMA) PRiority MEdicines (PRIME) scheme, along with its scientific advice pilot, aims to accelerate the development of innovative medicines that meet unmet medical needs, demonstrating a commitment to fostering collaboration. However, this is a medicine only initiative and formats like these are currently missing for MDs in the EU (Fraser et al., 2023). Additionally, the involvement of patients/patient organizations and advocacy groups can ensure that new technologies are designed with end-user needs in mind, promoting equity and accessibility (Holmes et al., 2024; Izmailova et al., 2023). Stakeholder dialogue is also essential for addressing data access and privacy concerns, particularly in cross-border research. Trust and transparency among collaborators are foundational to achieving the regulatory oversight necessary for the safe and effective deployment of DHTs (Angehrn et al., 2020; Wichmann et al., 2020).

3.1.8. Advancing clinical validation

The development and implementation of robust frameworks to measure the clinical and technical efficacy of DHTs are emphasized as critical for their successful integration into healthcare (Fraser et al., 2023). Refining clinical evidence thresholds for decision-making and ensuring the rigorous validation of algorithms remain pivotal for establishing trust and reliability in these technologies (Woodford et al., 2021). Furthermore, usability, interoperability, and real-world application testing are essential to ensure that DHTs can seamlessly integrate into complex healthcare systems.

Traditional clinical trial methodologies, often considered the gold standard, may not be well-suited to the agile development characteristic of DHTs. Emerging approaches, such as lifecycle frameworks incorporating EFS, offer a flexible alternative (Holmes et al., 2024). These methodologies facilitate iterative testing and refinement, a necessity given the dynamic nature of DHTs, particularly those leveraging AI/ML algorithms. Early evaluations often forego comparator groups, focusing instead on preliminary safety and performance data in small-scale studies, which are better suited to the iterative innovation cycles characteristic of digital solutions (Herrmann et al., 2022).

Unlike CIs, clinical simulation uses high-fidelity retrospective or synthetic patient cases to deliver rapid feedback, enabling iterative refinement and assessment across diverse clinical contexts (Lau et al., 2023; Py et al., 2021). Clinical simulation offers a dynamic and flexible approach to pre-clinical DHT evaluation. By enabling iterative testing, it supports continuous refinement while adapting to varying clinical workflows and resource constraints. It also provides a holistic assessment of usability, cognitive load, and system integration. Moreover, simulation promotes equity by using synthetic cases to test high-risk or underserved populations, ensuring inclusivity without real patient risks (Lau et al., 2023; Py et al., 2021). While simulation is a powerful and complementary method, it should not replace early clinical evidence generation (Lau et al., 2023). Simulation generates critical preliminary evidence of usability, feasibility, and safety, ensuring technologies are ready for CIs. However, real-world testing remains essential to validate DHTs under the complexity and unpredictability of actual healthcare environments.

Py et al. present a CI plan that integrates innovative approaches for validating a pediatric emergency software tool aimed at reducing medication errors and improving caregiver performance (Py et al., 2021). The study's design includes a two-phase pilot study combining real-life situations and high-fidelity simulations. Key endpoints of the investigation encompass error classification by severity, evaluating teamwork effectiveness, and assessments of caregiver anxiety and self-efficacy using visual analog scales. The study's indirect evaluation of risk/benefit through error reduction underscores its potential contribution to clinical safety, particularly in time-sensitive paediatric emergencies. Furthermore, the inclusion of a simulation phase provides an active learning platform, fostering reflective practice among caregivers and aligning with modern pedagogical standards in

clinical education. Py et al.'s plan demonstrates a thoughtful, iterative approach to clinical validation, with an emphasis on practical application and end-user needs.

Schidek and Timinger emphasize that integrating connections between design phases and clinical studies, along with HTA, plays a critical role in establishing a cohesive pathway for feasible market entry (Schidek & Timinger, 2021). They highlight that the structured process in regulated environments, such as those for MDs, necessitates aligning design verification and validation stages with regulatory standards. By embedding these assessments early in the development cycle, the framework ensures that product design not only meets safety and effectiveness criteria but also aligns with HTA requirements. This integration fosters iterative feedback loops, allowing for adaptability while adhering to regulatory demands, ultimately smoothing the pathway to market readiness.

Silburn et al. highlight the importance of EFS in DHT, an aspect that in the past has been underappreciated and underused (Silburn et al., 2022). They highlight that EFS played a pivotal role in the development of the remote neuromodulation platform (incl. patient app), enabling the study team to assess safety, usability, and feasibility in real-world settings. By identifying key challenges, such as connectivity issues leading to unintended stimulation, EFS informed critical refinements, including a Protected Recovery Program and enhanced network monitoring. These studies also integrated feedback from clinicians and patients to optimize the platform's design and usability, aligning it with user needs and regulatory standards. Ultimately, EFS provided a foundation for iterative improvements, de-risking innovation and paving the way for successful regulatory approvals and market adoption.

A push for rigorous evaluation methods ranging from early clinical evidence generation to randomized controlled trials are particularly being requested for AI/ML DHTs. Guidelines for these trials, like the Consolidated Standards of Reporting Trials extension for Artificial Intelligence interventions (CONSORT-AI) and Standard Protocol Items: Recommendations for interventional Trials – Artificial Intelligence (SPIRIT-AI) (2019), aim to create a cohesive framework for conducting and reporting AI-related clinical studies (The CONSORT-AI and SPIRIT-AI Steering Group, 2019). Vasey et al. highlight that early-stage clinical evaluation of AI systems faces similar challenges to those of complex interventions (e.g., surgical interventions), such as iterative device modification and the characteristics of the operators or users (Vasey et al., 2022). Other challenges include the implementation environment, user characteristics and selection process, training provided, underlying algorithm identification, and disclosure of funding sources. Early-stage clinical evaluation of AI systems should place a strong emphasis on validation of performance and safety.

Despite some AI algorithms matching human expert accuracy in preclinical in silico or simulation studies, there is little high-quality evidence of improved clinician performance or patient outcomes in

clinical settings. Early-stage clinical evaluation is crucial for evaluating clinical utility, usability, safety, and human factors in live clinical settings (Vasey et al., 2022).

The regulatory landscape is evolving to meet these challenges, exemplified by the European Union's AI Act. This legislation emphasizes real-world testing and mandates the disclosure of testing impacts on individuals, along with comprehensive risk minimization plans. As these frameworks evolve, they must balance innovation and safety, facilitating the seamless adoption of DHTs into healthcare systems.

Future evaluations should incorporate structured human factors assessments, as adoption at a larger scale requires technologies to align with clinician workflows and patient needs. Transparent methodologies and consistent reporting standards are vital to address the current lack of uniformity in usability and performance assessments (Silburn et al., 2022; Vasey et al., 2022). Emphasizing these areas will ensure that DHTs can reliably enhance clinician performance and improve patient outcomes, aligning with the broader goals of healthcare innovation.

Lastly, the lack of standardized metrics for success beyond EFS creates ambiguity in defining milestones for progress. Researchers advocate for the establishment of universal guidelines that align technological advancements with clinical and patient outcomes (Vasey et al., 2022; Wichmann et al., 2020).

3.1.9. Fostering International Cooperation

Promoting international collaboration is essential for reducing fragmentation and establishing standardized protocols. Harmonizing regulatory practices across nations and fostering partnerships between global organizations can accelerate innovation and scalability (Ho, 2023; Wichmann et al., 2020). International cooperation also ensures the alignment of clinical research standards and reduces redundancy in pre-market assessments (Aune et al., 2023).

3.1.10. Ethical and legal aspects of an EFS and early clinical investigations in DHTs

The review and development of methodologies in the ethical and legal aspects of EFS and early clinical evidence generation in DHTs revealed several critical considerations. Key findings from the literature emphasize the importance of ethical frameworks tailored specifically for DHTs. One study highlighted the need for alignment with overarching ethical standards while incorporating specific considerations unique to digital health, such as data privacy and the dynamic nature of algorithm-based interventions (Ford et al., 2021). Ethical approval processes and obtaining informed consent are recurrent challenges, requiring innovation to address the nuanced risks posed by emerging digital tools (Haig et al., 2023).

The issue of data governance is another focal point. Researchers underscored the complexity of ensuring transparent, fair, and accountable use of patient data, especially when it involves cross-

border collaboration (Angehrn et al., 2020). Additionally, fostering trust among stakeholders by enhancing data security and clarity in data-sharing protocols was deemed essential for advancing digital health technologies responsibly (Fraser et al., 2023).

Another important aspect involves patient engagement and the co-creation of research designs. Wichmann et al. argued for an inclusive approach that actively involves patients in the development and evaluation of digital tools, ensuring that ethical considerations align with patient perspectives and needs (Wichmann et al., 2020). The evolving nature of AI/ML further complicates these dynamics, necessitating iterative ethical evaluations throughout the lifecycle of these technologies (Ford et al., 2021). Moreover, the review called for adaptive CI methodologies. These methodologies must reflect the iterative nature of digital technologies, allowing for real-time updates to ethical and legal frameworks without compromising research integrity or patient safety (Fraser et al., 2023).

Legal challenges also emerged as a significant area of concern. Regulatory compliance across different jurisdictions worldwide remains a persistent obstacle, particularly given the rapid pace of technological innovation. Harmonizing regulations to accommodate EFS was proposed to mitigate these challenges and accelerate the implementation of digital health solutions (Haig et al., 2023).

Studies also emphasize the ethical and legal challenges that arise as technologies progress beyond EFS. These include questions about data privacy, equitable access, and informed consent, which must be addressed to ensure widespread adoption and trust (Aune et al., 2023; Ho, 2023).

3.1.11. What happens after an EFS and early clinical investigation stages in DHTs?

One prominent finding is that after EFS, developers often face significant hurdles in transitioning to subsequent stages, such as regulatory approval, funding, and scalability. These challenges stem from the lack of streamlined processes and a cohesive regulatory framework for DHTs (Ford et al., 2021). Additionally, fragmented pathways and the absence of clear guidelines for scaling successful prototypes further exacerbate these challenges. This lack of direction creates uncertainty for innovators aiming to move from pilot projects to broader implementation (Hedderich et al., 2023; Hernandez-Boussard et al., 2021).

3.1.12. Evidence generation and clinical validation beyond the first clinical use

Another observation highlights the fragmentation of evidence generation and the need for robust clinical validation. The DEFINED framework (Evidence in Digital health for Effectiveness of Interventions with Evaluative Depth) addresses the unique evidence considerations of DHTs and proposes guidelines to facilitate evidence-based recommendations and aims to streamline assessment processes for various stakeholders (Silberman, 2023). Some DHTs can proceed to conformity assessment and market access even if they are early in development and lack pivotal trial evidence. Adoption levels should be adjusted according to the maturity of a DHT's clinical evidence,

with the Evidence DEFINED framework providing an evidence-to-recommendations component that assigns actionability levels. Studies suggest that without a clear pathway for generating clinically relevant data, many technologies struggle to demonstrate efficacy and safety beyond pilot phases (Angehrn et al., 2020).

3.1.13. The role of collaboration, co-design and interdisciplinary partnerships

Some researchers emphasize the importance of interdisciplinary collaboration in overcoming post-EFS challenges. Building partnerships between developers, clinicians, and regulators can facilitate smoother transitions and foster trust in emerging technologies (Fraser et al., 2023; Lottes et al., 2022). The role of patient-centric design in addressing barriers after EFS is also critical. Incorporating user feedback early and continuously in the development cycle has been shown to improve adoption and usability in clinical settings (Haig et al., 2023; Prodan et al., 2022).

3.2. Focused Review of EU AI Act and its interplay with MDR

A total of eleven publications were identified and analyzed for this study. The methodologies employed across these studies varied, reflecting diverse approaches to exploring the topic. Most of the studies utilized regulatory analysis (nine publications), often in combination with other methodologies. Theoretical/conceptual analysis was employed in six publications, providing foundational insights and frameworks. Additionally, five publications incorporated expert opinion/commentary, offering perspectives informed by practical and professional expertise.

This synthesis analyses eleven publications addressing the interplay of the EU AI Act and MDR. The analysis is structured around four refined themes:

1. Regulatory Alignment and Challenges
2. Compliance and Implementation Considerations
3. Technical Considerations
4. Broader Systemic & International Perspectives
5. Implications of the interplay of the EU AI Act and MDR on early clinical evidence/EFS

3.2.1. Regulatory Alignment and Challenges

This theme explores the regulatory gaps, overlaps, and ambiguities between the EU AI Act and MDR. It includes legal concerns such as liability and jurisdictional conflicts, which arise from these misalignments

Key Insights:

- **Definitional ambiguities:** Several publications propose emphasize the lack of clear definitions for terms like "high-risk AI" or "medical device software," complicating compliance efforts (Biasin et al., 2023; Haden, 2024; Hauglid & Mahler, 2023).
- **Harmonization needs:** Several publications propose clearer regulatory guidelines and frameworks to align these regulations effectively (Biasin et al., 2023)
- **Overlapping requirements:** Some publications highlight how definitions and cybersecurity provisions under the MDR and AI Act create duplicative or conflicting obligations, increasing complexity for stakeholders (Biasin et al., 2023; Gilbert et al., 2023).
- **Liability challenges:** Haden et al. identifies potential liability gaps due to unclear jurisdictional boundaries, particularly for AI applications that straddle both regulatory regimes (Haden, 2024).

Implications:

- Greater harmonization is needed to address these challenges, potentially through unified guidelines or revisions to the existing regulatory frameworks.
- Stakeholder collaboration is critical to ensure consistent interpretation of overlapping provisions.

3.2.2. Compliance and Implementation Considerations

This theme examines practical challenges faced by manufacturers and healthcare providers in implementing the dual regulatory requirements of the AI Act and MDR.

Key Insights:

- **Fragmented guidance:** Several publications emphasize the need for clearer, harmonized guidelines to reduce confusion during the implementation phase (Biasin et al., 2023; Gilbert et al., 2023)
- **Disproportionate burdens on SMEs:** Gilbert et al. highlight the resource strain on smaller entities in meeting the rigorous documentation and reporting requirements of both frameworks, emphasizing resource constraints and fragmented documentation requirements for SMEs as critical factors contributing to these challenges (Gilbert et al., 2023).
- **Integration of monitoring requirements:** Some publications note difficulties in aligning post-market surveillance protocols, which are critical under both the MDR and EU AI Act (Hauglid & Mahler, 2023; Li et al., 2023).

Implications:

- Harmonized templates and tools are needed to streamline documentation and reporting.
- Development of simplified compliance pathways could serve as a solution.

3.2.3. Technical Considerations

This theme focuses on the technological challenges, particularly cybersecurity and the need for interoperable standards, which are central to harmonizing the AI Act and MDR.

Key Insights:

- **Cybersecurity misalignment:** Several authors identify gaps in cybersecurity requirements, with the AI Act introducing stringent obligations that may conflict with MDR provisions (Biasin et al., 2023; Gilbert et al., 2023; Haden, 2024; Hauglid & Mahler, 2023).
- **Interoperable standards:** Gilbert et al. stress the importance of common technical standards to facilitate compliance across both frameworks (Gilbert, 2024; Gilbert et al., 2023).
- **Data integrity and safety:** Several publications highlight effective cybersecurity measures as essential for ensuring the safety and reliability of AI-enabled MDs (Biasin et al., 2023; Gilbert et al., 2023)

Recommendations:

- Adoption of EU-wide interoperable cybersecurity standards to harmonize current discrepancies.
- Collaboration with international organizations, such as ISO, to align with global best practices.

3.2.4. Broader Systemic & International Perspectives

This theme examines the broader implications of the interplay between the AI Act and MDR, including ethical considerations, global regulatory comparisons, and systemic challenges.

Key Insights:

- **Ethical considerations:** Algorithmic bias and patient safety are recurring themes. Several publications argue for safeguards to ensure fairness and trust in AI systems (Hauglid & Mahler, 2023; Li et al., 2023; Onitiu et al., 2024)
- **Global comparisons:** Several authors highlight differences between the EU and U.S. regulatory approaches, noting that the FDA's risk-tiered framework could inform EU reforms (Biasin et al., 2023; Gilbert, 2024; Hauglid & Mahler, 2023).

- **International standards:** The role of ISO and other global organizations in shaping cybersecurity and interoperability norms is emphasized in multiple publications (Cepeda Zapata, Patil, et al., 2023; Cepeda Zapata, Ward, et al., 2023; Ward et al., 2023)

Recommendations:

- Incorporating ethical review mechanisms into the regulatory process to address concerns like bias and fairness.
- Leveraging international collaboration to develop globally consistent regulatory frameworks.

3.2.5. Implications of the interplay of the EU AI Act and MDR on early clinical evidence/EFS

Most of the reviewed articles focus on the broader concepts of clinical evidence, while mentions of EFS are sparse and often inferred rather than explicitly stated. Of the 11 reviewed articles, five explicitly address early clinical evidence generation/EFS. This synthesis integrates the key themes identified across the literature, emphasizing the foundational role of early clinical evidence generation, regulatory challenges, clinical validation for AI systems, and operational complexities.

Early clinical evidence generation serves as a critical mechanism for mitigating risks and ensuring the safety and efficacy of healthcare innovations of DHTs and AI-MDs. Fraser et al. emphasize the importance of early-stage evidence generation, which reduces the likelihood of late-stage failures and supports iterative development processes (Fraser et al., 2023). Early trials provide a structured approach to identifying potential issues, improving the likelihood of successful regulatory approval.

Quaranta et al. emphasize the mandatory requirement for CI in high-risk MDs, including AI-driven medical device software, ensuring compliance with evolving regulatory frameworks. While they do not explicitly reference EFS, their analysis aligns with the core objectives of such studies by advocating for robust and systematic evidence-generation processes in early development stages (Quaranta et al., 2023). This is particularly crucial for AI-based DHTs, where continuous monitoring, iterative validation, and regulatory alignment are essential for real-world deployment and patient safety.

The regulatory interplay of MDR and EU AI Act is a crucial driver in shaping early clinical evidence generation strategies. Li et al. propose adaptive regulatory models that balance safety with innovation, advocating for flexible pathways tailored to AI-based MDSW. They emphasize the role of pilot studies, regulatory sandboxes, and total product life cycle approaches to facilitate iterative improvements in AI-driven health technologies. While EFS is not explicitly mentioned, their recommendations align with the need for early-stage, real-world validation frameworks to support evidence generation in evolving AI-enabled medical software (Li et al., 2023).

Onitiu et al. discuss the importance of developing robust methodologies to validate AI systems, emphasizing the need for early evidence to ensure safety, efficacy, and reliability. Unlike traditional

MDs, AI technologies must address specific concerns such as explainability, performance consistency, and ethical considerations (Onitiu et al., 2024). While EFS is not directly referenced, the authors highlight the need for prospective evaluations and early-stage studies tailored to the complexities of AI systems. These studies are critical for building trust with regulators and stakeholders and for ensuring that high-risk AI systems comply with evolving regulatory standards.

Operational complexities emerge as a recurring theme across the reviewed articles. Authors like Gilbert et al. and Fraser et al. highlight the logistical barriers to early-stage clinical evidence generation, including financial costs, extended timelines, and intricate regulatory requirements (Fraser et al., 2023; Gilbert et al., 2023). These challenges are particularly pronounced in systems governed by stringent regulations, such as the EU MDR. Addressing these barriers requires streamlined processes, enhanced funding mechanisms, and regulatory adaptations that lower costs and simplify compliance. Improved accessibility to early clinical evidence generation frameworks would enable broader participation by innovators, particularly those with limited resources, while maintaining high standards of safety and efficacy.

3.3. Interviews on DHTs in the context of early clinical evidence generation/EFS

Interviews were conducted in December 2024 and January 2025. Fifteen individual interviews were conducted with representatives from 12 DHT companies and three CROs. Nine interview partners were female, six male. The duration of the interview ranged from 39 to 62 minutes (mean 52 minutes). All risk classes as defined under the MDR and company sizes were covered (descriptive statistics are presented in [Table 1](#)).

Table 1. Descriptive statistics of interview partners company profile

Company size	Number
Large enterprise: ≥250 employees	7
Medium enterprise: 51 - 249 employees	4
Small enterprise: 11 - 50 employees	3
Micro enterprise: ≤10 employees	1
Risk classification (MDR)	
I	2
IIa	10
IIb	5
III	3

* Since some companies managed multiple products spanning different risk classes, the number of products is greater than the number of companies.

The results are displayed according to the five key topic areas:

1. Understanding the clinical evidence required for market access of their products.
2. Experiences with EFS and early clinical evidence generation for DHTs.
3. Perceptions of the EU regulatory framework, particularly the practical application of MDR guidance, ISO standards, and how these standards impact early clinical evidence generation.
4. Anticipations around the impact of the EU AI Act on regulatory requirements for DHTs.
5. Expectations and recommendations for a future EU harmonized EFS program, specifically tailored to the needs of DHT companies.

3.3.1. Understanding the clinical evidence required for CE marking

3.3.1.1. Types of DHTs and Their Intended Uses

The companies interviewed in this study develop a wide range of DHTs, including AI-driven clinical, surgical and imaging tools as well as symptom assessment solutions, predictive analytics platforms, telemonitoring solutions with wearable and implantable devices and digital therapies. These products aim to improve diagnostic accuracy, enable remote patient monitoring, support medication, birth control/fertility management and support early medical interventions. Specific use cases include cardiology, radiology, surgery, lung disease and chronic back pain management, medication and neonatal care. Several companies are also focused on scalable platforms that can be adapted for multiple conditions.

3.3.1.2. Medical Device Qualification

All interviewed companies confirmed that most of their products qualify as MDs under the European Union's MDR. However, some also developed non-MD solutions for healthcare, requiring different regulatory pathways. Challenges arose particularly for hybrid or emerging technologies, where qualification pathways were less clear. Transitioning from the Medical Device Directive (MDD) to the more stringent MDR posed additional regulatory hurdles, particularly for newer or unconventional products. While some companies found straightforward pathways for AI-driven applications, others struggled with the lack of specific guidance. Some companies initially considered developing new AIeMDs but opted to rather integrate AI features into existing MDs due to uncertainties around early clinical evidence requirements.

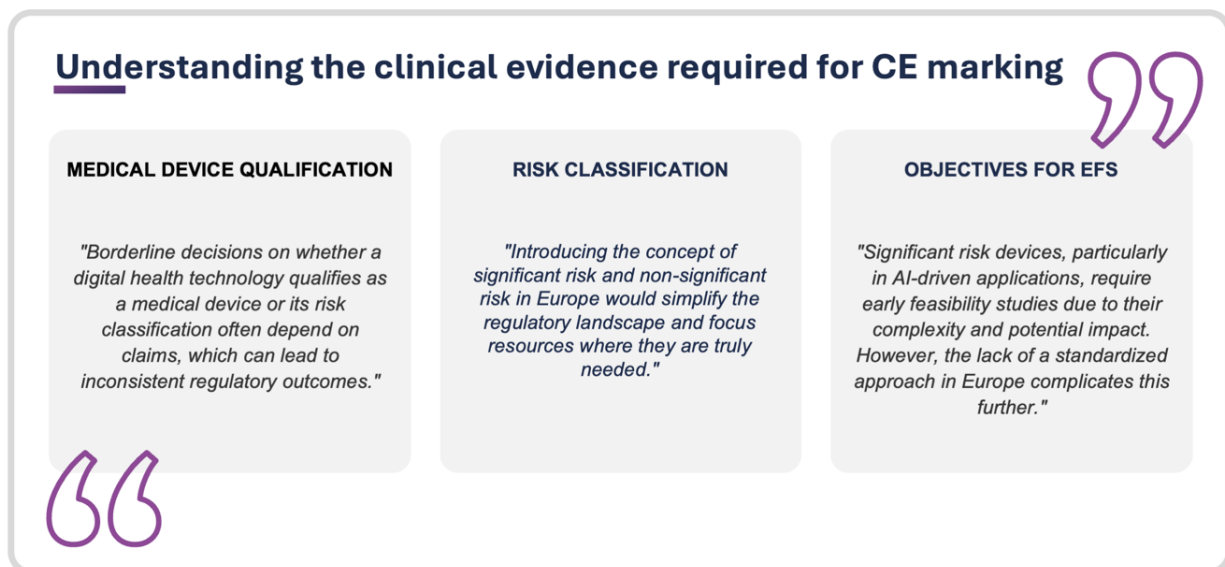
3.3.1.3. Risk Classification

The process of determining risk classification also presented challenges in some cases. Companies had to interpret the regulatory criteria within the MDR framework, often seeking external consultation to ensure accurate classification. Internal and external risk assessment processes as well as engaging in structured dialogue with Notified Bodies (NBs) and regulatory experts were vital, though these stakeholders sometimes struggled with consistent interpretations of MDR requirements. Several companies noted the lack of detailed EU-specific DHT guidance, leveraged FDA guidance to navigate regulatory challenges, or opted for a "US-first" strategy.

3.3.1.4. Objectives of early clinical investigations

The primary goals of early CIs performed by these companies were multifaceted. Clinical validation of technology was a core objective, with companies aiming to demonstrate the safety and performance of their products in real-world settings. Another significant goal was to gain insights into user experiences, both from clinicians and patients, to refine the technologies. Many companies highlighted the importance of understanding how their DHTs would be used in practice, particularly in terms of clinician and patient workflow. Regulatory milestones, such as achieving CE-marking or FDA approval, were crucial in guiding these early investigations, with several companies also focusing on provisional reimbursement strategies to support market entry for lower risk devices.

Figure 1. Quotes of the DHT interview partners regarding understanding the clinical evidence required for CE marking



3.3.2. Experiences with EFS

3.3.2.1. Engagement with EFS and decision drivers

While the concept of EFS is well recognized, most interviewees indicated that the concept of an EFS is not routinely used within the industry. Instead, companies refer to pilot studies, preliminary validation, or early-stage CIs. Large or AI-intensive firms were more likely to run multiple EFS or EFS-like studies annually, driven by regulatory needs (especially for novel AI features) or specific requirements (e.g., for higher-risk classes). In contrast, many smaller DHT companies tried to avoid EFS when possible, given the resource burden.

3.3.2.2. Key Challenges in designing and conducting EFS

A common challenge was navigating unclear regulatory expectations for DHTs, which created barriers to designing and implementing effective studies. Interviewees also highlighted the limited dialogue with regulators, unpredictable timelines, and specialized expertise required, contributing to increased costs and operational complexity. EFS add resource demands—particularly burdensome for SMEs with limited budgets and specialized expertise. National competent authorities are reported to have different levels of expertise, especially regarding DHTs and AI-MDs, leading to fragmented national requirements, and varied outcomes, and inconsistent regulatory interpretation across EU countries further complicates the process. Companies described varied experiences with NB readiness, fuelling delays or miscommunications. Additionally, the process of transitioning to an EFS framework itself was cited as a significant hurdle, especially for SMEs with limited experience. These challenges collectively deterred many companies from pursuing EFS as a preferred strategy.

3.3.2.3. Alternative methods for evidence generation

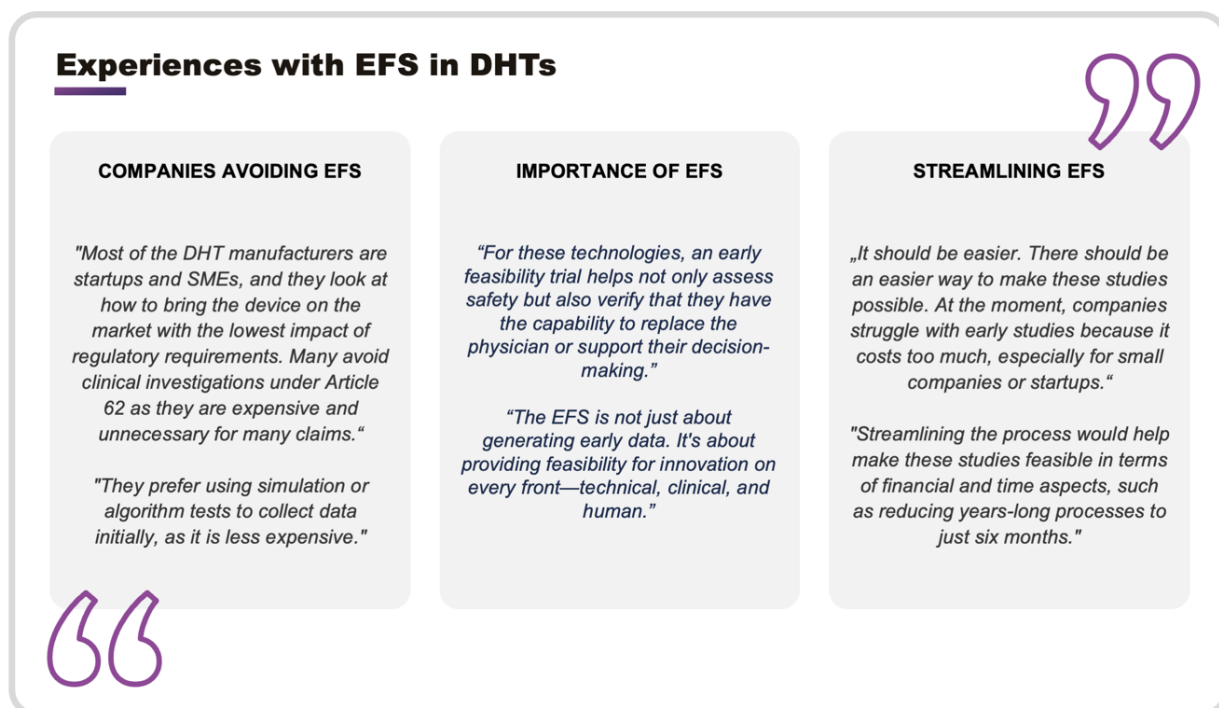
Several companies discussed alternatives to EFS due to their approach to avoid EFS/EFS-like studies whenever possible. These include conducting simulations with retrospective datasets, which allow for the testing of algorithms or models in a controlled environment without the need for live clinical trials. Others leveraged RWE by analyzing patient data from existing databases or partnerships with healthcare providers. For instance, some companies used synthetic datasets to mimic clinical scenarios, while others relied on feasibility analyses conducted *in silico* to refine product design and validate initial assumptions. In addition, some participants engaged in pilot collaborations with academic centers, focusing on user feasibility while avoiding formal EFS. These approaches were favored for their cost-effectiveness, efficiency, and reduced regulatory burden compared to traditional EFS.

3.3.2.4. The missed opportunity of EFS

Despite the challenges and alternatives, some companies emphasized that avoiding EFS entirely may represent a missed opportunity for DHTs and AI-MDs. EFS can provide crucial insights early in the development process, enabling timely device modifications before large-scale clinical studies are

undertaken. It is about providing feasibility for innovation on every front—technical, clinical, and human. In particular, EFS allows for the investigation of the "human" aspect of DHTs in clinical settings—capturing real-world interactions between users and devices. This enables the collection of critical usability and performance data in real-world settings. This feedback is invaluable for prototype modifications refining user interfaces, improving usability for both patients and professional users, and addressing unforeseen issues. Companies advocating for EFS highlighted its role in optimizing device design, ensuring user-centric solutions, and de-risking subsequent stages of development. Streamlining the process would help make EFS more feasible and attractive, encouraging broader adoption and fostering innovation in digital health technologies.

Figure 2. Quotes of the DHT interview partners regarding experience with EFS in DHTs



3.3.3. Clarity and applicability of the EU regulatory framework

3.3.3.1. Hardware-Centric vs. Software-Driven Realities

While many companies acknowledged improvements in transparency with MDR, most agreed the framework and ISO standards remain primarily oriented toward traditional hardware devices, failing to address DHT nuances such as iterative software updates or AI model changes. They emphasized that this hardware-centric focus often overlooks the fundamental nature of SaMD and AIeMDs, leading to significant barriers for early clinical evidence generation.

3.3.3.2. Clinical Investigation Planning

CI planning for DHTs presents a substantial obstacle. Companies report that the MDR's requirements for detailed pre-validation and documentation do not align with the exploratory and adaptive approach characteristic of early-stage development in DHTs. MDRs focus on extensive pre-validation often conflicts with the rapid refinements and protocol adjustments needed for DHTs, stifling the ability to adapt study designs based on interim findings. Interviewees highlighted that the framework's one-size-fits-all approach to CI is particularly unsuited to the iterative and dynamic processes central to DHT innovation. Additionally, companies report a lack of guidance on the clinical validation of AI/ML and regarding AI feature upgrades within existing MDs.

3.3.3.3. Risk management frameworks

Risk management frameworks, which are heavily adapted from traditional MDs, were also flagged as insufficiently tailored to DHTs. The inclusion of risks specific to software and algorithms often lacks clarity, leaving companies uncertain about the level of depth and validation required. These ambiguities hinder the effective alignment of risk management practices with regulatory expectations.

3.3.3.4. Fragmented Regulatory Landscape

Fragmented regulations across EU member states further complicate compliance. Companies struggle to reconcile disparate national requirements, particularly when managing cross-border patient data. This fragmentation increases compliance costs, delays timelines, and constrains the dynamic, data-driven nature of DHT development.

3.3.3.5. Familiarity with standards and regulatory pathways

The level of familiarity with MDR and ISO standards significantly shapes companies' regulatory strategies. Companies with robust internal expertise manage EU compliance more effectively, while those with less experience often rely heavily on external guidance. A notable number of companies prioritize the U.S. FDA regulatory pathway due to its perceived clarity, adaptability, and the availability of DHT-specific guidance. Some explicitly follow a "US first, EU second" approach, noting that this trend has reversed what was previously a "EU first" strategy.

Furthermore, several companies reported using U.S. FDA guidance and documents to address EU regulatory processes because of the lack of DHT-specific resources within the EU framework. This underscores the need for the EU to develop targeted guidance to remain competitive and supportive of DHT innovation.

3.3.3.6. Lack of dialogue with regulatory bodies

A lack of regular dialogue with CAs and NBs early on and throughout the process was also frequently cited as a critical issue. Companies emphasized the need for regular, constructive engagement with

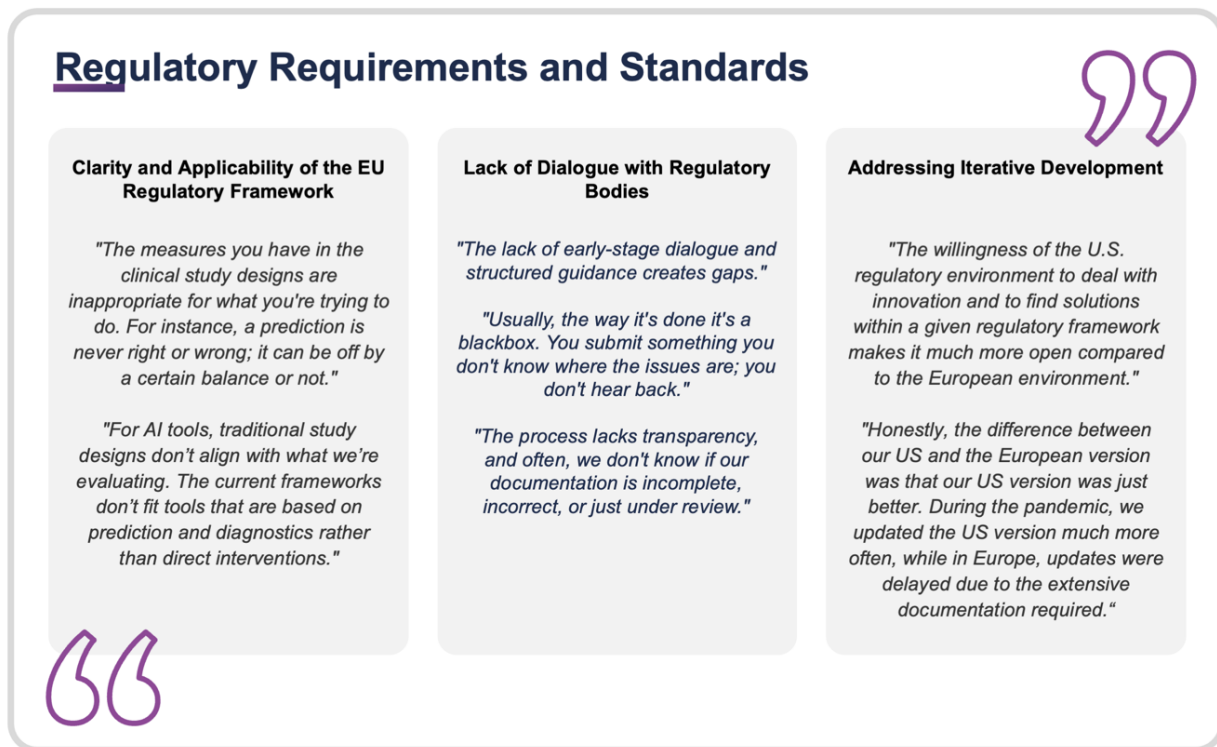
regulatory authorities to clarify expectations, address uncertainties, and navigate a regulatory framework that was not initially designed for the unique characteristics of DHTs. Such dialogue is especially important for finding pathways for innovative devices, where companies struggle to fit novel features and methodologies into pre-existing frameworks. The absence of these interactions often leaves companies operating under assumptions, increasing the risk of regulatory non-compliance or delays.

Additionally, a recurring theme in the interviews was the challenging role of NBs. Companies reported variability in the expertise of assessors/evaluators regarding DHTs, with some lacking sufficient familiarity with the complexities of SaMDs and AIeMDs.

3.3.3.7. Addressing iterative development within regulatory requirements

The iterative nature of DHT development remains a key regulatory challenge. While companies employ strategies such as design change control processes, many still find regulatory timelines incompatible with frequent updates and improvements. This misalignment creates uncertainty about how to manage ongoing changes without triggering new regulatory submissions or extensive documentation. Notably, some companies reported delaying or excluding innovative features from their EU products, prioritizing their introduction in the U.S. market instead. This decision is driven by the perception that the EU regulatory framework's rigidity, coupled with lengthy review processes, and the excessive burden of Post-Market Clinical Follow-Up (PMCF) requirements, which necessitate new documentation for each software iteration, limits the ability to efficiently launch updated or enhanced features.

Figure 3. Quotes of the DHT interview partners regarding regulatory requirements and standards



3.3.4. EU AI Act

3.3.4.1. Increased regulatory requirements for DHTs

The interviews indicate a widespread expectation that the EU AI Act will significantly increase regulatory requirements for DHTs, layering new obligations atop MDR. A recurring theme across interviews was the unclear interplay between the EU AI Act and the MDR, leaving many companies unsure how to handle overlapping or duplicate evidence demands. This ambiguity has led to uncertainty and emphasized the need for clearer guidance.

While some stakeholders expressed concerns that the heightened requirements could hinder innovation, especially for smaller enterprises, others identified the AI Act's staged introduction as an opportunity to progressively clarify regulatory guidance. Transparent enforcement, could support a more structured pathway for DHT development, fostering consistency across the EU. Aligning these requirements with international standards would further benefit companies operating globally, reducing regulatory fragmentation and uncertainty.

3.3.4.2. Varied levels of preparedness among companies

The interviews revealed a significant disparity in how prepared companies are for the EU AI Act. Companies heavily focused on AI began preparing years ago, forming dedicated teams or "AI

chapters,” to integrate AI-specific standards into their processes. In contrast, those with minimal reliance on AI have taken a more reactive approach, monitoring regulatory developments without implementing significant changes. Smaller companies expressed concerns about limited resources, potentially putting them at a disadvantage compared to larger organizations.

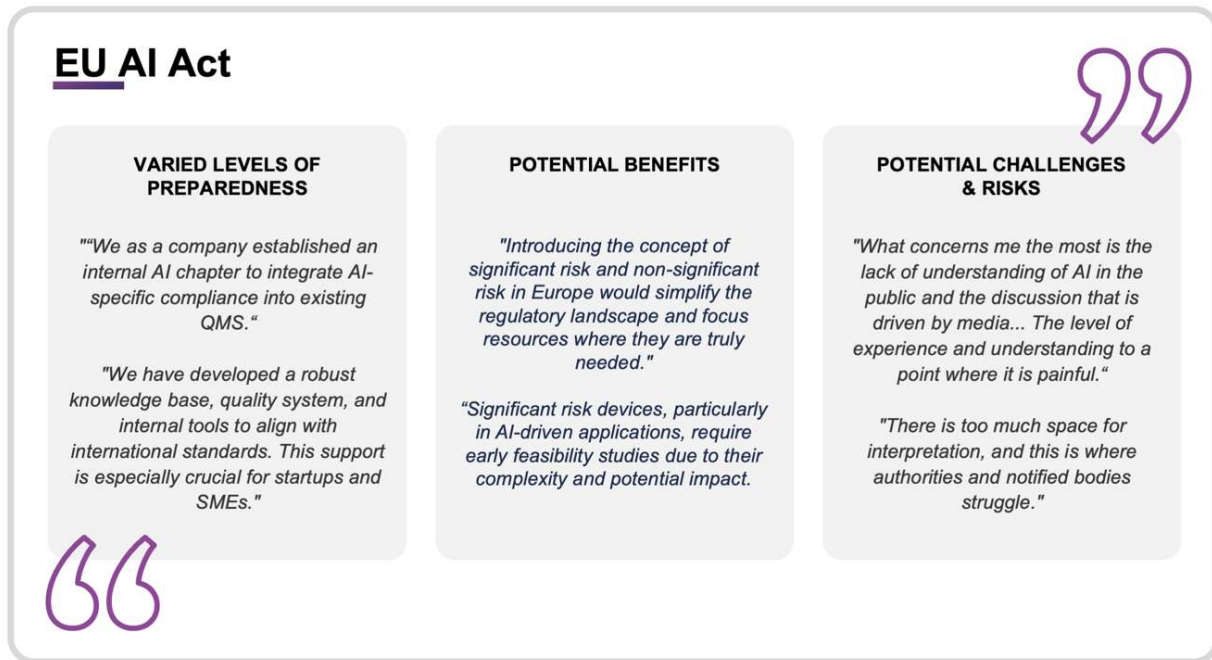
3.3.4.3. Potential benefits of the EU AI Act

Participants identified benefits including enhanced patient safety, greater data transparency, and increased trust in AI-driven healthcare solutions. Clearer AI regulation and an emphasis on accountability and fairness may address bias or misinformation and support public acceptance of these technologies. Some stakeholders noted that a more structured approach could reduce uncertainties in EFS, providing more predictable pathways to compliance. Alignment with international standards was also viewed as crucial for competitiveness and cross - border innovation.

3.3.4.4. Key challenges and risks

Highlighted regulatory complexity could slow innovation, especially for smaller companies, which may struggle to meet the stringent resource and expertise demands for compliance. Another significant challenge is the risk of public confusion about AI, which could undermine trust. Participants emphasized the need for the AI Act to address this through transparent communication and robust safeguards. Moreover, the potential for differing interpretations of the AI Act’s provisions across EU member states was flagged as a risk, potentially leading to inconsistent enforcement and added regulatory hurdles.

Figure 4. Quotes of the DHT interview partners regarding the EU AI Act



3.3.5. Expectations for a future EU EFS program

3.3.5.1. Key features of an EU harmonized EFS program

Based on the interviews, the following elements were considered critical for an EU harmonized EFS program that also addresses the specific needs of DHTs:

- DHT-specific guidelines
- Harmonization across EU member states
- Clear EFS pathway
- Transparent and collaborative Culture

3.3.5.2. Expectations for timelines, documentation, and feedback

Nearly all interviewees stressed the importance of predictable timelines in an EFS program. Specifically, about half of the companies interviewed considered a structured timeframe of 6-8 weeks for regulatory feedback to be reasonable. Participants also highlighted a distinction between informal and formal decisions: informal guidance was seen as valuable for addressing ambiguities early in the process, while formal regulatory decisions were viewed as necessary milestones to confirm and secure the development pathway.

The interviews also underscored the importance of fostering a regulatory culture focused on efficient communication and transparency. Companies called for clear guidance on documentation requirements through standardized templates to reduce administrative complexity and ensure consistency across member states. Reliable communication processes were seen as critical for building trust and enabling effective collaboration between innovators and regulators.

3.3.5.3. Structural supports to enhance EFS opportunities

Many respondents advocated for a centralized approach to regulatory guidance and resources, including a single EU-wide portal for templates, guidelines, and updates. They also suggested educational tools such as chatbots and community forums to create a common knowledge base and Training programs and workshops were proposed to help stakeholders navigate the EFS process effectively.

3.3.5.4. Insights from international models

Several companies pointed to the US FDA's EFS program as a model for the EU to consider. The FDA's structured timelines, Q-submission process, and detailed guidance documents were seen as strengths that could be adapted to the EU context. The FDA's Digital Health Center of Excellence, which provides specialized expertise and support on iterative software updates, artificial intelligence integration, and data-driven functionalities. Such dedicated support was seen as instrumental in fostering clarity and efficiency for DHT innovators. In addition, the US "PCCP" (Predetermined Change Control Plan) allows developers to implement iterative software improvements under a predefined regulatory framework, supporting rapid updates of DHTs.

One company reported on the Danish approach, which offers a streamlined process with one umbrella protocol approved by a single Ethics Committee, facilitating incremental changes without repeated full submissions (they ran more than 20 modifications under one umbrella protocol). This centralized system typically grants approval usually within two months and helps accelerate early feasibility work. In addition, the German Federal Institute for Drugs and Medical Devices DiGA guidance from Germany was highlighted as a best practice, particularly for its clarity and specificity in handling digital health technologies. A few interviewees suggested that the EU should harmonize international best practices to create a globally consistent approach to EFS, which also addresses DHTs and AIeMDs.

Figure 5. Quotes of the DHT interview partners regarding expectation for a future EFS program

Expectations for a Future EU EFS Program

KEY FEATURES

"We have developed a robust knowledge base, quality system, and internal tools to align with international standards. This support is especially crucial for startups and SMEs."

"The FDA provides detailed guidance, clear processes, and a pathway that goes from generating early clinical evidence to clearance and integration. Europe does not have this...but needs this."

STRUCTURAL SUPPORTS



"A toolbox or generally tools are really important ... tools that are ready, that have worked, and that are useful would make it easier for companies to collect and analyze data."

"It would be helpful to have a regulatory chatbot that you can just ask questions to, even without a guarantee of it always being 100% right."

REGULATORY CULTURE

"The U.S. mindset is centered on making it possible to bring innovation to market, even when the regulatory pathway is not completely laid out."

"In the European environment, the focus is rightly on protecting the patient from malfunctioning medical solutions, but the concept of supporting innovation to make it available is not necessarily the number one priority."

Source: Institute for Digital Medicine, University Hospital of Giessen and Marburg, Philipps University Marburg, Germany

4. Discussion

The findings from our scoping literature reviews, the focused review of the EU AI Act, and interviews with DHT companies and CROs highlight both the promise of EFS for DHT development and the complex challenges posed by overlapping or missing regulatory frameworks. Taken together, these results underscore an urgent need for greater clarity, harmonization, and collaboration among stakeholders in order to realize the full potential of EFS in accelerating innovation while also safeguarding patient safety and device performance in DHTs.

Several themes emerge that help contextualize these findings. First, our results reaffirm the rapidly evolving nature of DHTs and the growing awareness of their potential to improve diagnostic accuracy, personalize treatment, and streamline clinical workflows. However, the high degree of iteration and rapid software updates inherent to most DHTs strains traditional regulatory processes, which were typically designed for hardware-based MDs. The introduction of the AI Act adds an additional layer of scrutiny for AI-driven functionalities, yet its interplay with the MDR remains only partially defined.

4.1. The underutilization of EFS in DHTs

One of the most consistent messages emerging from the interviews and literature reviews is the relative underutilization of EFS in DHTs, despite its recognized value in iterative innovation. Despite its role in early-stage device assessment, few DHT companies systematically use EFS. Instead, many developers try to avoid EFS (or other forms of early CI) by relying on simulation studies, in silico analysis, or pilot studies that stop short of EFS. This avoidance often stems from regulatory uncertainties and fragmented guidance regarding DHTs, which leads developers to forego the benefits of refining their devices in real clinical environments before design finalization.

Yet, both the scoping reviews and stakeholder interviews underscore the critical role that early CIs can play in refining user interfaces, testing algorithmic performance, and identifying unforeseen safety issues arising from human-DHT interaction. EFS offers a structured means of gathering real-world clinician and patient feedback through iterative processes early in a DHT product's lifecycle. If the EU aims to remain competitive and foster innovation, addressing the barriers that currently disincentivize EFS may yield significant benefits for the timely adoption of novel DHTs.

4.2. Regulatory complexity and fragmentation

MDR applies to a broad range of MDs including DHTs, requiring compliance with clinical evaluation standards and risk classification. However, both the literature and interview data illustrate that many of these requirements - in particular, clinical evaluation for software-based technologies - are rooted in frameworks originally designed for hardware.

In addition, the fragmentation of regulatory interpretations across EU member states compounds these difficulties. Interviews from DHT companies and CROs revealed diverging interpretations of MDR's software classification rule, inconsistent documentation expectations for early clinical evidence generation and variability in national ethics committees' expertise for DHTs. This adds to development costs and prolongs timelines, often leading companies to pursue "US-first" market strategies where FDA guidance and processes - although rigorous - are perceived as more predictable. Such divergence not only hampers EU competitiveness but also stifles opportunities for European-based early-stage clinical research on DHTs.

Companies face ongoing tensions in meeting risk management standards under MDR, particularly regarding AI model updates. The perceived unpredictability of reclassification or re-approval processes for software updates can inadvertently slow the iterative improvements that define DHT innovation. For AIeMDs, compliance is set to become even more complex with the additional provisions of the EU AI Act, which aims to mitigate risks specific to high-risk AI systems. While these goals align with the MDR's emphasis on patient safety, the dual compliance burden is not yet clearly defined and can be particularly burdensome for SMEs with limited resources.

4.3. Need for an EU EFS program reflecting DHT-specific aspects

Findings from the scoping literature reviews and stakeholder interviews affirm the need for a harmonized EFS program also tailored to DHTs. Although certain hurdles, like complex clinical evidence requirements and multi-country fragmentation, are shared with non-digital MDs, EFS in DHTs is further complicated by specific needs.

Interviewees frequently referenced the FDA's Digital Health Center of Excellence and PCCP as promising blueprints for Europe. Additional international best practices highlighted the Danish "umbrella protocol" approach, which expedites incremental study changes via centralized ethics approvals, and Germany's DiGA guidance for digital health application, praised for its clarity on digital health requirements. Embracing these approaches, while aligning them with EU regulatory mandates

and core elements of the FDA's EFS program, could foster a cohesive, innovation-friendly environment that benefits both DHTs and MDs.

4.4. Implications for policy and practice

Several conclusions for future policy and practice can be drawn from these findings. First, developing more explicit guidance that addresses the unique characteristics of DHTs and AIeMDs is paramount. Although the MDCG's current documentation on clinical evaluation for medical device software is perceived as helpful, it could be expanded to more concretely define the scope and requirements of EFS across different software risk classes. Emerging HTA frameworks for DHTs, such as the ASSESS-DHT and EDiHTA projects, are developing methodological approaches (e.g., harmonized criteria, digital toolkits, and evidence repositories) that could inform DHT-specific needs. Although primarily aimed at HTA, these initiatives share complementary principles, like robust evidence generation and stakeholder engagement, potentially beneficial for better defining EFS in DHTs.

Second, the phased introduction of the AI Act may offer an opportunity to ensure synergy rather than duplication with the MDR. Establishing clear cross-references to the MDR's rules on clinical evaluation and clarifying how DHT developers can meet overlapping demands for AI risk management would be mutually beneficial.

Third, there is a clear need to address financial challenges through targeted funding initiatives or incentive programs that support the costs of EFS, especially for SMEs. Because early-stage clinical research can be resource-intensive, manufacturers may be dissuaded from pursuing formal EFS. Creating EU-backed grants or other financial incentives could significantly reduce these financial barriers, ensuring that innovative DHTs proceed through the rigorous evaluation needed to balance rapid innovation and patient safety.

5. Conclusion

Overall, the findings show that EFS remains an underutilized yet potentially transformative format to accelerate safe, user-centric and effective DHT development in the EU. Although stringent regulations and complex approval pathways aim to ensure safety and effectiveness, the current regulatory framework risks inadvertently hindering early clinical innovation for DHTs and AIaMDs. Clearer definitions, harmonized requirements, and enhanced structured dialogue could counteract these challenges. As the AI Act and MDR converge, creating a more cohesive regulatory environment becomes even more critical. A targeted, EU-wide EFS program that acknowledges the iterative and data-driven nature of DHTs could serve as an essential foundation for balancing innovation, safety, and patient benefit. The insights gained from our scoping reviews and interviews will inform the subsequent work packages of the HEU-EFS project, in particular, WP3's development of standardized processes, WP4's focus on protocol design, and WP6's exploration of ethical and legal issues.

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Appendix 1 Methods Scoping Literature Review

Search 3: DHTs and Regulation

The following distinct search was conducted the search terms described below using PubMed.

Search terms: ("digital health technology" OR "digital medical device" OR "software as a medical device") AND ("regulatory" OR "regulation")

Filters: from 01.01.2019 – 15.4.2024

Inclusion Criteria:

Publications must cover at least one of the following topics:

- **Regulatory frameworks** for DHT, SAMD, embedded software, AI algorithms, and telemedicine.
- **Early stage CI** related to all pilot stage studies such as EFS, First in Human (FIH) and other early-stage feasibility studies.
- **Gaps, challenges, or regulatory barriers** encountered in conducting early stage CI or other pre-market programs for DHTs.

Exclusion Criteria:

Publications will be excluded if they:

- Focus on post-market studies.
- Are not directly related to SAMD/DHT or regulatory issues.
- Were published before January 1, 2019.

Search was conducted using PubMed. The search results were managed using the following workflow:

- Results were loaded into Zotero for field standardization.
- Data were converted into CSV files and imported into Stata (v. 18) to remove duplicates.
- The cleaned CSV files were uploaded onto Rayyan.ai for screening.

Screening and Selection Process

The screening process followed PRISMA guidelines and included:

- Title/Abstract screening.
- Full text/content screening.
- Further in-depth screening using snowballing methods and consulting colleagues.
- Data analysis and synthesis.

Data Extraction

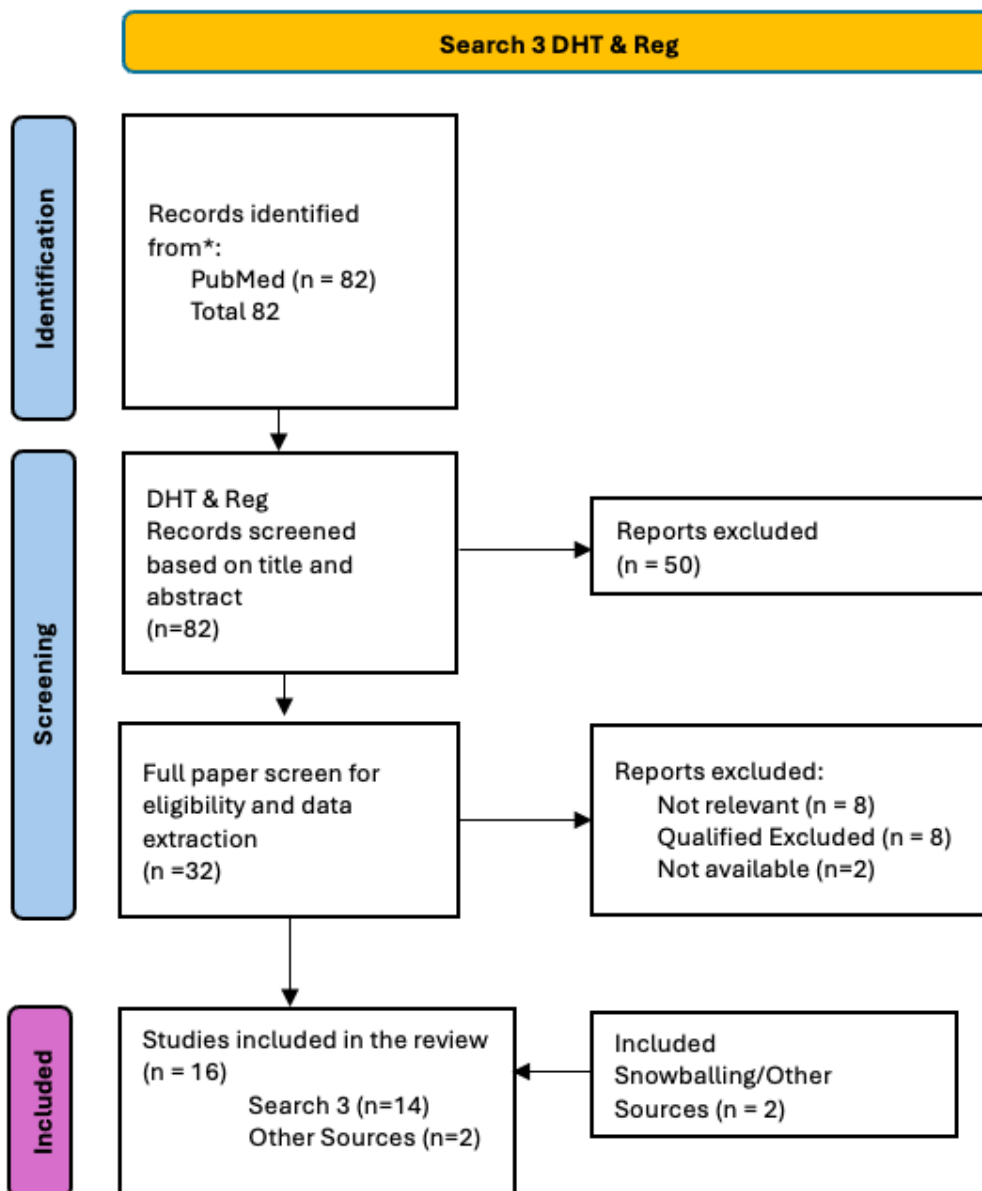
A standardised data extraction table was established to harmonise information gathering. Themes relevant to our task included: Regulatory hurdles, quality and risk management, economic sustainability, eligibility criteria for EFS, evidence of early dialogue, and the roles of stakeholders before, during and after an EFS.

Screening results and PRISMA flow diagram

Search 3: Regulatory based search – DHTs and Regulation

The study selection retrieved a total of 82. 50 records were excluded and 32 were included based on title and abstract. Among the 32 DHT & Reg, 2 were not retrievable, 8 not relevant and 8 were qualified excluded mainly because the publications bear no reference to an EFS program but provide overviews and supporting information for subsequent work packages. At the conclusion of the full-text screening process, within the DHT & Reg publication group, 14 publications were selected for inclusion in the review. 2 publications were added through snowballing and other sources, The total inclusion in the review is 16. Of these, 9 focus on regulatory frameworks, 3 on specific applications of digital therapeutics and AI, and 4 on barriers and enablers for scaling digital health innovations.

Figure 6. PRISMA flow diagrams for the scoping literature review (DHT & Regulatory)



Appendix 2 Methods Interviews on DHTs in the context of early clinical evidence generation/EFS

Semi-structured interview guide

1. Introductory Questions to understanding the clinical evidence required for CE marking

"Can you share an overview of your company's focus and recent medical devices in digital health technologies?"

Follow-up questions:

- "What types of digital health technologies (DHTs) have you/are you currently developing, and what are their intended uses?"
- "What was your experience in deciding if your product qualifies as a medical device (or not) under the current EU regulations?"

"How did you determine the risk classification of your product, and were there challenges in this process?"

- "Did you seek any regulatory advice to support your clinical development plan? If so, what type and how useful was it?"
- "For early clinical evidence generation, what were the primary goals, such as:
 - Clinical validation of the technology
 - To understand patient or clinician experiences in using the DHT
 - To assess safety/performance/effectiveness outcomes of the DHT
 - To achieve CE-marking and provisional reimbursement
 - Other

2. Experiences with EFS / early clinical evidence generation

"Can you describe any recent experiences with EFS/early clinical evidence generation for your digital health products?"

Follow-up questions:

- "How frequently do you engage in EFS, and what drives the decision to initiate these studies?"
- "What major challenges have you encountered when designing or conducting EFS for DHT
 - if no EFS experience: why not?
 - If EFS planned but not conducted: Why was it not conducted/cancelled?

3. Regulatory Requirements and Standards

"How clear and applicable do you find the EU regulatory framework, especially MDR guidance and ISO standards, for early clinical evidence generation in DHTs?"

Follow-up questions:

- "Do you feel that the current regulatory guidelines adequately cover EFS for DHTs, or are there areas that lack clarity?"
- "Are there specific regulatory aspects (such as risk management or CI planning), that have been challenging?"
- "How does your familiarity with these standards influence your approach to early CI?"
- "How do you address the iterative nature of DHT development within the framework of regulatory requirements?"

4. EU AI Act

"How do you anticipate the EU AI Act will impact the regulatory requirements for DHTs, especially MDR guidance and ISO standards, for early clinical evidence generation in DHTs?"

Follow-up questions:

- "How is your company preparing to comply with AI-specific regulations in addition to existing medical device standards?"
- "How is your company preparing to comply with AI-specific regulations in addition to existing medical device standards?"
- "Do you see potential benefits or challenges from the EU AI Act that could influence the way DHTs are developed and assessed in early feasibility stages?"

5. Expectations for a Future EU EFS Program

"What features or support would be most valuable in a potential EU harmonized EFS program for DHTs?"

Follow-up questions:

- "How important is early-stage regulatory consultation, and how could it be improved to support EFS in DHTs?"
- "What are your expectations regarding timelines, documentation, and feedback in an EU EFS program?"

- "Are there specific supports or structures that you believe would strengthen EFS opportunities in the EU?"
- "Are there any international EFS programs, such as the US FDA's EFS program or the Center for Digital Excellence, that you feel the EU could model to improve its own EFS framework?"

6. Closing Questions

"Do you have any additional feedback or thoughts on EFS /early clinical evidence generation in DHTs that we haven't yet discussed?"



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