

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 2.1

EU regulatory framework and international standards

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ABBREVIATIONS

Abbreviation	Definitions
AI	Artificial Intelligence
BfArM,	Bundesinstitut für Arzneimittel und Medizinprodukte (The Federal Institute for Drugs and Medical Devices)
CE	Conformité Européene
CEC	Clinical Events Committee
CHPL	Certified Health IT Product List
CI	Clinical Investigation
CIP	Clinical Investigation Plan
CIRCA-BC	Communication and Information Resource Centre for Administrations, Businesses and Citizens
CONSORT-AI	Consolidated Standards of Reporting Trials extension for Artificial Intelligence interventions
CORE-MD	Coordinating Research and Evidence for Medical Devices
DHCoE	Digital Health Center of Excellence
DHRP	Digital Health Regulatory Pathways
DHTs	Digital Health Technologies
DiGA	Digitale Gesundheitsanwendungen (Digital Health Applications)
DiGAV	Digitale-Gesundheitsanwendungen-Verordnung (Digital Health Applications Ordinance)
DigiG	Digital-Gesetz (Digital Act)
DSMB	Data and Safety Monitoring Board
EFS	Early Feasibility Study
EMA	European Medicines Agency
EU	European Union
EUDAMED	European Database on Medical Devices.
EXPH	Expert Panel on effective ways of investing in Health
FIH	First in Human
FDA	Food and Drug Administration
GSPR	General Safety and Performance Requirements
HEU-EFS	Harmonised approach to Early Feasibility Studies for Medical Devices in the European Union
HTAR	Health Technology Assessment Regulation ((EU) 2021/2282)
IB	Investigator's Brochure
IDE	Investigational Device Exemption
IEC	International Electrotechnical Commission
IHI	Innovative Health Initiative
IMDRF	International Medical Device Regulators Forum
IRB	Institutional Review Boards
ISO	International Standards Organization
JAMS 2.0	Joint Action on Reinforced Market Surveillance of Medical Devices and In Vitro Medical Devices

Abbreviation	Definitions
MDIC	Medical Device Innovation Consortium
ML	Machine Learning
MDCG	Medical Device Coordination Group
MDD	Medical Device Directive
MDSW	Medical Device Software
MDR	Medical Device Regulation ((EU) 2017/745)
MEDDEV	Medical Device Documents
MHRA	Medicines and Healthcare products Regulatory Agency
MINIMAR	Minimum Information for Medical AI Reporting
NBCG	Notified Body Co-ordination Group
NCA	National Competent Authority
NICE	National Institute for Clinical Excellence
OBP	Online Browsing Platform
PECAN	Prise en Charge Anticipée Numerique (Early access to reimbursement for digital devices)
PMAP	Pre-market Approval Pathways
PMAP-DB	Pre-market Approval Pathways database
PMCF	Post Market Clinical Follow up
Pre-Cert	Software Precertification Pilot Program.
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
RCT	Randomized Clinical Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SaMD	Software as a Medical Device
SiMD	Software in a Medical Device
SPIRIT-AI	Standard Protocol Items: Recommendations for Interventional Trials – Artificial Intelligence
UDI	Unique Device Identifier
US	United States
WHO	World Health Organisation
WMD	Wearable Medical Device
WP	Work Package

EXECUTIVE SUMMARY

Early Feasibility Studies (EFS) are limited clinical investigations (CI), early in the development of a medical device (MD) to evaluate the device design concept and understand initial safety and performance. EFS are typically undertaken for higher risk class MDs (referred to as class IIb or class III in the Medical Device Regulation ((EU) 2017/745) (MDR)), although an EFS is possible for any risk class.

Requirements in the MDR typically refer to clinical investigations generally, rather than EFS specifically, and as such the specificity of requirements relating to EFS in particular is limited. There are new requirements in the MDR to consider study phasing as part of clinical development planning.

EFS are not supported by a specific program in the EU. The United States Food and Drug Administration (US FDA) launched a specific program for EFS in 2013. We conducted an analysis of the European Union (EU) regulatory framework relating to EFS of medical devices to understand the best fit for a possible future EU EFS program. To do this, we reviewed EU regulations, international standards, and guidelines, in addition to a specific analysis of EU and international research projects relating to Digital Health Technologies (DHTs).

Before preparing an EFS, it is essential to address key development questions, such as whether an EFS is necessary, if sufficient pre-clinical development has been conducted, and how the EFS should be designed. All in all, development activities related to EFS can be divided into three stages: activities before an EFS, activities directly related to an EFS, and activities following an EFS.

Device developers engaged in clinical development, are required to comply with MDR requirements, and they need to consider International Standards Organisation (ISO) standards and Medical Device Coordination Group (MDCG) guidance.

Overall, we found that EFS are possible in the EU system although they are not specifically facilitated. MDR requirements and associated regulatory guidance are predominantly framed towards clinical investigations generally rather than EFS specifically. Consequently, available guidance, standards and templates do not tend to address EFS specific considerations.

ISO standards can be vertical (relating to technologies) or horizontal (relating to activities such as clinical investigations). For vertical standards, there can be variable amounts of specificity relating to EFS activities; this can range from detailed information concerning generating a research hypothesis, designing an EFS and analysing the results, to limited references to considering the need for an EFS.

Guidance documents from the MDCG contain templates and guidance for clinical investigations that are relevant to EFS. Guidance developed to support the US FDA EFS program allows for different

types of pre-clinical development compared to other clinical investigations. In the EU, MDCG guidance relating to clinical investigation documentation includes similar concepts; for example guidance relating to the clinical investigators brochure (IB) permits incomplete testing in compliance with available standards when a scientific justification is provided. Although both jurisdictions have guidance concerning this concept, the guidance is less detailed in the EU and relates to clinical investigations generally.

There are some advice structures available in the EU to support developers in meeting regulatory expectations. These are at an earlier stage of development when compared to the US FDA advice structures.

DHTs that qualify as medical devices have unique characteristics and EFS studies for these technologies can have different purposes. Historically, EFS studies were not commonly conducted for DHTs. Instead, a wide range of clinical pilot studies were performed, often involving more participants than what is typical for EFS. EFS for DHTs can, in some cases, be used to achieve both CE-marking (Conformité Européenne), and provisional reimbursement in some Member States; this is significantly different to EFS of MDs, where an EFS is insufficient for CE-marking. The updated MDR classification results in higher risk classifications for many DHTs, with software for decision-making in diagnostics or therapeutics classified as Class IIa unless it could cause death or irreversible health deterioration (Class III), or serious health deterioration or surgical intervention (Class IIb). This up-classification has increased the expectations for pre-market clinical investigations and hence EFS. Specific guidance on medical software, addressing gaps and uncertainties, has been issued, particularly in the US. Additionally, regulatory agencies need to ensure that sufficient expertise and human resources for DHTs are available.

For some general medical device technologies (for example devices considered ‘breakthrough’ devices in the US), and for the vast majority of DHTs, multiple changes to the technology may be justified in the EFS setting. Substantial iterations during EFS are conceptually important and a future program would benefit from an expert led, agile and timely procedure for their assessment. Different types of dialogue, e.g., early advice, and continuous dialogue with national competent authorities (NCAs) appear to be vital to a future EFS program success. MDR has minimal references to other key stakeholders such as patients and clinicians. Literature reporting on the US experience of EFS since 2013 has highlighted the importance of stakeholder engagement to refine EFS planning and development.

1. Introduction

This report describes the research and analysis of the EU regulatory framework relating to EFS of medical devices. The objective of this report is to understand the best fit for a possible future EU EFS program, and to account for possible interactions between such a program and current regulations (refer to the proposal for detailed descriptions of the objectives and tasks). Beyond this report, the regulatory landscape throughout the project's duration will be monitored to account for any changes that may affect the project.

To achieve this objective, we completed two tasks:

- An analysis of EU regulations, international standards, and guidelines to identify any gaps that could impact a possible future EU EFS Program. This includes an analysis of the MDR, relevant ISO standards and regulatory guidance. This analysis is complemented with a systematic literature review on EFS, conducted in collaboration with work package 1 (WP1).
- A specific analysis of research projects related to EFS for DHTs. Given the unique lifecycles and features of DHTs, this task involves a DHT-specific subgroup-analysis of the objective above and a mapping of relevant current EU-funded and international projects related to DHTs and clinical evidence generation.

With respect to the literature review, an interim analysis of scientific literature was also undertaken for DHTs, the complete review will be completed by month 15 of the project and it will be supplemented by interviews with relevant stakeholders to address specific regulatory aspects of these products.

To aid comprehension, key terminology relevant to the medical technologies and clinical studies analysed in this report is presented in [Appendix 1.1](#). The two terms of key relevance to this report (EFS and DHT) are briefly introduced here due to their significance to the report:

“Early feasibility study” is not defined in the MDR. ISO 14155:2020 Annex I.5.3 provides a description of an “early feasibility clinical investigation” as follows: *“A limited clinical investigation 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). It can be used to evaluate the device design concept with respect to initial clinical safety and device clinical performance or effectiveness (if appropriate) as per intended use 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 clinical investigation can guide device modifications. An early feasibility clinical investigation does not necessarily involve the first clinical use of a device.”*

The term “digital health technology” is not used in the MDR, and it likely has a broader scope than medical device software (MDSW) regulated by MDR, including different forms of health and wellness apps, bioinformatics, and supportive digital applications that do not meet the definition of a medical device. The US FDA have a definition of DHT in the context of remote data acquisition in clinical investigations which is a ‘system that uses computing platforms, connectivity, software, and/or sensors, for healthcare and related uses.’ Related terminology is also presented in [Appendix 1.1](#).

This report is structured as follows: first, we will provide a brief explanation of our methodology. Second, we will present the results of the analyses and the mapping of EU-funded projects. Third, we will discuss five focus points, namely:

1. Can you currently undertake an EFS in the EU?
2. Do current EU regulatory frameworks, standards and guidance fully address key decision points for EFS preparation?
3. How does the system manage protocol and device modifications?
4. How could European institutions and Member States deliver a harmonised EFS program?
5. Is dialogue a vital feature of a Future EU EFS Program?

Finally, we conclude with future perspectives. To support orientation, an introduction to the EU and national processes related to an EFS is provided in [Appendix 1.2](#), and an introduction to the US EFS program (produced in collaboration with WP1) is provided in the next section.

1.1. An introduction to the US EFS program

In 2013, the US FDA launched the Early Feasibility Study program, for medical devices of medium and high risk (1). Designed to fit into the existing FDA medical device regulatory framework, the EFS program represented an opportunity to incentivise research, attract investments and ensure early access for US patients to new technology (2).

The clinical investigations undertaken as part of the EFS program are regulated by the FDA under the Investigational Device Exemption (IDE) regulations, which allow an MD to be used in a clinical study. At the time of launch, the FDA published specific guidelines for EFS, titled “Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Clinical Studies, Including First in Human Studies”, intended to support FDA staff, clinicians, innovators and the industry with the development and review of IDE applications for early feasibility studies of “significant risk devices” (1). The FDA guidance defines an EFS as “a clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication” (1). EFS are suitable when further nonclinical tests cannot provide information necessary to optimize design, function or

deliverability of the device, or provide insights for proof of principle or safety, or when appropriate nonclinical tests are unavailable. Although conducting an EFS is not a regulatory requirement applicable to all devices, it can be helpful to optimise the design, function and deliverability of the device, or provide clinical and safety data which non-clinical testing methods cannot provide (2). It may also serve to optimise operator technique or refine the patient population for the technology's intended use. As devices eligible for EFS are early in their development, the EFS program is characterised by a higher degree of uncertainty compared to other clinical investigations and must be justified by a risk-benefit analysis.

With respect to subject numbers, US FDA guidance refers to conducting EFS on a “small number” of patients, for example 5-10 subjects (3). Medical Device Innovation Consortium (MDIC) documents and several publications usually refer to numbers of patients as less than 15 (4–7).

To initiate an EFS, the sponsor contacts the Center for Devices and Radiological Health (CDRH) within the FDA to understand whether the device is suitable for this program. If it is, a meeting is set up within two weeks to present the device, discuss possible criticalities and clarify the rationale for performing an EFS. The FDA is responsible for identifying the most appropriate team (among 8 review groups broken down by technology areas, e.g. orthopedics or cardiovascular, Table 1) which will provide feedback on the device during the review process. Feedback is available after 45 days from the beginning of the pre-submission process (see Figure 1) (8). During this process, the FDA becomes more familiar with the device and collaborates with the sponsor to agree on the information to be included in the report of prior investigation (including any prior clinical, laboratory and animal testing previously conducted) and the investigational plan (reporting risk analysis, clinical protocol, protection measures and monitoring procedures) (8). At this stage, the sponsor should seek approval from the Institutional Review Board (IRB) responsible for assuring the study is ethical and participants' rights and welfare are protected.

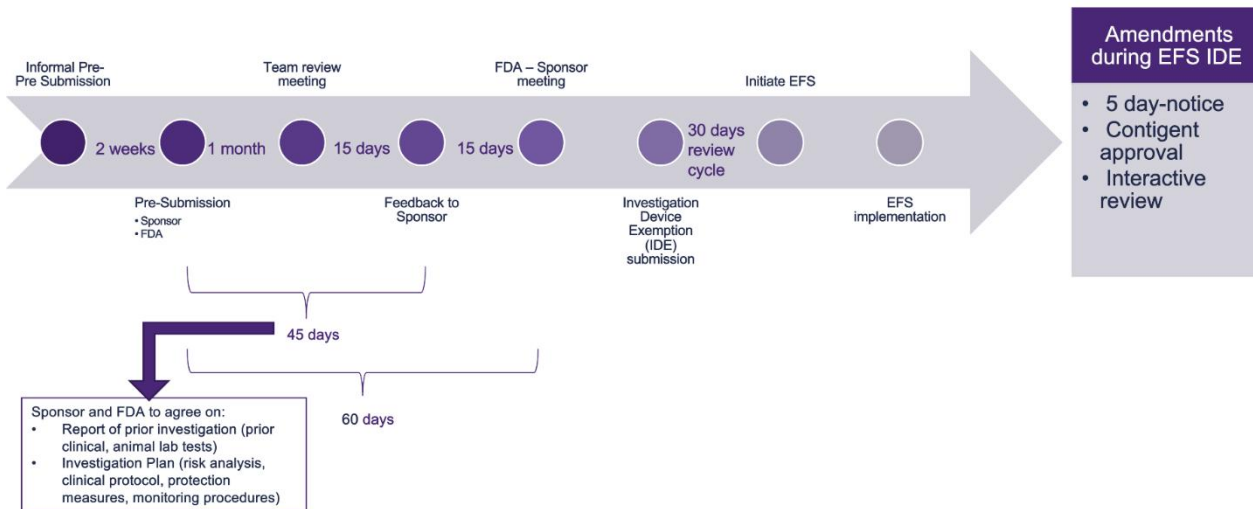
Table 1. FDA Center for Devices and Radiological Health (CDRH) Review Group Areas

FDA review group areas
Ophthalmic, Anesthesia Respiratory, ENT and Dental Devices
Cardiovascular Devices
Reproductive, Gastro-Renal, Urological, General Hospital Devices and Human Factors
Surgical and Infection Control Devices
Neurological and Physical Medicine Devices
Orthopedic Devices
<i>In Vitro</i> Diagnostics
Radiological Health

Source: (FDA Center for Devices and Radiological Health, 2022) (7)

Following the incorporation of US FDA advice, the sponsor can proceed with the IDE regulatory submission, which allows the use of a specific significant risk device in clinical trials to collect data (Figure 1). The submission goes through a 30-day review cycle to ensure that the study design is appropriate and does not pose any unreasonable risk to patients. This review period is generally highly interactive with FDA, usually characterized by frequent exchanges with questions and requests for clarification from FDA for the sponsor (8). Once IDE approval has been obtained the EFS study can begin, provided, as for all clinical investigations, IRB approval from the study site has also been obtained (8).

Figure 1. EFS Submission and Review Process



Source: adapted from Medical Device Innovation Consortium (MDIC), 2016, p. 25. (8)

Since “changes to the device design and materials, procedure, instructions, and even patient population are to be expected” (8), continued interaction with the FDA is encouraged, this serves to lower the risk of regulatory delays. Given that the aim of conducting an EFS is to gather data to help optimise the device design, its function or deliverability, there are different approaches that sponsors can take to make changes to the device during the EFS study, including: a 5-day notification period for non-significant changes, for which FDA approval is not needed; a contingent approval for significant changes which have been previously discussed and agreed upon with the FDA, which requires a 10-day notification before making the change; and an interactive review, for those cases when non clinical testing is completed to evaluate changes, and the FDA requires additional information that will be reviewed within a 30 day review timeline.

Once an EFS is completed, the sponsor and the FDA may determine that further changes to the device are needed. In this case, an expansion of the EFS study may be requested. On the other hand, if the design is near final or final and sufficient non-clinical data are available (an introduction to the terms ‘pre-clinical’ and ‘non-clinical’ is presented in [Appendix 1.1](#)), the EFS could be further developed into a traditional feasibility study or a pivotal study, depending on whether the preliminary safety and effectiveness information is adequate or further data is needed (Table 2). This decision must be reached in conjunction with the FDA.

Table 2. Comparison between Early feasibility study, a traditional feasibility study, and a pivotal study

	EFS	Traditional Feasibility	Pivotal
Design	Not final	Near final	Final
Data	Less nonclinical data available	More nonclinical data available	Nonclinical data completed
Aims	Provide initial insights regarding clinical safety and performance or effectiveness	Capture safety and effectiveness info to plan pivotal study	Capture safety and effectiveness info to support marketing application

2. Methods

For the purpose of this report, this section will only include a brief description of the methodology. For a complete detailed version, please refer to [Appendix 2.1](#).

The methodology involved an in-depth examination of the current regulatory framework and specificities of DHTs. This included a comprehensive review of the MDR, the Health Technology Assessment Regulation (EU) 2021/2282 (HTAR), international standards, and guidelines governing clinical investigations. To address potential gaps that may not have been fully covered in the regulatory review, a systematic literature review based on a comprehensive search of grey and scientific literature was conducted, including DHTs. The full texts of the documents were retrieved and analysed using extraction templates. Additionally, for DHTs specifically, a mapping of EU and international projects was conducted.

This chapter is divided into two parts, firstly the methods used for the analysis of EU regulations, international standards and guidelines and secondly, the methods used for the mapping of EU-funded and International DHTs Projects.

2.1. Analysis of EU regulations, international standards and guidelines

This section includes the methods used for both the regulatory review and the systematic literature review.

The Regulatory Review

We prepared a consolidation of approaches to analyse the regulatory guidance documents, which included: first, the collection of documents pertaining to clinical investigations; second, a screening of the full text of the documents; and finally, the extraction of relevant data on clinical investigations and EFS. Individual strategies were prepared for the MDR, the HTAR, and international standards reviews. The different strategies are presented below. At the time of writing, the proposed Artificial Intelligence Act is proceeding through the last legislative steps prior to finalisation (9), this was not subject to a detailed analysis, however it will be monitored throughout the project, given its relevance to DHTs.

MDR and HTAR Review

For the MDR review, a table was prepared in Microsoft Excel with the recitals / chapters / annexes in separate tabs. A screening of the full text of MDR was then undertaken to identify parts of the MDR relevant to EFS. To identify these parts, the specific aspects listed in Table 3 were determined by WP2 and iteratively refined prior to finalisation. A DHT-specific subgroup-analysis was conducted. To provide a clear and structured overview of the EFS process, a chronological categorisation of the specific aspects was chosen and is organised into three phases: before EFS, directly related to EFS (during), and after EFS.

Table 3. Development activities and other specific aspects relevant to the MDR review

Before EFS	Directly related to EFS	After EFS
Is an EFS (or CI) needed?	Preclinical development requirements	What further studies are needed?
Clinical development strategy	Understanding when sufficient pre-clinical work has been completed?	What data should be collected pre- or post-market?
Advice for understanding clinical requirements.	Pre-clinical evaluation	Sufficient clinical data and EFS
Intended purpose description	Use of ISO to justify pre-clinical development.	Equivalence* and EFS.
	Availability of advice for CI planning?	

**Equivalence refers to the use of clinical data from the device of another manufacturer, or to the use of clinical data relating to a previous device from the same manufacturer (MDR, Article 61(4), Article 61(5)).*

For the HTAR review, a simple annotated reading was undertaken to identify any aspects of relevance to EFS.

Standards Review

The systematic analysis of standards documents lacks a directly applicable methodology and therefore the approach below was developed. Separate search strategies were applied for standards concerning DHTs which are discussed in the next subsection.

A search strategy was prepared for the ISO Online Browsing Platform (OBP) to identify all ISO standards specific to medical devices. Two searches were conducted. A first 'broad' search to identify all medical device ISO standards containing the terms "medical devices" and "clinical". The use of

broad search terminology (rather than the use of EFS or synonyms) was selected in the first instance to ensure that all relevant standards were included for analysis. The title and the notes sections of retrieved standards were then screened for reference to the following terms: “clinical”, “preclinical”, “clinical investigation”. Following this, the table of contents and informative sections were reviewed to determine whether clinical investigations was within the scope of the standard. Where this was the case, the standard was selected for retrieval and further extraction. Standards were retrieved from the SAI Global i2i Platform. This is a platform which allows access to ISO standards, and it was available to reviewers via the library service of TCD. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the screening process is provided in [Appendix 2.2](#).

The Selected Standards were grouped into device types (See [Appendix 2.2](#) Figure 12). Standards relating to biocompatibility, health informatics, risk management, post-market surveillance, medical laboratories were excluded. In instances where the text of the standard under evaluation referenced other standards, the relevant standards were also extracted if deemed applicable. A total of 43 standards were extracted using the extraction template.

For completeness, to ensure that any standard relevant to EFS or synonyms was included, a second search utilising the terms described in Table 4 was undertaken using the ISO OBP. This did not result in the identification of any other standards.

Table 4. Search Terms Early Feasibility Studies

Search Terms		
“Early feasibility study”	“iterative development”	“proof of concept”
“preclinical feasibility study”	“translational research”	“prototype study”
“pre-clinical feasibility study”	“early stage clinical”	proof of principle”
“pre-clinical feasibility study”	“early clinical evaluation”	“initial clinical safety”
“early clinical feasibility”	“early clinical evaluation”	“early clinical study”

DHT Review Methods

The ISO OBP was interrogated to identify all standards that were applicable to DHTs and Pilot / EFS clinical investigations. A total of 5 searches of the ISO OBP were completed using the following search terms to complete a comprehensive interrogation of the platform (Table 5).

Table 5. Search Terms DHTs

Search Terms				
Search 1	Search 2	Search 3	Search 4	Search 5
"DHT Software as a medical device"	"Clinical DHT Software as a medical device"	"DHT and Clinical Investigation"	"Clinical Investigation and Software as a medical device"	"Software as a medical device"

The title and the notes were initially screened for reference to the following terms: "clinical investigation", "clinical", "clinical evaluation".

The scope of the standard was reviewed for relevance. If a decision could not be reached on the relevance of the standard, the standard was retrieved for discussion/extraction with the team, which included DHT experts.

The following terms were excluded: risk, devices that were not Software/DHT, IVD, Medical Electrical Equipment, any devices other than software, health informatics, Medical Laboratories that were not deemed to have relevance to the topic.

The selected standards were retrieved from the SAI Global i2i Platform and an extraction performed. The PRISMA flow diagram of the screening process is provided in [Appendix 2.3](#).

Regulatory guidance documents (MDCG, MEDDEV, IMDRF, NBCG, TEAM-NB) Review

A rationale for the selection of these sources is provided in [Appendix 2.4](#). Key sources included the MDCG guidance documents, Medical Device Documents (MEDDEV) guidance documents, and other relevant regulatory information (International Medical Device regulatory Forum (IMDRF), NBCG (Notified Body Co-ordination group) and the Team-NB guidance documents. Regular meetings helped finalise the plan for analysing these documents.

Documents were sourced from the European Commission's website, the TEAM-NB, NBCG and IMDRF websites. A screening, annotation and text summarisation based on the full text of each document referencing clinical investigations for medical devices and DHTs was conducted.

Data extraction focused on themes such as coverage of clinical investigations, methodological guidance on EFS, eligibility criteria for EFS, and evidential requirements. The PRISMA flow diagrams of the screening process are provided in [Appendix 2.5](#), [Appendix 2.6](#), [Appendix 2.7](#), and [Appendix 2.8](#). The findings are presented in the results section.

The Systematic Literature Review

The systematic literature review aimed to find additional information pertaining to EFS that may not be completely addressed in the regulatory review. The review focused on identifying gaps and barriers in the current EFS program for medical devices and DHTs in the EU and other relevant jurisdictions. Searches were conducted using Web of Science, Scopus, and 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.

The criteria defined for the systematic literature review were as follows:

- Inclusion: Papers related to EFS, early stage clinical investigation* and/or pre-market programs, papers discussing the gaps, barriers, and challenges encountered during the execution of an EFS or a pre-market program, including the monitoring of such programs.

**Early stage clinical investigation: related to all pilot stage studies, such as first in human (FIH), early and traditional feasibility studies, as well as clinical investigations with a sample size of approximately 15 subjects.*

- Exclusion: Papers focusing on post-market studies, pharmaceuticals, animal studies, or published before 2013.

For DHTs, additional criteria were defined to narrow the review and make it more specific to DHTs:

- Inclusion: Papers related to software as a medical device, including pilot or early feasibility trials, medical applications, telemedicine, embedded software, AI algorithms, and papers related to DHT regulations.
- Exclusion: Papers not related to software as a medical device, 3D printed devices.

The screening process followed PRISMA guidelines and included:

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

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. The PRISMA flow diagram of the screening process is provided in [Appendix 2.9](#) with findings presented in the results section.

2.2. Mapping of EU-funded and International Digital Health Technologies (DHTs) Projects

Given the unique lifecycles and features of DHTs, this task involves mapping current EU-funded and international projects related to DHTs, as well as Member States initiatives focused on DHTs, to support future research activities, such as stakeholder interviews and scientific exchange.

To identify EU-funded Horizon projects, we primarily used the official EU funding and tender's portal as our data source for Horizon Europe projects. We then conducted searches for projects related to digital health technologies. We have also checked other websites, including EuroHealthNet and Innovative Health Initiative (IHI) with respective search terms. To identify Member States' initiatives on DHTs, we have relied on knowledge derived from WP1 and an independent research project by consortium members. Additionally, we asked project partners to identify initiatives on DHTs at all levels, which are relevant to the project.

3. Results

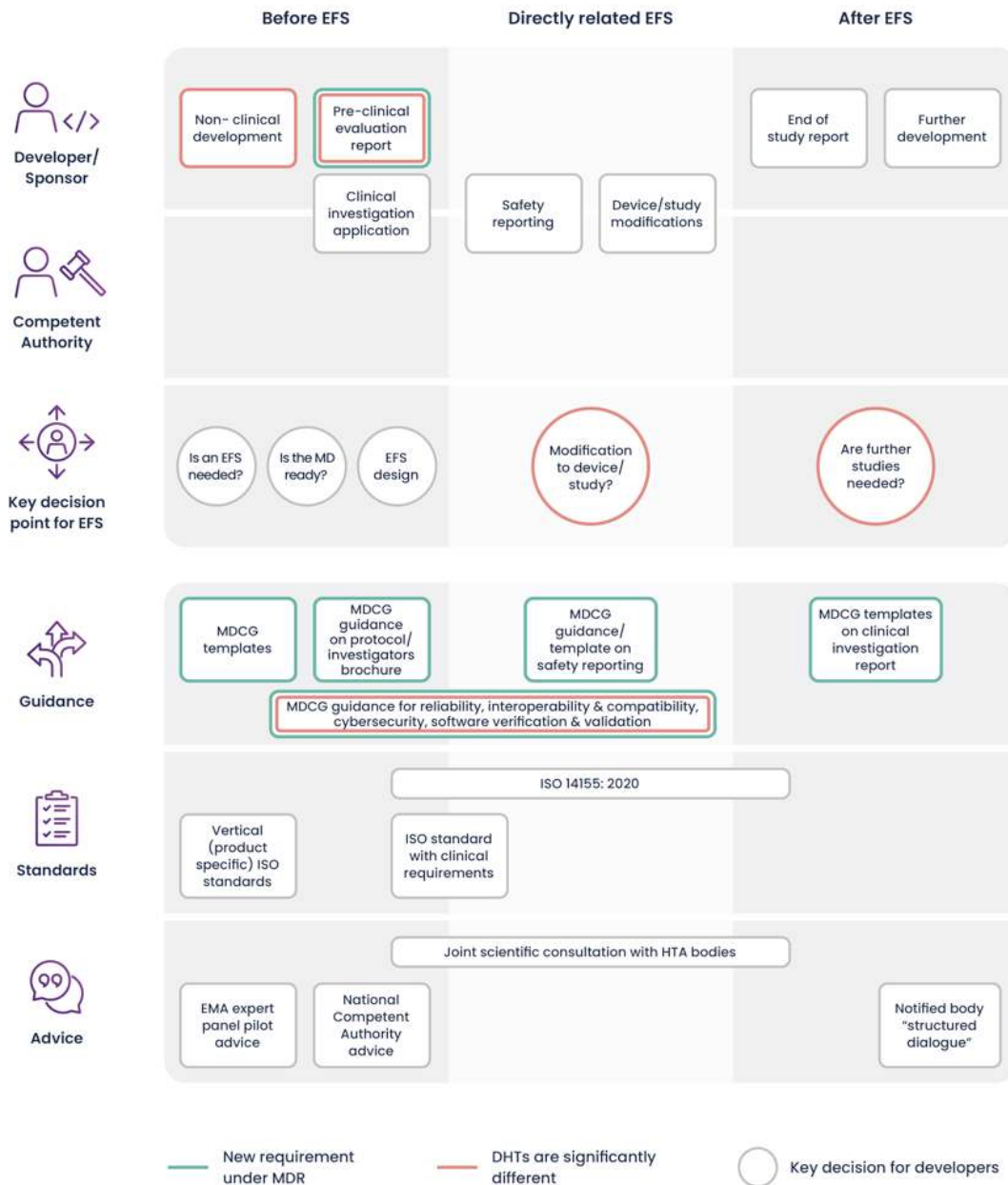
This chapter provides an analysis of the most significant aspects of this research. The intricate details of the analysis (results of searches, numbers of included papers etc.) are available in the Appendices.

For ease of reading, this chapter is divided into two sections,

- 1) 'Analysis of EU regulations, international standards, and guidelines' and
- 2) 'Mapping of EU-funded and International Digital Health Technologies (DHTs) Projects'.

For Section 1, results are stratified by their applicability to various stages of an EFS (before, during and after), in addition to other relevant considerations. A non-exhaustive overview of the current EU regulatory framework for clinical evidence generation for medical devices and DHTs is presented in Figure 2.

Figure 2. An overview of the current EU regulatory framework for generating clinical evidence for medical devices and digital health technologies, focusing on early feasibility studies



3.1. Analysis of EU regulations, international standards and guidelines

Before an EFS

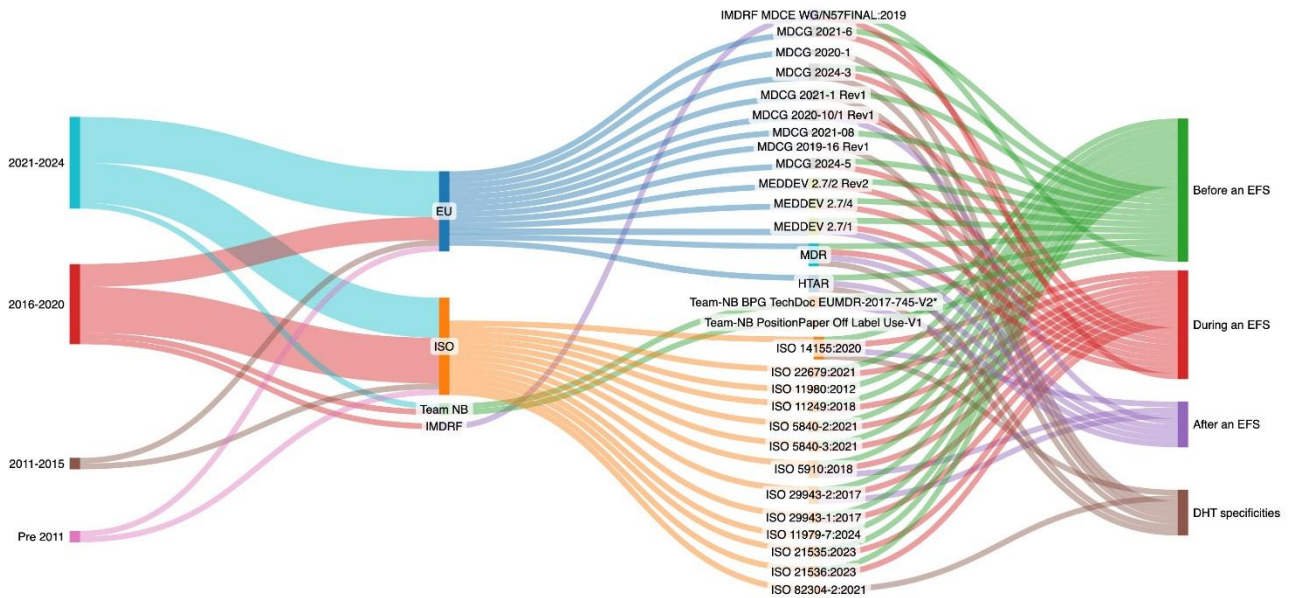
Is an EFS needed?

An important early consideration for developers is determining whether a clinical investigation is needed, and whether a phased approach to clinical investigations is appropriate. Medical device developers typically take regulatory factors, technology factors and clinical factors into account in order to address these considerations. Key terminology is presented in [Appendix 1.1](#). For new devices, particularly those classified as high risk under the MDR classification rules, there are requirements to conduct ‘clinical investigations’ (MDR, Article 61) (10).

MDR does not explicitly require phases of clinical investigations, but merely uses the term ‘clinical investigations’ in Article 62 and 82. Nevertheless, there are references to a phased clinical investigation approach, which developers must now consider. MDR introduced a requirement for developers to prepare a clinical development plan, which includes reference to “(...) exploratory investigations, such as first-in-man studies, feasibility and pilot studies (...)”, and MDCG guidance notes that developers must consider how an EFS would fit into an overall clinical development plan. Further explanation of these parts of MDR/MDCG guidance is presented in [Appendix 3.1](#).

The determination as to whether an EFS is required as part of a phased clinical development plan is not answered decisively in any single part of existing regulatory documents (MDR/MDCG/ISO). In Figure 3, we present a Sankey diagram demonstrating the identified guidance and standards documents that contain information relevant to activities, before, directly related and after an EFS.

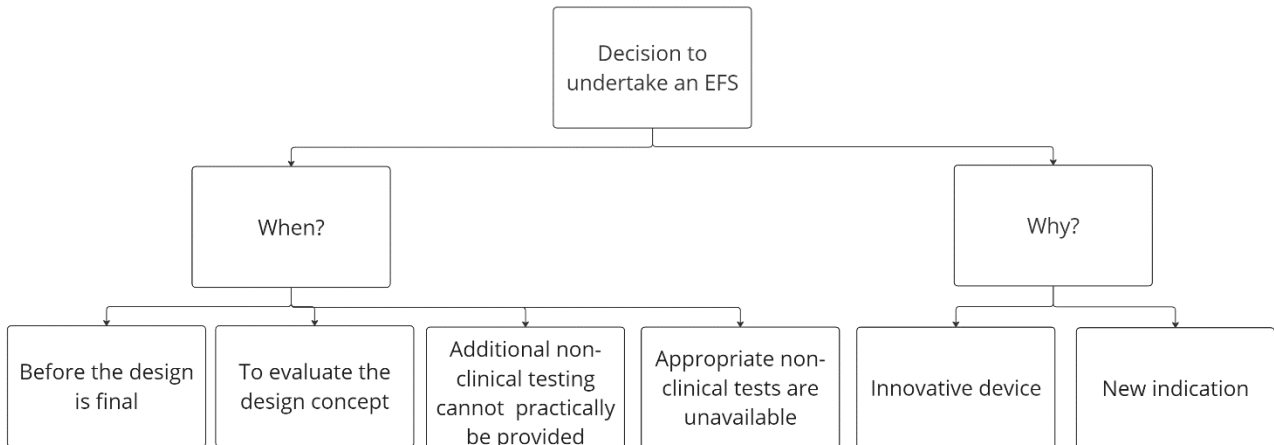
Figure 3. Sankey Diagram showing the origins of various regulatory and guidance documents and their applicability to the stages of an EFS



Developers undertake pre-clinical or non-clinical development activity consisting of bench, animal testing etc. as part of early development. An introduction to the terms ‘pre-clinical’ and ‘non-clinical’ is presented in [Appendix 1.1](#). A schematic representation of activities for developers and national competent authorities when moving from pre-clinical to clinical development is presented in [Appendix 3.2](#). This is technology dependent, and it is typically informed by available ISO standards and MDCG guidance. For example, before starting an EFS for DHTs, the requirements in terms of MDCG 2024-5 for reliability (section 2.3.2.2.2.), interoperability and compatibility (section 2.3.2.2.3.), cybersecurity (section 2.3.2.3.4.) and software verification and validation (section 2.3.2.3.3.) of DHTs must be determined (9). Regulatory review of MDR/MDCG regarding DHTs is presented in [Appendix 3.3](#). The role of ISO standards in the MDR framework is summarised in [Appendix 3.4](#). For some technologies, available ISO standards provide information which helps to determine if an EFS is appropriate. These are discussed later in this chapter.

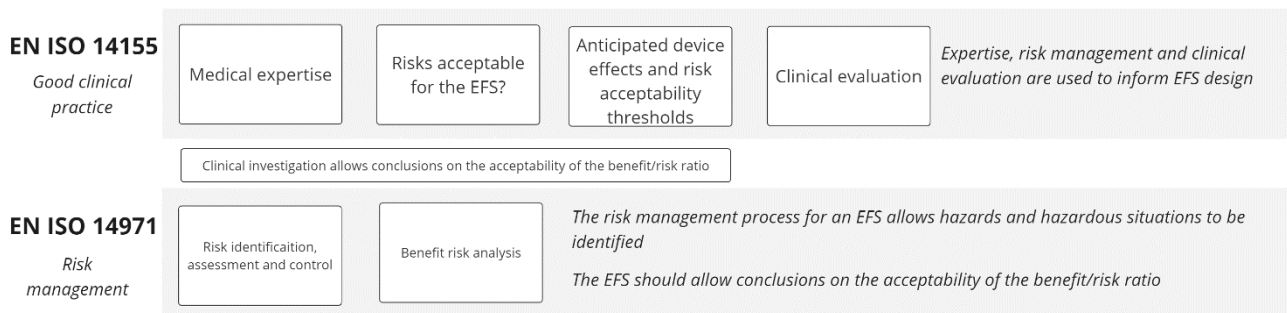
There are horizontal and vertical ISO standards. A glossary to explain the meaning of these is presented in [Appendix 3.5](#). ISO 14155:2020 (hereafter ISO 14155) is the only horizontal standard applicable to clinical investigations. ISO 14155 provides a contextual description that can help developers to understand when an EFS may be considered (11). This is presented in Figure 4.

Figure 4. Contextual description to determine if an EFS is needed based on clause I.5.3 of ISO 14155



As we can see from this contextual description, much of the rationale concerning the need for an EFS is based upon the knowledge generated from non-clinical test methods. ISO 14155 has a normative reference to the ISO standard for risk management (ISO 14971:2019 Medical devices — Application of risk management to medical devices) (12). When applying ISO 14155, developers are required to consider a number of specific aspects based upon both risk management and an evaluation of available clinical data, to understand if a clinical investigation is required. These are presented in Figure 5.

Figure 5. Considerations to determine if a CI / EFS is required.



Developers are required to utilise medical expertise, consider the outcome of risk management and conduct an early clinical evaluation (this is likely to be more focussed to the clinical evaluation used for marketing) to reach a determination about necessity for EFS.

In addition to the horizontal standard for clinical investigations (ISO 14155), the vertical standards contain product specific information. The relationship between ISO 14155 and the vertical standards is described in ISO 14155, which states that “users of this document need to consider whether other standards and/or national requirements also apply to the investigational device(s) under consideration

or the clinical investigation. If differences in requirements exist, the most stringent apply”. The detail provided in vertical standards is presented differently to the contextual description in Figure 4, with variable amounts of detail provided across the different vertical standards.

Applying the approach described in the methods section, 11 ISO standards relevant to EFS were identified. Within these 11 standards, some contain information regarding premarket, EFS, exploratory stage, or pilot phase studies. A summary table describing the terms used within the standards and a short commentary is presented in [Appendix 3.6](#). Overall, a lack of consistency was found in the terminology used to describe EFS, pilot, and premarket studies between different standards when compared to the terminology in Annex I of ISO 14155. This is apparent for standards published before and after 2020 (when the Annex I was added in ISO 14155). Inconsistency in terminology has the potential to cause misinterpretations and misapplications of the standards' requirements.

There was inconsistency in the amount of content regarding EFS studies within the 11 vertical standards. One standard being entirely dedicated to clinical studies, including requirements for defining a hypothesis, designing the study, and reviewing the results (Figure 6). In contrast, other standards included either detailed or minimal requirements related to an EFS (Figure 7 and Figure 8).

Figure 6. Vertical standard focussed solely on clinical study design (13,14)

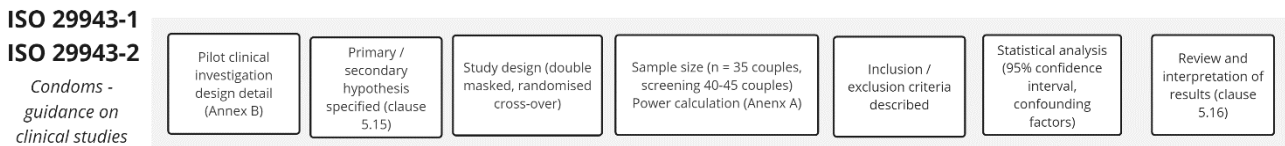


Figure 7. Examples of vertical standards with minimal clinical requirements for EFS (15,16)

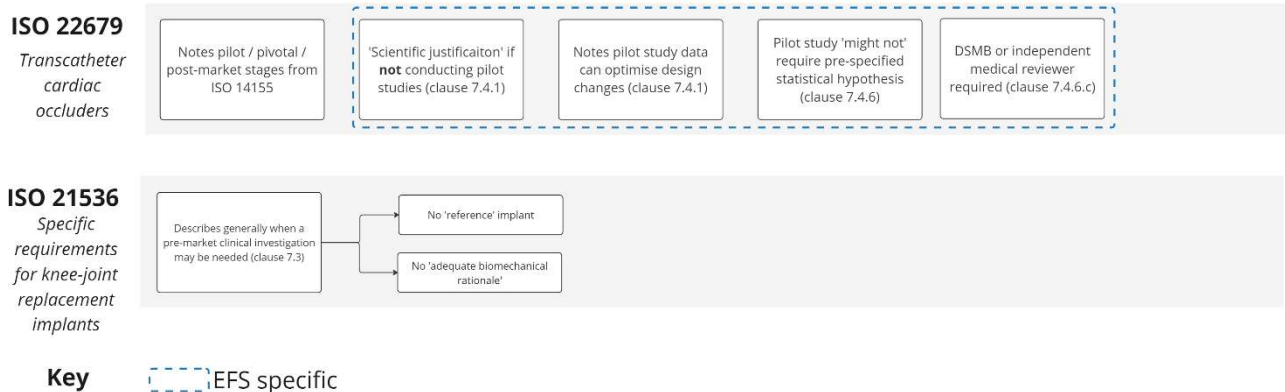
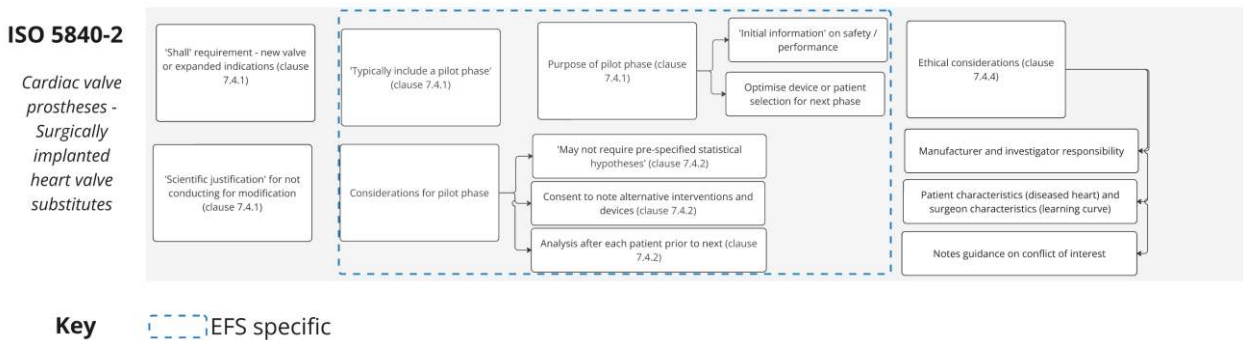


Figure 8. Example of a vertical standard with detailed clinical requirements for EFS (17)



[Appendix 3.7](#) contains a summary of the findings from these 11 vertical standards, concerning the requirement to conduct an EFS.

In summary, MDR and available standards (with the exception of ISO 29943-1 and -2) and guidance do not describe the circumstances under which an EFS is required. This is the responsibility of manufacturers to determine as part of clinical development planning. As a result of our review, the key considerations that we have identified to understand whether an EFS is needed, can be summarised as follows:

Conclusion of Clinical Evaluation:

- The necessity for an EFS must be grounded in a thorough clinical evaluation.
- This evaluation assesses existing clinical data, identifying gaps that an EFS aims to fill.
- It supports development of a scientific rationale for conducting the study on human subjects.

Alignment with Risk Assessment:

- The decision to proceed with an EFS must align with the results of a comprehensive risk assessment.
- This assessment evaluates potential risks associated with the investigational device and determines whether these risks are acceptable when weighed against the anticipated benefits.

Pre-clinical Testing and Assessment:

- Pre-clinical tests are essential to justify the transition from non-clinical (e.g., bench and animal studies) to human trials.
- These tests may include, but are not limited to *in vitro* studies, *ex vivo* animal testing, and other relevant assessments depending on the type of device.
- The data obtained from these tests provide evidence that the investigational device is safe and potentially effective for initial human use.

It is important to note that the MDCG 2024-5 document stipulates that any missing preclinical tests must be explained although no further information on what would constitute a reasonable justification for missing tests is available (18).

DHT specificities

MDSW is regulated similarly to traditional medical devices, but its unique characteristics and functionalities often necessitate additional regulatory requirements. These include ensuring electrical safety, robust cybersecurity measures, safeguarding personal data, and providing user manuals in electronic formats prior to conducting and EFS. Currently, the specific regulations applicable to each DHT must be determined on a case-by-case basis, taking into account the distinct features and functionalities of each product. MDCG 2024-5 provides more detailed implementation instructions (18,19).

The updated classification rules in MDR are more stringent compared to the previous MDD, leading to higher risk classifications for many medical devices, which significantly impacts manufacturer requirements regarding conduction of early clinical studies. With regard to clinical trials in general, Articles 61 to 82 of the MDR, which deal with clinical evaluation and clinical trials, do not specifically address the particular requirements for DHTs. In the past, the lack of effective regulation has allowed inferior, non-evidence-based products to enter the market (20). The MDR has evolved to encompass technological advancements and implications that arise from them, explicitly including Software as a Medical Device (SaMD) and classifying them as active devices. Rule 11 of Annex VIII addresses risks related to information provided by SaMD. It classifies software used for decision-making in diagnostics or therapeutics as Class IIa, unless the decisions could lead to death or irreversible health deterioration, which elevates it to Class III, or serious health deterioration or surgical intervention, making it Class IIb.

A relevant number of wearable DHTs have transitioned from consumer products to medical devices. During early-stage product development, it is crucial for developers and manufacturers to define the intended use and target user population of their WMDs (Wearable Medical Device) and to devise a regulatory approval strategy (21). The US FDA has had to adapt its traditional frameworks to accommodate the unique characteristics of DHTs, which often blur the lines between general wellness products and medical devices (22). The agency's approach includes the development of specific guidelines, such as the "General Wellness: Policy for Low-Risk Devices" and the risk-based framework applied in the "Mobile Medical Applications Guidance" (23). In wearable DHTs, the premarket approval process typically requires 2–3 years and an investment of US\$10–20 million for thorough preliminary testing (21). Consequently, manufacturers should incorporate (early) clinical studies into their development process or outsource this testing to validate their prototypes early on.

The MDCG 2020-1 emphasizes conducting proof of concept studies to validate the clinical performance of MDSW. In addition, according to Annex XV, 2.3 of the MDR, the pre-clinical evaluation should include relevant tests and experimental data, e.g., software verification and validation (24).

In summary, DHT developers are required to determine the need for an EFS as part of clinical development planning, similarly to other medical device developers. The key considerations that we have identified to understand if an EFS for DHTs is needed, can be summarised as follows:

- The updated MDR classification results in higher risk classifications for many DHTs, with software for decision making in diagnostics or therapeutics classified as Class IIa unless it could cause death or irreversible health deterioration (Class III), or serious health deterioration or surgical intervention (Class IIb). This up-classification has increased the expectations for pre-market clinical investigations and hence EFS.
- DHTs require additional regulatory measures due to their unique characteristics, including robust cybersecurity, data protection, and electronic user manuals.
- A relevant number of DHTs transition(ed) from consumer products to regulated medical devices, necessitating compliance with the stringent MDR classification rules and need for early clinical evidence generation, in a similar manner to general MDs.

Advice structures

Articles 106 and 48 (6) of the MDR respectively require the European Commission to create expert panels to support scientific assessment and advice. To date, 11 expert panels, across a range of medical technologies have been appointed, in addition to the screening panel which uses resources from all the aforementioned panels. The European Medicines Agency (EMA) is responsible for the secretariat of these panels. These panels provide opinions as part of the clinical evaluation consultation procedure for the marketing of new and high-risk devices (MDR, Article 54). Additionally, these panels also have a legal empowerment to provide scientific advice for developers of certain high-risk devices (MDR, Article 61(2)) (10).

The EMA is currently running a pilot for scientific advice for certain high-risk medical devices. This pilot began in February 2023 and is focussed on breakthrough or orphan type devices (25):

- devices that benefit a small group of patients in the treatment or diagnosis of a disease or condition, such as devices intended for the treatment of a rare condition, known as 'orphan devices', and devices for paediatric use.
- devices addressing medical conditions that are life threatening or cause permanent impairment of a body function and for which current medical alternatives are insufficient or carry significant risks.

- novel devices with a possible major clinical or health impact.

The nature of the advice delivered regarding the EFS is confidential, with no publicly available information on this matter.

In addition to the expert panels, national competent authorities may also provide advice concerning clinical investigations (which they are responsible to approve the application of) and thereby an EFS planned to be conducted in their territory. A mapping of these advice structures was not undertaken as part of WP2, although a mapping of pre-market approval pathways is underway in WP1.

Presently, there are no harmonised advice structures within the EU for developers of medical devices in the pre-market phase. Notified bodies can provide some advice in the form of a structured dialogue (26). This advice is to ensure efficiency and predictability of the conformity assessment (i.e., the assessment for market access). Given this focus, it is unlikely that notified bodies can provide advice concerning EFS, which happen at an earlier stage of product development (26).

In contrast, in the US, the FDA oversees the advice, approval of clinical trials, and final regulatory market approval, all under one authority. The Q-Submission process, which includes Informational Meetings and Pre-Submissions, helps initiate dialogue and obtain feedback on regulatory and technical questions. As noted earlier, the EU lacks a harmonised advisory structure applicable to any developer considering an EFS, which is a significant difference compared to the US FDA EFS program. The importance of early dialogue was also emphasized in systematic literature reviews by Brooks et al., (2017), Herrmann et al., (2022), and Holmes et al., (2022). They independently stressed the importance of early dialogue between sponsors and regulatory authorities before conducting an EFS. In the US, early dialogue is known to take the form of pre-submission meetings where the FDA EFS teams offer sponsors the opportunity to gain a deeper understanding of EFS guidance policies and prepare for engagements with the technical review team (4,5,27). Additionally, as articulated by Ibrahim *et al.*, (2020) “these meetings may also involve the submission of background material and specific questions for feedback, with responses typically provided within 75-90 days, either in a written format or during face-to-face meetings” (6). Holmes *et al.*, (2016) state that a key benefit of this approach is the potential to address device performance issues and safety concerns (28). Herrmann *et al.*, (2022) underline the importance of having the FDA’s active involvement in the study, which shortens the time-frames for the collection of data to support marketing applications and results in early access to new medical devices for US patients (4).

DHT specificities

With the DHTs, early and ongoing communication with regulatory authorities is essential to ensure compliance with regulations (29,30). Institutional structures, prolonged Institutional Review Boards

(IRB) reviews (an IRB is the US equivalent of research ethics committees) and lack of communication were identified as major hindering aspects (20). Several recommendations for improving advice structures for (early) clinical studies in DHTs have been made and include the development of networks to share best practices and provide training opportunities for trial staff. Regulatory agencies are required to ensure that sufficient expertise and human resources are available. For example, the US FDA has established a Digital Health Center of Excellence (31) where relevant knowledge skills and resources have been allocated. This demonstrates the importance of developing regulatory knowledge in the context of a rapidly developing technological field.

Consistent communication within the US FDA processes has been identified as a critical factor (29). The Digital Health Centre of Excellence can provide guidance on whether a technology falls under FDA regulation, aiding innovators in navigating the regulatory landscape (31).

Additionally, suggestions for an interactive Regulatory Process have been made. Hands-on demonstrations and discussions with FDA experts can improve understanding of novel digital health technologies (29). This interactive process can streamline the review process, benefiting both product developers and regulators.

EFS design

From the MDR/MDCG guidance, and the description of EFS documented in ISO 14155, an EFS should be conceptually considered to be an exploratory, or proof of concept study. Conceptually, all clinical research should begin with a research question or clinical hypothesis. ISO 29943 further specifies that CIs should have both a primary and secondary hypothesis. This is not reflected in any other vertical standards. MEDDEV 2.7/1 rev.4 (guidance prepared for the previous Medical Device Directive 93/42/EC system) adds that any hypothesis should be testable (32).

The design characteristics identified from MDR/MDCG/ISO documents focus on the number of subjects, statistical hypothesis, and study population. These were addressed in a variety of different ways in the documents reviewed. [Appendix 3.8](#) contains a summary of how these characteristics are presented in ISO standards. The ISO standards also included a variety of other considerations, with varying amounts of detail presented in different standards. These include:

- Informed Consent
- Monitoring Plan/Oversight
- The use of External Organizations / Core laboratories
- Rate of Enrolment
- Patient Selection
- Subject follow up

- Ethics Committee
- Compensation and additional health care

A summary of how these are presented in vertical standards is presented in [Appendix 3.9](#). In summary, these considerations are addressed in a variable and inconsistent way in the standards reviewed. This may be because ISO standards typically focus on non-clinical evaluative methods.

A key component of EFS design is a risk evaluation and risk management plan. MDCG 2024-3 guidance on the content of the Clinical Investigation Plan (CIP) for clinical investigations of medical devices highlights the importance of implementing additional safety precautions, particularly in early studies involving new or high-risk devices (33). These precautions may include close monitoring by both the sponsor and an independent safety reviewer, as well as controlling the rate of enrolment.

MDCG 2024-3 emphasises safety and risk management, suggesting additional precautions in early studies, such as close monitoring and phased patient enrolment (33). The CIP must outline benefits and risks, including direct benefits to subjects and potential benefits to others. It should also assess alternative therapies and identify potential risks, detailing strategies to minimise them.

In addition, MDCG 2024-5 states that the investigator's brochure (IB) should summarize the risk-benefit analysis, describe risk management processes, and list warnings and contraindications (18). The IB must also detail clinical procedures, deviations from standard practice, and justify the choice of investigation sites. It should finally clearly define the study's objectives and endpoints, ensuring ethical considerations and informed consent processes are thoroughly addressed (18).

The IMDRF MDCE WG/N57FINAL:2019 emphasises that the design of the clinical investigation should enable the collection of clinical data that is essential for addressing residual risks and evaluating various aspects of clinical performance. It is also suggested to engage in discussion with regulatory authorities when there are uncertainties about the adequacy of the clinical investigational plan (CIP) (33). It further recommends that statistical considerations are prospectively defined using rigorous scientific principles and methodologies (33). Statistical considerations with respect to EFS studies are sporadically defined in the ISO standards. ISO 14155 states "that no mandatory (pre-) specification of a statistical hypothesis is required". The vertical standards contained variable amounts of information on the theme of statistical hypothesis. As an example, ISO 5840-2 outlining the limitations of a "robust" interpretation of the use of such limited numbers and ISO 22679 advising, although not required "the design of the clinical investigation and the interpretation of the outcome can be more straightforward if statistical considerations are provided in the CIP". A further in-depth assessment is presented in [Appendix 3.8](#).

The US FDA EFS program has accompanying guidance concerning the design of an EFS. One important aspect is the number of patients to be involved in the EFS. The US FDA specifies that an

EFS should enrol a small number of subjects (typically fewer than 15) (4–6). MDCG 2021-6 also emphasizes the importance of enrolling a limited number of subjects in pilot stage clinical investigations (34).

The FDA suggests that an EFS submission should provide a comprehensive risk analysis detailing the types and estimated severity of risks to the subjects, how these risks will be mitigated, and a justification that the risks are reasonable relative to the expected benefits (35). As part of EFS design, sponsors may also consider aspects related to securing reimbursement. The 2017 FDA Guidance “Categorization of Investigational Device Exemption Devices to Assist the Centers for Medicare and Medicaid Services with Coverage Decisions” defines two device categories related to reimbursement: Category A (Experimental), with limited cost coverage, and Category B (Nonexperimental / Investigational), offering broader coverage options. Furthermore, the guidance also outlines criteria for transitioning from Category A to B as more performance data is gathered (36). Therefore, to secure reimbursement, emphasis should be placed on justifying the suitability for EFS participation, conducting comprehensive risk analyses, and implementing risk mitigation strategies with contributions from specialized experts on patient safety (37).

Notably, Marcus *et al.*, (2022) also recommend a comprehensive, proactive analysis of the potential risks posed by a new device using an approach based on the principles of failure modes and effects analysis, an approach to stratifying risk of device malfunction (38). Strategies for managing these risks may also include collecting human factor information, defining specific eligibility criteria, limiting the sample size, increasing the frequency of follow-up assessments, and implementing staged enrolment (4).

EFS protocols may include guidelines for pausing or terminating the clinical study when specific safety events occur (39). Restricting the number of participants in the EFS helps to minimise the overall risk to subjects during the initial stages of the investigation. Participants in an EFS must be fully informed of all risks related to the study (18).

As described by Holmes *et al.*, (2016), it is possible to identify key qualities for clinical sites for conducting EFS. These sites should have a well-developed infrastructure to support clinical studies and a proven track record of efficient and successful completion of research trials. Experience in human research subject monitoring and patient protection measures is crucial. Sites should have technically qualified investigators. Additionally, timely contracting and budgeting in parallel with ethical and legal review, access to the target patient population, efficient use of resources, appropriate cost constraints, and an understanding of the challenges associated with FIH and EFS are essential qualities (28).

The literature frequently addresses the optimal number of sites to engage in the study. According to Holmes *et al.*, (2022), EFS studies usually engage three to five carefully chosen centres, collaborating closely with the medical device company in protocol design, data collection, and procedural evaluation (5). Furthermore, Callea *et al.*, (2022), in providing recommendations for an EU EFS program, cite the need to pay particular attention to cultural and clinical expertise and patient risk profiles in choosing sites (37).

DHT specificities

The MDR introduced new requirements of which some are challenging to interpret for DHTs. Templates and guidelines are being developed to help with ethics committee and regulatory submissions, but the regulation remains complex. National guidance relating to competent authorities, research ethics committees, and HTA bodies varies substantially in the context of DHTs, creating a fragmented landscape and resulting in confusion and inconsistencies for researchers working internationally.

A major gap in the current resources is the absence of a concise and comprehensive guide for conducting (early) clinical evaluations to fulfil certification procedures under the MDR (30). This absence leaves clinical researchers without a clear roadmap, making it challenging to design and execute studies that meet the new regulatory requirements. The MDCG 2020-1 only describes the clinical evaluation of DHT as an ongoing process and the feasibility also by means of a proof of concept (24). Consequently, this can lead to delays and complications in the clinical study process, as researchers navigate the complexities of the new rules and strive to achieve compliance within the MDR framework.

ISO 82304 provides an accessible entry point into the subject matter during the pre-development and early development stages of DHTs. Notably, chapters 5.2.2 (Health Risks) and 5.2.4 (Health Benefits) offer clear and structured guidance. These chapters should be evaluated for their potential to help develop guidelines for the planning and execution of early pilot studies for SaMD.

Traditional clinical trial methodologies can be overly rigid and not well-suited to the rapid iteration cycles typical of digital technologies. The reliance on randomized clinical trials (RCTs) as the gold standard often does not fit the agile development and deployment of digital health solutions. A lifecycle approach to DHTs incorporating EFS is currently being discussed and promoted by various researchers and stakeholders as a purposeful way forward (40). In early-stage clinical evaluations, comparator groups are often unnecessary since the focus is not on comparative efficacy, and small-scale studies are typically underpowered for statistically significant efficacy conclusions (41). Implementing decentralized clinical studies can decrease the burden on clinical site staff and reduce

costs associated with patient visits. This approach can help facilitate smoother entry into clinical studies (30).

Especially for Artificial Intelligence/Machine Learning (AI/ML) DHTs, a push for rigorous evaluation methods ranging from early clinical evidence generation to randomized controlled trials are being requested. 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 (42). Vasey *et al.*, (2023) 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 (41). Other challenges are 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 (similar to phase 1 and 2 pharmaceutical trials).

Despite some AI algorithms matching human expert accuracy in preclinical *in silico* 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 (41).

In early clinical investigations of DHTs including AI/ML-enabled decision support systems and their integration into healthcare ecosystems it's crucial to consider the complex nature, accounting for user variability and biases. Evaluations must also address the collaboration between human and AI intelligence by incorporating human factors as a core component. However, few clinical AI studies structurally acquire and later report on human factors, and usability evaluations often lack consistent methodology and reporting. Human factors are essential for AI system adoption at scale, as a comprehensive appraisal of clinical utility depends on evaluating these factors. The AI Act will place an increased emphasis on testing in real world conditions and the need to take into account the possible consequences of testing on individuals; competent authorities will need to oversee real-world testing plans and the risk minimisation plans of AI developers (recital 141) (1). The implementation plan for the AI Act in the medical device regulatory system has not yet been announced, however it will be monitored throughout the HEU-EFS project.

Patient/user participation

Although MDR mentions patients 138 times it does not integrate them into any regulatory procedures, either in general or specifically for processes related to EFS. MDR notes that the organisation of assessments by national competent authorities and ethics committees is a 'matter of internal

organisation for each Member State’ and that each Member State ‘should ensure the involvement of laypersons, in particular patients or patients’ organisations’ (MDR, recital 65). The extent to which this is implemented in practice is unknown and further information concerning this was not uncovered in our review, but will be further investigated as part of WP1, where the premarket pathways with national Competent Authorities is mapped.

As EFS studies investigate the use of technologies which have typically not demonstrated proof of concept, ensuring that patients are fully aware of possible benefits and risks is imperative. In addition, including patient experience data and data on outcomes that matter to patients (e.g., impacts on quality of life, etc.) can also inform the benefit/risk assessment. Notably, MDR/MDCG/ISO do not require patient involvement in the drafting of an informed consent form or patient information leaflet when designing clinical investigations including an EFS. This is particularly important when we consider that for some EFS there is limited or no expected personal benefit to the study subject (29).

Two cardiovascular standards (ISO 22679 and ISO 5840-3) outline requirements for patient selection. ISO 22679 addresses the patient values and preferences stating: “Patient selection shall be a shared decision process between physician and patient that takes into account the best scientific evidence available, as well as the patient’s values and preferences” (15,43).

MDCG 2024-5, which concerns the clinical investigators brochure, requires developers to clearly state the intended purpose of a medical device. MDCG 2024-5 also states that it is necessary to describe the clinical performance of the medical device, by detailing how it achieves its intended purpose as claimed by the manufacturer. This description should elucidate the mechanisms through which the device brings about clinical benefits for patients when used as intended. The intended clinical benefits should be specified with relevant clinical outcome parameters, considering both direct and indirect medical effects resulting from the device's technical or functional characteristics (18).

‘Clinical benefit’ is defined in MDR (Article 2(53)) as ‘the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health’. MDR/MDCG/ISO documents do not provide further detail to determine how outcomes can be judged to be patient relevant.

In the absence of the EUDAMED clinical module, it is not possible for patients to access information relating to ongoing or approved EFS studies, or to access a central database for clinical investigation reports of completed EFS studies.

DHT specificities

In DHT, engaging end-users, patients and professional end-user groups, throughout the complete development cycle is essential and will enhance development, pre-clinical and clinical evaluations, usability and acceptance (29,44). Researchers and industry should focus on user needs, product usability, and fitting seamlessly into current workflows. MDCG 2024-5 considers usability testing to be of critical importance and requires a comprehensive description of the software design and development process, including validation, verification and testing conducted both in-house and in simulated or actual user environments (18).

Developers of MD/DHTs may choose to integrate patients and professional end users as part of product development. For EFS, patient integration was not referenced in the MDCG/ISO documents reviewed. However, for DHTs which often are used by patients, a patient centric design or co-design involving patients is important. It is crucial to detail the inclusion of representatives from intended end-user groups especially in (early) clinical DHT studies, specifying their roles and participation extent (44). Due to the agile nature of DHT development, with DHT iterations and updates, traditional approaches may be insufficient. Applying User-Centered Design principles, strategies, and methods, which ensure participation throughout the whole process, can effectively ensure meaningful end-user involvement, addressing potential limitations in conventional evaluation methods.

To maximize public health benefits from new digital health technologies, it's essential for patients and health care systems to trust the information used in their development. Transparency, inclusivity, and engagement are key to building this trust.

EFS technical documentation preparation

The MDR Articles describing clinical investigation pathways relevant to EFS are described in Article 62 and Article 82. There are other types of clinical investigation applications possible (Article 74 and Article 78). These are not relevant to EFS as Post Market Clinical Follow up (PMCF) investigations are conducted after the device has gained market access (CE mark), and Article 78 (coordinated assessments) are not yet active. MDCG guidance notes that in general, EFS studies should proceed under Article 62, although it is possible that EFS may have been submitted with respect to Article 82 based on national implementing law (34).

Annex XV, Chapter II of MDR describes the documentation requirements for an application for clinical investigation. This annex describes some of the minimal content for the application form, protocol and other documents. Reference is also made to evidence of software verification and validation for DHTs as part of a preclinical evaluation.

When available, EUDAMED will be the portal used for clinical investigation applications (45). In the interim, national procedures are used. MDCG has produced a set of templates for applications (46). These templates may not be used by all Member States, and in the absence of EUDAMED, national competent authorities tend to use their own templates, rather than a standardised one. This was not subject to an analysis in WP2, however it is part of the activities relating to pre-marked program mapping in WP1. It is important to check with each national competent authority to understand the document expectations.

Standard templates are not used by research ethics committees (RECs), as these fall under national or even regional jurisdictions. In practice, the precise responsibility of either the NCA or REC is less clear for medical devices than it is for medicines, where there is a clear delineation between 'Part 1' of an application (for the NCA) and 'Part 2' which is for the REC. As a result, both the NCA and REC can receive the same application documents. However, in the event of a parallel submission, this could lead to issues, in particular delays in obtaining the required approval.

Directly related to EFS

Safety oversight – Serious adverse events / safety reporting, Data and Safety Monitoring Board, Clinical Events Committee

MDR requires sponsors to conduct safety reporting to national competent authorities. MDR requires the reporting of serious adverse events (SAEs) or certain device deficiencies (Article 73) with timelines defined in MDR. In the absence of EUDAMED, a template and guidance to harmonise these reports is available (MDCG 2020-10) (10,47).

Furthermore, additional safety monitoring techniques, such as the use of a Data and Safety Monitoring Board (DSMB) or Clinical Events Committee (CEC) are provided for in four of the vertical cardiovascular standards reviewed. These are summarised in [Appendix 3.8](#). These standards reference a DSMB or an independent medical reviewer. ISO 5910 requires oversight of the study safety by a CEC and/or a DSMB. The adjudication of adverse events by a CEC is specifically called out in for ISO 5840-2 and -3 and ISO 22679 where a clinical events committee “should” be used (15,17,43,48). In addition, DHTs require ongoing cybersecurity and data protection monitoring throughout the EFS (9).

Additionally, according to Article 77 of MDR, manufacturers must notify authorities within 15 days if a CI is halted or terminated, especially if such a suspension occurs for safety reasons. This should be reported to the national competent authority, and clear explanations must be provided. Sponsors should regularly review clinical data and the device's risk-benefit profile, adjusting for any serious adverse events (39).

Managing modifications (device / protocol)

Under MDR, modifications are considered substantial or non-substantial. Substantial modifications require an application and approval prior to implementation (MDR, Article 75). The timeline for assessment is 38 days, with an additional 7 days in the event that a consultation with experts is required (MDR, Article 75(4)) (10). Moreover, MDCG 2021-6 Rev. 1, Annex II contains a non-exhaustive list of changes that may be considered substantial. Conversely, non-substantial modifications should be recorded and they may require an advance approval depending on national law (34).

In the United States, Herrmann *et al.*, (2022) state that the U.S. EFS framework allows for modifications to the device or protocol with a 5-day notification, provided certain requirements outlined in the Investigational Device Exemption (IDE) regulations are met. This flexibility enables a broader range of changes to be acceptable, as Herrmann *et al.*, (2022) notes “the evaluation of the study does not depend on a statistical analysis plan or data pooling among subjects treated with different device versions” (4). Additionally, EFS facilitates “device iteration during the study and supports “just-in-time” testing. Just-in-time testing is a guiding principle of the U.S. EFS framework, which applies to the type and timing of non-clinical testing needed to justify study initiation. It recognises that comprehensive testing during the early phases of device development may add cost without return, and it acknowledges that it may be acceptable to defer some testing until the device design has been finalised for a pivotal study (49). Furthermore, this approach focuses on addressing high-risk failure modes before initial clinical use and allows for the deferral of non-clinical tests, when appropriate, until the device has been finalised”, as mentioned by Ibrahim *et al.* (2020) (6)

DHT specificities

The complexity in device changes encapsulates the multifaceted challenges associated with developing DHTs as well as the concurrent setup of feasibility studies. Woodford *et al.*, (2021) highlight the iterative, interactive, and resource-intensive nature of these processes, which involve managing multiple procedural, methodological, and clinical uncertainties, and the interdependencies between intervention development and feasibility study preparation and conduction (50). The requirements of MDDG 2024-5 regarding reliability, interoperability, compatibility, cyber security, and software verification and validation must also be observed (9).

Changes to DHTs may result from ongoing product development, (pre-)clinical investigations, version updates, or continuous learning design. In early-stage clinical investigations of digital health products, managing and documenting changes to technology poses challenges (29). A risk-based assessment and thorough documentation are crucial to justify changes and ensure they do not impact study results. Safely conducted and transparently reported modifications can support the development and

evaluation to tailor the intervention to professional users and/or patients, enhancing the likelihood of adopting an optimized, fixed version in later summative evaluations.

Distinguishing and managing substantial versus non-substantial changes/modifications are challenging. The primary challenge lies in defining what constitutes a substantial change as opposed to a minor one, and subsequently determining the appropriate regulatory response for each category. Three criteria for substantial changes have been suggested: changes in intended use, high-risk changes and agreed changes during initial FDA communications (51).

The implementation of semantic versioning could be utilized to differentiate between substantial and non-substantial changes systematically (51). While not solely related to EFS, all device modifications should comply with ISO 13485 and International Electrotechnical Commission (IEC) 62304 standards to better inform regulators about device changes. DHT developers may not be applying ISO 13485 in full at the time of conducting an EFS, however using document and process control is important with respect to managing changes. This method involves assigning version numbers that clearly indicate the scale of changes, thereby aiding in the clarity and consistency of reporting. While IEC 62304 does not prescribe a semantic versioning system, it requires that changes to the software be categorized and managed based on their impact on the software and its safety. The standard emphasizes the importance of identifying and documenting different types of changes. This can typically be broken down into categories such as major changes, minor changes, and bug fixes. Furthermore, leveraging existing frameworks such as the Certified Health IT Product List (CHPL) and Unique Device Identifiers (UDIs) could facilitate more streamlined and efficient reporting processes. These frameworks can provide a structured approach to documenting and communicating changes, ensuring that both minor and major updates are appropriately tracked and reviewed (51). This method involves assigning version numbers that clearly indicate the scale of changes, thereby aiding in the clarity and consistency of reporting.

In April 2023, the US FDA introduced a process for the development of devices incorporating AI/ML with a "pre-determined change control plan" to allow iterative changes to algorithms in a pre-planned manner (52). The plan emphasizes public engagement and partnerships, as demonstrated by the joint development of guiding principles for Good Machine Learning Practices (GMLP) by regulators in the USA, Canada, and the United Kingdom.

After an EFS

Reporting of evidence

MDR introduced a requirement for sponsors of clinical investigations to publish a clinical investigation report within one year of completion of the investigation, or within three months in the event of an

early termination or temporary halt (MDR, Article 77(5)). This report is required to be accompanied by a summary presented in terms that are easily understandable to the intended user. These reports will be hosted in the EUDAMED database when available.

DHT specificities

Robust reporting guidelines are essential for transparency and reliability in DHTs. MINIMAR (Minimum Information for Medical AI Reporting) is a key guideline that standardizes reporting practices and provides a checklist to enhance the reporting of medical AI studies, focusing on cohort selection, training data, model development, performance metrics, and data processing procedures (53).

DECIDE-AI (2023) provides a multistakeholder, consensus-based reporting guideline of decision support systems based on AI (41). It is used in live clinical settings for small scale, formative evaluation, independently of the study design and AI system modality (diagnostic, prognostic, therapeutic). It focuses on the clinical utility, safety, and human factors aspects. DECIDE-AI aims to improve the reporting and appraisal around four key aspects of early-stage live AI evaluation: proof of clinical utility at small scale, safety, human factors evaluation, and preparation for larger scale summative trials.

Early-stage scientific studies of DHTs can inform regulatory decisions and contribute to clinical evidence generation. DECIDE-AI initial item list aligned with common regulatory agency requirements (41). Despite this, due to differing focuses and jurisdictional variations, DECIDE-AI does not reference specific regulatory processes or frameworks.

Assessment of evidence from EFS

Device developers will assess the outcomes of an EFS in order to determine further development plans. This may result in changes to the device or the intended the patient population. A further EFS may be indicated, or the device may proceed to the next stage of clinical development. For some technologies, in particular for DHTs, it may be possible to proceed to conformity assessment and marketing. These activities are discussed further in this section.

DHT specificities

Evaluating evidence from DHTs has been challenging due to inconsistent methodologies and the frequent omission of established frameworks (54,55), such as those from the World Health Organisation (WHO), National Institute for Clinical Excellence (NICE), Expert Panel on effective ways of investing in Health (EXPH) report, the Spanish / Catalan framework and the Swiss Evaluation framework (44). Weirauch *et al.*, (2024) shows a lack of consensus on evaluation methods and standardized indicators, leading to varied practices (44). Despite existing frameworks, the persistent

heterogeneity and variability in DHT evaluations hinder the collection of reliable evidence. In January 2024, the EDiHTA project was initiated, aiming to establish a flexible and validated European HTA framework for various DHTs within the next four years (56).

The DEFINED framework (Evidence in Digital health for EEffectiveness of INterventions with Evaluative Depth) (2023) aims to enhance the rigor and speed of evidence assessment for DHT clinical studies (57). The framework addresses the unique evidence considerations of DHTs and proposes guidelines to facilitate evidence-based recommendations and aims to streamline assessment processes for various stakeholders.

Next phase of evidence generation' (another EFS, pivotal, market access)

Upon completion of the EFS, the subsequent steps are determined by several factors, including the stability of the device design, the data obtained from the EFS, and the primary objectives of the clinical study. Based on these considerations, sponsors engaging in the US FDA EFS program may choose between two main pathways. The first option is to expand the EFS if further device modifications are anticipated. Alternatively, the sponsor may proceed with either traditional feasibility studies or a pivotal study. This decision hinges on whether the device design is near final and if the results support its feasibility and effectiveness, along with the availability of relevant non-clinical data. In practice, manufacturers frequently bypass the traditional feasibility study, opting instead to expand the EFS to ensure comprehensive understanding before proceeding to a pivotal study.

When moving from an EFS to a later stage study, Grohmann *et al.*, (2016) advocate for a systematic re-evaluation in a prospective and multicenter setting (58). Holmes *et al.*, (2022) also emphasise the necessity of a smooth transition to pivotal trials as a crucial component of device approval (5). Herrman *et al.*, (2022) suggest that a traditional feasibility study may follow, which focuses on evaluating a device design that is nearly finalised, utilising extensive nonclinical or existing clinical data (4). Moreover, Ibrahim *et al.*, (2020) mention that the clinical data gathered from the EFS can be used to support future regulatory submissions (6). Additionally, Herrmann *et al.*, (2022) reported that following FDA approval of an EFS Investigational Device Exemption, US patients gain early access to new medical devices, benefiting from the FDA's active involvement which shortens data collection periods for marketing applications (4).

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-recommendation component that assigns actionability levels (57).

Challenges and Solutions: Considerations from Literature and International Practice

Throughout the systematic literature review, the EFS program in the US has been recognised as a key facilitator for the development and commercialization of medical devices. Specifically, this program is noted for its efficiency in reducing both time and costs, a benefit underscored in the CDRH 2018–2020 Strategic Priorities report (37).

The US FDA EFS program has been praised for supporting capabilities in early trials, ensuring patient protection under Investigational Device Exemption regulations, and facilitating the collection of preliminary data to support larger studies and eventual marketing authorization in the US. Notably, in the neurological device sector, the EFS program has significantly influenced initial evaluation and development processes (4).

Nonetheless, conducting an EFS presents challenges that invite solutions and open discussion. Among the challenges, below is a summary of those pertaining to regulatory barriers in both the development and commercialisation of medical devices.

In the EU, there is a noted lack of standardised procedural frameworks for EFS, with existing procedures being challenging for the frequent protocol or device modifications typical of such studies (37). Additionally, there are increased barriers for market access of high-risk medical devices under EU MDR, which disproportionately affect children and patients with rare diseases (59).

Conversely, despite the presence of an EFS program, in the US the process can still be considered daunting, time-consuming, and expensive, aspects of which are frequently unknown to physicians (27). Additionally, other challenges include lengthy reviews by IRB, inadequate infrastructure, limited access to suitable patient populations, complex contract negotiations, reimbursement issues, and unpredictability in study launch justification (28,60). These factors are compounded by the stringent requirements for Investigational Device Exemption protocol approval, despite evidence of the FDA's collaborative involvement in the process (61).

Proposed solutions to these regulatory challenges have been identified. For instance, Brooks *et al.*, (2017) mentioned utilizing mathematical modelling in the preclinical phase to minimize animal and human testing (27). Similarly, Weiss *et al.*, (2023) advocated for efforts to facilitate early interaction with regulatory authorities, streamline contracting processes, and leverage public-private resources such as the Medical Device Innovation Consortium. Furthermore, the introduction of regulatory pathways characterized by short timelines and low assessment fees should also be considered (59).

Holmes *et al.*, (2016) emphasized the importance of understanding U.S. regulatory requirements, providing regulatory toolkits, addressing IRB considerations, and clarifying responsibilities and liabilities (28). Moreover, other proposed measures include issuing an EFS Guidance document, creating working groups, applying "just-in-time testing," facilitating device modifications, and

standardizing consent forms and IRB processes (62). Additionally, managing liability risk through contractual agreements and collaborating with regulatory agencies and payers for reimbursement are also recommended (2).

DHT specificities

In 2017 the FDA published the Digital Health Innovation Action Plan which defined an innovative approach to ensuring timely access to high-quality, safe, and effective digital health products (63). The plan outlined the vision for fostering digital health innovation while continuing to protect and promote public health interest by three central approaches: Issuing Guidance on Medical Software, creating the FDA Digital Health Center of Excellence (DHCoE) and piloting a FDA's Software Precertification (Pre-Cert) Pilot Program.

The FDA has published 23 guidance documents to support its approach to DHTs (31). These documents cover a broad range of topics including mobile medical applications, general wellness, software as a medical device, AI/ML-based enabled device software, and real-world evidence. These publications have shaped the regulatory landscape by clarifying definitions, establishing risk-based frameworks, and promoting the use of alternative forms of evidence such as patient experience data and real-world evidence. The scope of these documents spans from detailed regulatory requirements to high-level policy frameworks, ensuring that stakeholders have the necessary guidance to navigate the evolving digital health landscape.

The FDA DHCoE, established in September 2020, aims to advance digital health technologies (DHTs) by fostering innovation, ensuring safety and efficacy, and providing guidance to developers and regulators (31). The DHCoE emphasizes robust clinical evidence generation, using real-world data alongside traditional trials, and supports regulatory science with new methodologies like adaptive and decentralized trials. It promotes collaboration among stakeholders, offers educational resources, and conducts pilot programs to streamline DHT development and regulatory approval. Additionally, the DHCoE empowers stakeholders by setting strategic directions, launching initiatives, providing expertise, and sharing resources; connects stakeholders through partnerships and international harmonization; shares knowledge to advance best practices; and innovates regulatory approaches for efficient product review and oversight.

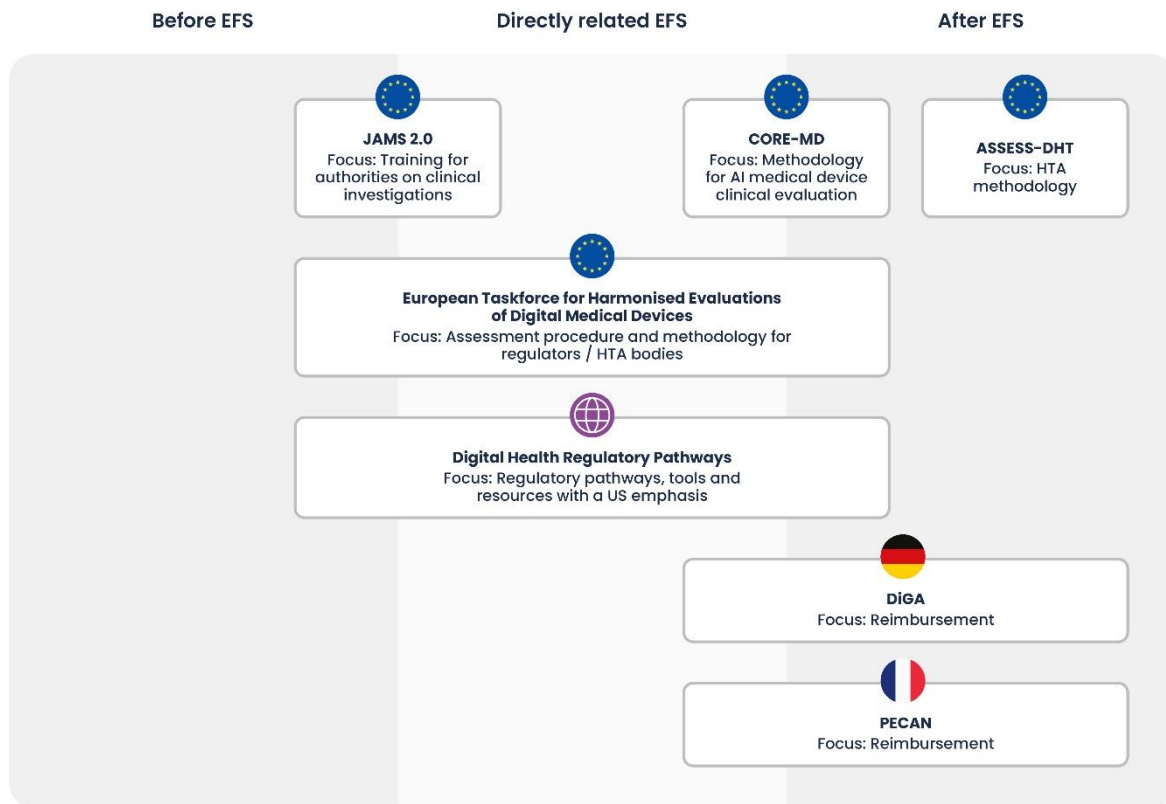
The FDA's Software Precertification (Pre-Cert) Pilot Program ran from 2017-2022 and was designed to streamline the regulatory process for SaMD (64), and while not continued beyond the pilot phase, it provided valuable insights and data that have informed subsequent regulatory frameworks and initiatives aimed at improving the approval process for software-based medical devices. The Pre-Cert program emphasized the iterative nature of software development, which includes continuous integration, delivery, and testing. To qualify for the Pre-Cert Program, companies had to demonstrate

a commitment to quality and organizational excellence, a robust software development lifecycle, continuous improvement and monitoring processes and proactive risk management practices. The report issued in September 2022 concluded that the program highlighted the need for new legislative authority to support a more adaptive regulatory approach suitable for the rapid innovation seen in digital health technologies. The FDA stated that they will continue to develop policies and tools within the existing regulatory framework and explore the potential for legislative changes that could enable a more flexible and efficient regulatory approach in the future. The Pre-Cert program demonstrates the need for regulatory authorities and agencies to engage with the SaMD/DHT communities in order to understand the different regulatory approaches that are possible under current frameworks, and to understand how frameworks may need to further develop to support compliant translational development, and hence EFS of these technologies.

3.2. Mapping of EU-funded and International Digital Health Technologies (DHTs) Projects

Mapping of current EU-funded and international projects and Member States' initiatives focused on DHTs identified a total of 57 projects (Figure 9). Of these, 41 are international projects and 16 projects are national initiatives. Overall, there are 45 ongoing projects and 12 closed projects. Several projects were added to the list from partner suggestions, and partners advised on prioritizing projects for comparison purposes and to inform subsequent stakeholder interviews. Seven projects (5 international and 2 national) were identified as highly relevant regarding HEU-EFS. A detailed description of the 7 highly relevant projects is described in Appendix 3.11. Presented below is a summary of projects with a specific emphasis on relevance to EFS and the HEU-EFS project

Figure 9. Overview of EU-funded and international DHT projects and their potential input regarding the three phases of EFS



ASSESS-HTA: Development and harmonisation of methodologies for assessing digital health technologies in Europe; CORE-MD: Coordinating Research and Evidence for Medical Devices; DiGA: HTA: Health technology assessment; JAMS 2.0: Joint Action on Reinforced Market Surveillance of Medical Devices and In Vitro Medical Devices; Digitale Gesundheitsanwendungen (Digital Health Applications); PECAN: Prise en Charge Anticipée Numerique (Early access to reimbursement for digital devices)

International Projects

Development and harmonisation of methodologies for assessing digital health technologies in Europe (ASSESS-DHT)

Status: Open (2024 - 2026)

Relevance to HEU-EFS: ASSESS-DHT's work on creating a cohesive assessment framework for DHTs aligns with the HEU-EFS project's goal of developing a harmonized framework for EFS in the EU which includes DHTs. Their approach to uniform health technology assessment (HTA) and addressing the complexities of digital therapeutics, AI, and telehealth can provide valuable insights and methodologies for EFS in DHTs, particularly for high-risk medical devices. They aim to establish a sustainable repository with the ASSESS-DHT framework, pathways, criteria, a searchable evidence

library, checklists, tools for evidence generation, health system value evidence from DHT, and online practice communities.

Coordinating Research and Evidence for Medical Devices (CORE-MD)

Status: Closed (2021 - 2024)

Relevance to HEU-EFS: CORE-MD's focus on enhancing evaluation methods for high-risk medical devices and translating expert evidence into regulatory advice supports the HEU-EFS project's objective of creating an EFS framework. The CORE-MD group is expected to provide guidance or suggest a framework related to clinical evaluation, which will assist stakeholders in navigating the complexities of the Medical Device Regulation, potentially also DHTs.

Joint Action on Reinforced Market Surveillance of Medical Devices and In Vitro Medical Devices (JAMS 2.0)

Status: Open (2023 - 2026)

Relevance to HEU-EFS: JAMS 2.0's efforts to harmonize market surveillance of medical devices and promote consistent regulatory practices across EU national competent authorities are crucial for the HEU-EFS project. By ensuring that medical devices comply with safety and performance standards in a way that meets regulators expectations, JAMS 2.0 contributes to creating a reliable regulatory environment that can support early feasibility studies and the subsequent market entry of innovative devices.

European Taskforce for Harmonised Evaluations of Digital Medical Devices

Status: Open (2022 - ongoing)

Relevance to HEU-EFS: The taskforce's mission to develop a European-level blueprint for DMD assessment procedures and methodologies supports the HEU-EFS project's goals. By establishing harmonized evaluation categories and procedures for digital medical devices, this taskforce facilitates a standardized approach to EFS, ensuring that early-stage innovations are evaluated consistently and effectively across the EU.

Digital Health Regulatory Pathways (DHRP)

Status: Open (2022 - ongoing)

Relevance to HEU-EFS: DHRP's collaboration with regulatory bodies like the US FDA to develop tools and resources for digital health product innovation is highly relevant for the DHT-specific part of HEU-EFS project. The regulatory pathways and clarifications provided by DHRP with an international and US-specific perspective can aid the development of a harmonized European EFS framework,

ensuring that digital health technologies are effectively evaluated and integrated into the European market and international synergies are being explored.

National Initiatives

DHTs present unique regulatory and reimbursement challenges at EU national levels. Within the EU, there is a dynamic landscape of DHT assessment frameworks, ranging from advanced national frameworks in Germany, France and Belgium, to less developed or non-existent frameworks in other Member States. This national approach for harmonization of Health Technology Assessment is further driven by the HTAR, aimed at standardizing comparative evaluations across the EU. However, significant gaps remain, particularly in integrating pre-market and post-market evaluations and leveraging real-world data for continuous assessment. The progress with advanced national frameworks is expected to guide and accelerate similar advancements in other nations, and also for an EU-wide consistency in DHT regulation. The German Digitale Gesundheitsanwendungen (DiGA) DiGA and the French PECAN process were considered most relevant at this stage:

Germany: Digitale Gesundheitsanwendungen (DiGA)

Status: Open (2019 - ongoing)

France: Prise en Charge Anticipée Numerique (PECAN)

Status: Open (2023 - ongoing)

The DiGA Fast Track process introduced in 2020 the swift evaluation, approval, and reimbursement of lower-risk digital health apps (Class I and IIa). This process, outlined in the Digital Health Applications Ordinance (DiGAV), sets comprehensive requirements for data protection, information security, interoperability, consumer protection, ease of use, support for healthcare providers, quality of medical service, and patient safety. Apps must also demonstrate a positive impact on patient care, such as medical benefits or improved healthcare access in (early) clinical investigation(s). If sufficient clinical evidence is provided, a direct permanent listing can be obtained; otherwise, a preliminary listing for 12 months (extendable to 24 months) is possible, requiring a supporting clinical investigation for permanent listing. In 2024, the Digital Law (DigiG) evolved the DiGA process, allowing for higher risk classes (up to IIb), indication compatibility with future EFS.

PECAN offers a fast-track process for reimbursement of innovative digital medical devices in France, applicable to all MD risk classes and not limited like Germany's DiGA. It includes therapeutic and telemedical applications not yet reimbursed. To qualify, a device must have sufficient benefit evidence, potentially from an EFS, indicating compatibility with a future EFS pathway.

We consider the mapping of DHTs-related projects as an exploratory task relevant to ongoing activities such as stakeholder interviews, scientific exchange to overlapping areas and dissemination. Therefore, we plan to update and enrich this list during the life of the project.

4. Discussion

This chapter is organised with a series of thematic questions, followed by discussion based on the findings.

4.1 Can you currently undertake an EFS in the EU?

EFS are possible in the EU system although they are not specifically facilitated.

Even though the MDR was published in 2017, there are still some parts of this system that are not yet implemented. For example, MDR requires a clinical development plan, which demonstrates milestones and acceptance criteria for progression from early stage to pivotal and post-market investigations. There is currently no guidance or template for product developers to support them in developing their clinical strategy. Consequently, it is not possible for developers to prepare a clinical development plan, which incorporates an EFS with confidence, as the applied strategy may not meet the expectations of the institutions with which they will engage while developing their product.

In the absence of the centralised EU database for medical devices (EUDAMED), to apply for an EFS, it is necessary to follow differing national procedures, and in some cases national law (see [Appendix 1.2](#) for further information on national approaches). From the perspective of developers this can present as a complex system. Further knowledge regarding this complexity will be generated from the WP1 pre-market program analysis and the WP2 interviews with national competent authorities.

4.2 Do current EU regulatory frameworks, standards and guidance fully address key decision points for EFS preparation?

MDR requirements and associated regulatory guidance is predominantly framed towards clinical investigations generally rather than EFS specifically. As a result of this, available guidance, standards and templates do not tend to address EFS specific considerations.

EFS imply a phased pre-market approach to evidence generation. At the same time, phased evidence generation is not standardised for medical devices/DHTs and the regulatory framework seeks to accommodate different types of evidence generation that may be utilised to support marketing.

Key decision points are not completely addressed in any single framework and available guidance and standards only provide partial information. For developers of both general medical devices and DHTs, key decision points are:

- a. Is an EFS needed?
- b. Has sufficient pre-clinical development been undertaken to justify an EFS?
- c. How should an EFS be designed?

One question that arises is the importance of medical device risk class in determining need for an EFS. In the US, the original scope of the FDA EFS program focused on the early evaluation of high-risk medical devices. Under MDR, clinical investigations are mandatory for Class III and implantable devices so an EU EFS program will likely be particularly useful for these medical devices. Nevertheless, there is nothing that precludes the extension of this future EFS program to medical devices in other risk categories. For instance, manufacturers of a Class IIb device may benefit from undertaking an EFS because device iterations to finalise the medical device design are possible during this type of study. Thus, manufacturers can refine their product and proceed through the evidence generation cycle without undue delay. In addition, an EFS may also be useful for when a manufacturer wants to use an already CE-marked device for a new indication, e.g., a stent first used for vascular indications repurposed for use in the biliary duct.

The use of EFS for lower-risk devices is perhaps best exemplified by DHTs which are often placed in Class IIa. EFS for these relatively low-risk DHTs are undertaken for significantly different purposes when compared with general MDs. Guidance, standards, and literature indicate that EFS are conducted for medical devices to evaluate the device's proof of concept and to gather insights into its safety and performance when used with patients. DHTs have different approaches to pre-clinical development, with different consequent approaches to early clinical investigation which is typically based upon a validation of the technology, rather than understanding the basic proof of concept. This has two important implications – firstly, the type of study design is different to general medical device EFS and secondly, the data generated from an EFS for a DHT may be used for market access (CE marking) and, in some cases, it may be sufficient to demonstrate a sufficient evidence-base for initial (or provisional) reimbursement via national reimbursement procedures.

There would appear to be two driving forces for this. The first is conceptual - DHTs can typically deliver value for healthcare systems that is separate to the safety and performance aspects which are focused on in MDR. A DHT may, for example deliver more timely access to data which speeds up the provision of care, however this is not a value which is assessed as part of regulatory assessments.

The second driving force is regulatory – as a result of the change in risk classification rules with the MDR, available DHTs which were CE-marked under the previous rules were often Class I devices

when they were ‘stand-alone’ software (i.e., not part of a software/hardware system). With the MDR, DHTs have in general been up-classified and therefore now require notified body assessment. Class I and ‘self-certification’ is possible but rare under MDR for these type of devices. This up-classification, combined with increased clinical evidence requirements generally, have required DHT developers to consider clinical investigations, and small studies are hence undertaken more often.

4.3 How does the system manage protocol and device modifications?

Substantial iterations during EFS are conceptually important and a future program would benefit from an expert led, agile and timely procedure for their assessment.

For some general MD technologies (for example devices considered ‘breakthrough’ devices in the US), and for the vast majority of DHTs, multiple changes to the technology may be justified in the EFS setting. MDR applies a timeline for the assessment of ‘substantial modifications’ (MDR, Article 75) and guidance provides examples of what changes may be considered ‘substantial’ or not (MDCG 2021-6 Rev. 1). For modifications which are not ‘substantial’, these can be logged by the developer and assessed at the time of the next substantial modification. For a future EFS program, greater clarity on how modifications can be assessed would be beneficial and likely to support overall program success.

The US FDA EFS program places an emphasis on agile methods for the assessment of modifications to the device or the clinical study protocol. This includes short timeframes for assessment, the opportunity to discuss modifications and the ability to agree on some changes that could be implemented without an application / approval. From our review of the literature discussing the US FDA experience, utilising an expert led, open and agile approach in a timely manner is seen as an important component of the program.

4.4 How could European institutions and Member States deliver a harmonised EFS program?

In section 4.6 below, we identify a range of factors that would support the development of a harmonised EU EFS program. To develop a future EU EFS pathway, it will be necessary to utilise a framework for clinical evidence generation. The application of the IDEAL-D framework could potentially offer a structured pathway for navigating the preclinical and early clinical phases of medical

device development (38). This framework theoretically delineates primary steps, including initiation, development, exploration, assessment, long-term study, and iterative development. In the initiation phase, the identification of unmet needs and assessment of economic viability could serve as crucial starting points. Subsequently, in the development phase, engaging with patients and clinicians through surveys and focus groups could ensure acceptability and usability. Laboratory studies, animal studies, and simulated manufacturing scenarios in the exploration phase could evaluate device safety and efficacy. The assessment phase, encompassing laboratory bench testing and cadaver studies, could further assess device performance. In the long-term study phase, animal studies could theoretically provide insights into device performance over time. Throughout these phases, adherence to relevant regulatory standards would be imperative. By documenting each step, regulatory compliance could be ensured, while also offering insights into the device's developmental journey before progression to early feasibility studies.

4.5 Is dialogue a vital feature of a Future EU EFS Program?

Different types of dialogue, e.g., early advice, continuous dialogue with competent authorities appear to be vital to a future EFS program success.

Literature, which commented on experience with the US FDA EFS program noted the value and importance of regulatory advice to support EFS study design and regulatory applications. This has obvious value to both developers, who can more confidently apply strategies, and for regulators, who receive applications which are more likely to meet expectations. This dialogue facilitates direct communication between engineers and clinicians from both sides, allowing for a detailed discussion on potential roadblocks moving forward. In the EU, systematic regulatory advice on whether an EFS is needed or how to prepare the design is not available at a European level.

The EU system has some national advice structures, available via national competent authorities. MDR provides for advice procedures provided by expert panels for certain high-risk medical devices (MDR, Article 61(2)). The MDR expert panels have run a series of advice pilots; this work is still underway. There is very limited information publicly available concerning the nature of advice received or how this is organised. Further development of this advice program beyond the pilot phase will be vital to identify how this could support a bespoke EFS program in the EU. Under HTAR Joint Scientific Consultation will be offered at European level and will, when requested, by the developer be combined with Expert Panel Scientific Advice, this would then allow developers to receive regulatory and advice from Health Technology Assessment Bodies in parallel.

4.6 Future directions

The ultimate outcome of concern related to our activity is a future EU EFS program. To categorise current and future regulatory activities that can contribute to this, we utilised the components of a generic causal map of regulation and its impact (65) (Table 6).

Table 6. Future directions and priority areas arising from the regulatory review

Component of Regulation	Possible future activity	Comment
Ultimate outcome of concern	Delivery of a harmonised EU EFS program	This is the overarching goal of the HEU-EFS project.
Other outcomes	Developing conceptual and methodological frameworks targeted towards EFS	Frameworks targeted at developers to support the key decisions related to EFS identified in this report would be essential for a harmonised EFS program. ISO/WD (Working Draft) 18969 Clinical evaluation of medical devices, (in development) concerning clinical evaluation and design validation may support this.
Behavioural components	Competency framework and training for assessors of EFS applications	Bespoke training to help national competent authority assessors, and device developers with EFS specifically may be helpful. Further information concerning this will be uncovered in later WP2 activities.
	Training material for developers	As above.
	Integration of patient and user considerations to early development activity	This appears to be a gap in current policy and practice. Consistent integration of patient perspectives in targeted development activity (informed consent, patient information, selection of outcomes) would be beneficial.
Implementation and enforcement	Standardising timelines for assessment of modifications	This would support bespoke assessments which are part of the US FDA program with short assessments, just in time testing etc.
	Standardising different national legal and regulatory requirements for EFS assessments by National Competent Authorities	Having a single approach across the EU for the assessment of EFS applications is necessary to deliver a harmonised program. This may become clearer when coordinated assessments (Article 78) begin.

Component of Regulation	Possible future activity	Comment
Regulation of Interest	MDR	The targeted evaluation by the Commission later this year may identify areas for improvement in the existing framework.
Other Regulations	HTAR	The pilot joint-scientific consultations with expert panels and HTA bodies may support better advice structures. In addition, support for life-time evidence generation for medical devices, where for example EFS can be used to inform HTAs.
Regulatory policy	Policy on how different institutions interact	A policy would need to delineate roles and responsibilities across the relevant institutions (eg. MDCG, EMA, NCA, HTA bodies)
Regulatory institutions	Greater coordination	<p>Sub-specialisation of NCA expertise similar to the US FDA EFS groups, or the expert panel groupings would help to build greater specialist knowledge in the assessments of applications to conduct EFS.</p> <p>Ensure that sufficient expertise and human resources for DHTs are available.</p> <p>Experience sharing and training are vital. The JAMS 2.0 project may support this.</p>

5. Conclusion

This report provides an analysis of EU regulations, international standards, and guidelines, in addition to a specific analysis of EU and international research projects relating to Digital Health Technologies (DHTs). We identified that EFS are possible in the EU system although they are not specifically facilitated. Key facilitators include opportunities for dialogue between developers and regulators, EFS focussed guidance and dedicated institutional resources.

The findings from this report will be complemented with further activities in WP2. This will consist of interviews with national competent authorities to further understand critical barriers and success factors, in addition to interviews with DHT developers and monitoring of key regulatory developments.

A final WP2 report with aggregated findings will be prepared and presented to the project at the mid-term open conference.

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7. Appendices

Appendix 1.1 Key terminology

We begin by introducing the definition of ‘medical device’ in MDR, and then discuss clinical investigations and subtypes such as EFS, before moving to introduce terms related to DHTs.

Medical device (MD)

“Medical device” is defined in Article 2(1) of the MDR as follows:

‘medical device’ means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
- *investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,*
- *providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,*

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

As we can see from this definition, there are product related concepts (e.g., instrument, apparatus and specifically software), followed by a listing of ‘medical purposes’ (e.g., diagnosis, prevention etc.), and then a delineation from the terminology used to define medicines (pharmacological, immunological or metabolic means). MDR only applies to products which meet this definition. One distinguishing feature of the medical device definition is that it places a heavy reliance on the ‘intended purpose’ defined by the manufacturer.

Clinical investigation

Clinical investigation is defined in both the MDR and ISO 14155:2020 in almost identical terms. Article 2 (45) of the MDR defines a CI as "*any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device.*" In contrast, ISO 14155:2020 defines a CI as "*a systematic investigation in one or more human subjects, undertaken to assess the clinical performance, effectiveness, or safety of a medical device.*" Under MDR, there can be both pre-market and post-market clinical investigations.

Medical Device Software (MDSW)

MDSW refers to software that is specifically intended to be used for medical purposes as defined under the EU MDR. This includes both standalone software and software that is part of or controls a medical device. The term MDSW is only used in the EU. Equally, SaMD is not used in the EU regulation. Medical Device Software for classification purposes is defined by Rule 11 of Chapter III in Annex VIII of the MDR and contains following provisions:

"Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa, except if such decisions have an impact that may cause:

- *Death or an irreversible deterioration of a person's state of health, in which case it is in class III; or*
- *Serious deterioration of a person's state of health or a surgical intervention, in which case it is classified as class IIb.*
- *Software intended to monitor physiological processes is classified as class IIa, except if it is intended for monitoring of vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient, in which case it is classified as class IIb. All other software are classified as class I."*

That rule applies to software-only devices and hardware devices that comprise MDSW as an integral part.

The MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR has also defined MDSW as such and provided more guidance on how to understand the MDR for software. Hereby it refers to Article 2 (1) of Regulation (EU) 2017/745 – MDR and Article 2 (2) of Regulation (EU) 2017/746 – IVDR (66):

"Medical Device Software (MDSW)

Medical device software is software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a "medical device" in the medical device regulation or in vitro diagnostic medical devices regulation."

The US FDA and IMDRF use the terms 'software as a medical device' (SaMD) and 'software in a medical device' (SiMD). This distinction is less clear in the EU, where the generic term MDSW is used and for SiMD, guidance refers to this as MDSW-hardware combinations. International standards use different terms, for example IEC 82304:2016 uses the term 'health software' which is defined as 'software intended to be used specifically for managing, maintaining or improving health of individual

persons, or the delivery of care’ and a note which accompanies the definition states ‘Health software fully includes what is considered software as a medical device (see rationale in A.1).’

Non-clinical and Pre-clinical testing

Non-clinical testing may be understood as testing which is not conducted on or with human subjects. Pre-clinical testing may be used synonymously with non-clinical testing, however it implies a smaller subset of testing when compared to non-clinical testing, as pre-clinical testing is the testing which is conducted prior to the first clinical use.

The FDA Modernization Act 2.0, enacted in December 2022, revises the regulatory framework for non-clinical tests in drug and medical device development. Crucially, the Act replaces the term "pre-clinical tests" with "non-clinical tests," broadening the scope to include various innovative methodologies beyond traditional animal testing. This change underscores the acceptance of advanced alternatives such as in vitro testing, computer modelling, and organ-on-a-chip technologies. These methods are recognized for their potential to enhance the ethical and scientific rigor of safety and efficacy evaluations, reduce reliance on animal models, and expedite the development of new therapies. (67)

Software as a Medical Device (SaMD)

SaMD is software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device. This software can run on general-purpose computing platforms, such as smartphones, tablets, or personal computers.

The term SaMD is defined by the International Medical Device Regulators Forum (IMDRF) as follows (68):

“The term “Software as a Medical Device” (SaMD) is defined as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.

- *SaMD is a medical device and includes in-vitro diagnostic (IVD) medical device.*
- *SaMD is capable of running on general purpose (non-medical purpose) computing platforms*
- *“without being part of” means software not necessary for a hardware medical device to achieve its intended medical purpose;*
- *Software does not meet the definition of SaMD if its intended purpose is to drive a hardware medical device.*
- *SaMD may be used in combination (e.g., as a module) with other products including medical devices;*

- *SaMD may be interfaced with other medical devices, including hardware medical devices and other SaMD software, as well as general purpose software*
- *Mobile apps that meet the definition above are considered SaMD”*

The US FDA also refers to the definition of SaMD provided by the IMDRF (69).

Software in a Medical Device (SiMD)

Software in a Medical Device (SiMD) is defined as software that is embedded within a medical device and is essential for its operation or to perform specific functions. The FDA, the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom and the European Union adopt analogous definitions, highlighting the role of SiMD in controlling and enhancing the functionality of medical devices.

Legacy devices

According to MDCG 2021-5, legacy devices should be understood as devices are placed on the market after the MDR's date of application and until 26 May 2024 if certain conditions are fulfilled. Those devices can be: (i) devices which are class I devices under Directive 93/42/EEC (MDD), for which an EC declaration of conformity was drawn up prior to 26 May 2021 and for which the conformity assessment procedure under the MDR requires the involvement of a notified body; (ii) devices covered by a valid EC certificate issued in accordance with Directive 90/385/EEC (AIMDD) or the MDD prior to 26 May 2021 (70).

Appendix 1.2 Introduction to the EU and national processes related to an EFS

By way of background, in 1992 the Treaty on European Union introduced “a contribution to the attainment of a high level of health protection” as one of the joint activities of Member States. The Treaty on the Functioning of the European Union (Article 168, paragraph 4c) further requires the adoption of “measures setting high standards of quality and safety for medicinal products and devices for medical use”. Recital 1 in the MDR notes that the regulatory framework should ensure “a high level of safety and health whilst supporting innovation”.

Although there is a European competence with respect to health protection, quality and safety of medical devices, there are also national competences which are accommodated outside of the MDR. Recital 65 of MDR notes that it ‘should be left to the Member State where a clinical investigation is to be conducted to determine the appropriate authority to be involved in the assessment of the application to conduct a clinical investigation and to organise the involvement of ethics committees within the timelines for the authorisation of that clinical investigation as set out in this Regulation.’ The MDR therefore sets principles, for example that clinical investigations are ‘designed and conducted in such a way that the rights, safety, dignity and well-being of the subjects participating in a clinical investigation are protected and prevail over all other interests and the clinical data generated are scientifically valid, reliable and robust. MDR also sets timelines and some basic requirements, for example relating to the requirement to have a layperson on an ethics committee established under national law. Beyond this however, it is up to each Member State to determine how to conduct the assessments on a national basis.

Under MDR, a sponsor (or manufacturer) can decide if they would like to undertake an EFS in the EU or not. In contrast to medicinal products, not all medical devices have pre-market clinical investigations to support them.

Sponsors prepare the documentation necessary for the ethics committee and NCA. The opportunity to avail of EU level advice is not generally available outside the EMA expert panel pilot. On a national basis, it may be possible to access some pre-submission advice from the NCA / ethics committee. A new advice possibility is ‘structured dialogue’ with a notified body (18), however the extent to which it would be possible to discuss an EFS is unknown.

Once a sponsor submits their application to the research ethics and NCA (which in some Member States can be done in parallel, or it may be required to apply sequentially) the NCA/ethics committee may authorize, authorise with conditions, or reject the application. If authorised, the sponsor is required to report serious adverse events, in addition to other sponsor responsibilities described in MDR Annex XV and ISO 14155:2020.

EFS, by definition tend to include medical devices at an earlier stage of development, and as such the likelihood that iterative changes need to be introduced is greater than later phase studies. For substantial modifications, sponsors are required to submit these in advance and Member States (which may be the NCA +/- ethics committee) have a maximum of 38 days to approve / refuse the change.

When the study is complete, MDR provides for a report to be made public via the EUDAMED system. This is not available so the use of Communication and Information Resource Centre for Administrations, Businesses and Citizens. (CIRCA-BC) is foreseen in the interim, however it is not clear if this portal is active or available publicly.

Appendix 2.1 Methods

This Appendix explains in depth the methodology used to conduct the systematic literature review. It also gives the rationale behind the regulatory documents screened and gives a review of the PRISMA flow diagrams.

To address potential gaps not fully covered in the regulatory review, a systematic literature review was conducted in parallel with WP1. This review was based on a comprehensive search of grey and scientific literature. As previously mentioned, there is an interconnection between WP2 and WP1. To ensure comprehensiveness and prevent redundancy, the systematic literature review strategies for Task 1.1 of WP1, as well as Tasks 2.1 and 2.2 of WP2, were developed in unison and structured following the PRISMA guidelines. Several meetings were held beforehand to define the search terms and establish the inclusion and exclusion criteria for both reviews, which are available in Appendix 2.

WP1 focuses on understanding the characteristics and impact of PMAP (Pre Market Approval Pathways) for medical devices in the EU and other relevant jurisdictions, while WP2 aims to identify the optimal fit for an EU EFS program, including DHTs. The complete results of the literature review will be included in the WP1 deliverable due in Month 15. However, this report includes the methodology and results relevant to Deliverable 2.1, particularly papers related to EFS and DHTs.

Medical device developers typically undertake EFS for various reasons, although publicly available information on this is limited. Rationales may include factors such as device design, available non-clinical and pre-clinical data, and supportive clinical information, like data from a prior version of the device.

Given that the rationales for conducting EFS are not publicly available and that terminology for different pilot stage studies is new, using standard terms such as 'early' and 'traditional' feasibility in the systematic literature may not yield all relevant information. In the United States, the sample size for an EFS generally involves fewer than 10 initial subjects; however, up to 15 subjects (and possibly more) may be accepted.

In light of these factors, we opted to include data related to all pilot stage studies, such as FIH, early, and traditional feasibility studies, and CI with a sample size of approximately 15 subjects. These clinical investigations are referred to as early-stage CI.

Databases

The databases used for the systematic literature searches were: Web of Science, Scopus, PubMed

The following distinct searches were conducted using different search terms described below.

1. Main Search - Pre-market approval pathways scientific and grey literature search in the EU and Other Jurisdictions

The PMAP search encompassed a systematic review to understand the characteristics and impact of pre-market programs for MDs and DHTs. This included:

- Mapping and identifying current pre-market programs in the EU and other jurisdictions.
- Identifying performance monitoring systems in place for these programs, including the FDA EFS Program.
- Outlining impacts, gaps, barriers, and challenges in pre-market research.

2. EFS-focused Search - Early Feasibility Studies for Medical Devices and DHTs

The EFS-focused search aimed to identify both EFS and EFS-like studies using various synonymous terms and to explore the goals, workings, and evolution of the US EFS program and similar program proposals elsewhere.

In addition, we employed snowballing methods such as pursuing references of references and electronic citation tracking, as well as the informal method of consulting colleagues, as recommended by Greenhalgh and Peacock (71).

Search terms

Search terms from Scopus: 610 results:

TITLE-ABS-KEY (("early feasibility stud*" OR "clinical feasibility" OR "first in human" OR "iterative development" OR (("premarket" OR "pre-market") AND "clinical") OR (("preapproval" OR "pre-approval") AND "clinical") OR "clinical investigation" OR "clinical evaluation")

AND ("medical device*" OR "medical technology" OR "digital health technology" OR "digital medical device" OR "digital software")

AND ("program" OR "approval" OR "pathway" OR "regulat*")

AND (perform* OR characteristic* OR impact OR evaluation OR assessment OR effectiveness OR analysis OR consequence* OR "barrier*" OR "challenge*" OR "feature*" OR "KPI" OR "recall*")

AND NOT "preclinical"

Web of Science - 307 results

ALL=(("early feasibility stud*" OR "clinical feasibility" OR "first in human" OR "iterative development"
OR (("premarket" OR "pre-market") AND "clinical") OR (("preapproval" OR "pre-approval") AND
"clinical") OR "clinical investigation" OR "clinical evaluation")

AND ("medical device*" OR "medical technology" OR "digital health technology" OR "digital medical
device" OR "digital software")

AND ("program" OR "approval" OR "pathway" OR "regulat*")

AND (perform* OR characteristic* OR impact OR evaluation OR assessment OR effectiveness OR
analysis OR consequence* OR "barrier*" OR "challenge*" OR "feature*" OR "KPI" OR "recall*")

Search terms from Pubmed: 108 results

same search on Title and abstract

Search: (("early feasibility stud*" OR "clinical feasibility" OR "first in human" OR "iterative
development" OR (("premarket" OR "pre-market") AND "clinical") OR (("preapproval" OR "pre-
approval") AND "clinical") OR "limited clinical investigation")

AND ("medical device*" OR "medical technology" OR "digital health technology" OR "digital medical
device" OR "digital software")

AND ("program" OR "approval" OR "pathway" OR "regulat*")

AND (perform* OR characteristic* OR impact OR evaluation OR assessment OR effectiveness OR
analysis OR consequence* OR "barrier*" OR "challenge*" OR "feature*" OR "KPI" OR "recall*")

Screening Method

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.

The outcomes of the searches were organized into three categories:

- Pre-market approval pathways papers for WP1.
- EFS papers for WP2.
- DHTs papers for WP2

**Rayyan.ai is a web-based tool designed to streamline systematic reviews and meta-analyses. It supports collaboration by allowing researchers to independently screen study titles and abstracts, assess full texts for eligibility, and extract data within a centralized platform. Key features include*

automatic de-duplication of references, blind review options, and customizable inclusion and exclusion criteria.

Inclusion and exclusion criteria

The criteria defined for the systematic literature review were as follows:

- Inclusion: Any paper related to an EFS, early stage clinical investigation, or a pre-market programs (i.e., pre-market approval pathways, especially as they relate to clinical investigations in the pre-market approval phase); any paper discussing the gaps, barriers, and challenges encountered during the execution of an EFS or a pre-market program, including the monitoring of such programs
- Exclusion: Papers focusing on post-market studies, pharmaceuticals, animal studies, or published before 2013.

For DHTs, additional inclusion and exclusion criteria were defined to narrow the review and make it more specific to DHTs:

- Inclusion: Any paper related to software as a medical device, including pilot or early feasibility trials, medical applications, telemedicine, embedded software, AI algorithms, and DHT regulations.
- Exclusion: Papers not related to software as a medical device, 3D printed devices.

Screening Process

The screening method followed the PRISMA guidelines. The screening process involved:

- i. Title/Abstract screening.
- ii. Full text/Content screening
- iii. Further in-depth screening (snowballing method and asking colleagues)
- iv. Data analysis and synthesis

Decision-Making for Document Inclusion

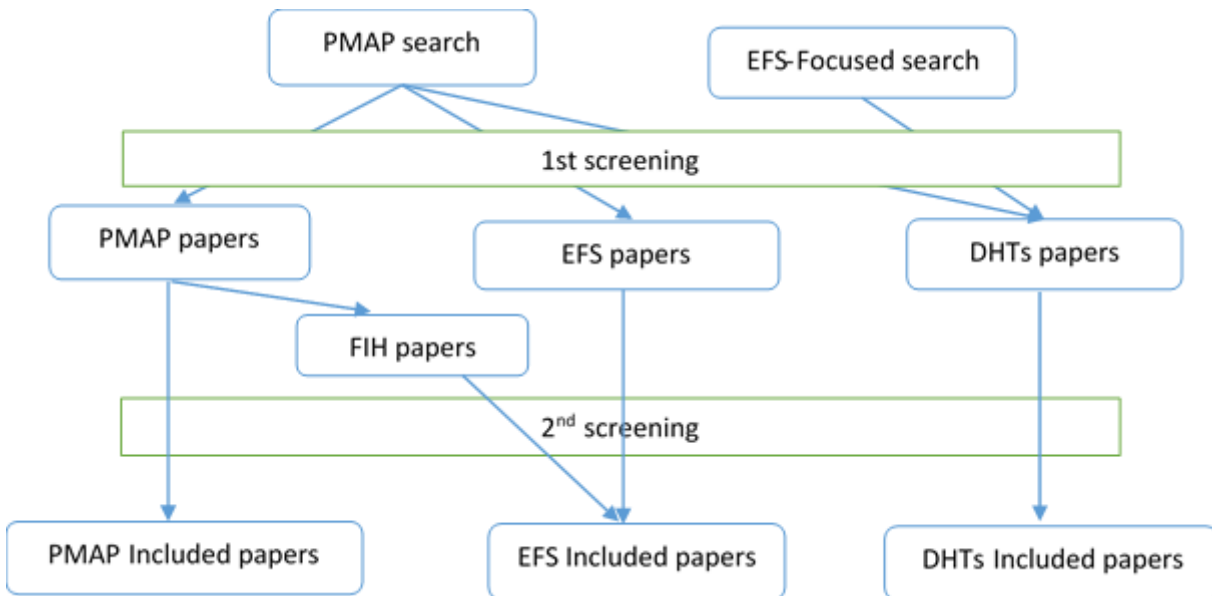
After the full text screening, papers were classified as one of:

- Include: Documents meeting inclusion criteria and containing relevant information on clinical investigations for MDs or DHTs.
- Qualified Exclude: Documents not fully meeting criteria but providing useful background or contributing to discussions.
- Exclude: Documents not meeting inclusion criteria and outside the scope of the review.

Five independent reviewers performed the initial screening based on titles and abstracts (Figure 10). Each paper was reviewed by at least two reviewers, with discrepancies resolved in meetings. Selected

papers underwent a second screening, focusing on detailed examination and data extraction. Discrepancies in exclusion decisions were collectively discussed and resolved.

Figure 10. Systematic literature review - Screening process



Data extraction process

To harmonise the extraction of information from the included papers, a standardized data table was established during consortium meetings. This foundational work is crucial for the entire project, as the information gathered from this literature review will inform various Work Packages (WPs) including WP3, WP4, and WP6. The data extraction table was designed to meet the specific needs of these WPs.

The table for data extraction is divided into nine major themes. For this report, only the themes relevant to WP2 are listed below:

Themes Informing WP1 and WP2

Impact: challenges, gaps, problems, barriers

- Regulatory hurdles, barriers, problems described or assessed
- Quality and risk management (e.g., adverse events, recalls, patient safety, off label use)
- Economic sustainability, issues with funding
- Dialogue between players, stakeholders, and regulators

Impact, R&D investments:

- Attracting R&D, issues related to R&D costs, impact on technological innovation, patient needs

Solutions

- Solutions (potential solutions)

Performance

- Market access: timeframe indications, timeframe evaluation, market strategy

Themes Specific to WP2

Before EFS

- Criteria for an EFS: eligibility (MDR, ISO), N. patients
- Evidence of Early dialogue: Advice/structured dialogue between the CA and developers? HTAR?
- Use of a clinical research organisation (CRO)
- Medical liabilities (insurance requirement mentioned?)
- Length of application review

During EFS

- Evidence of dialogue during the EFS
- Device and Protocol changes commentary
- What are the stakeholders' specific roles? (Manufacturer, sponsor, patients, clinical sites, national CA)

After EFS

- Was there a roadmap to next phases? (pivotal study)
- What was the scope of patient follow-up, if any?
- Impact on Market Access (MA) (did EFS accelerate MA?)

Appendix 2.2 PRISMA flow diagram for ISO Standards (excluding DHTS) review

The analysis of standards documents lacks a directly applicable methodology. Previous systematic analyses of standards documents have been conducted in other projects. WP2 identified a research protocol applied in the CORE-MD project (Coordination of Research and Evidence for Medical Devices).¹ That review examined three clinical domains - cardiovascular, orthopedic, and diabetes devices, to determine whether they contained substantial recommendations on clinical investigations (72).² As the objectives of WP2 were different from that of the CORE-MD project, a different search strategy was required.

For the WP2 standards review, we began by reviewing the standards that were subject to a full-text review in the CORE-MD project. This allowed us to:

Prepare a search strategy to support an interrogation of the ISO Online Browsing platform (OBP) (<https://www.iso.org/obp/ui>) to determine whether there had been any updates to the standards since the date of publication.

Determine whether there was any direct reference or any content directly / indirectly related to EFS.

Following this activity, we then prepared a search strategy to undertake a substantial interrogation of the ISO OBP to identify all device specific standards, and hence the device types containing information on clinical investigation, or information of direct / indirect relevance to EFS. The terms "Medical Devices Clinical" was entered into the OBP. The title and the notes were then screened for reference to the following terms: "Clinical", "Preclinical", "Clinical investigation". Following this, the table of contents and informative sections were reviewed to determine whether clinical investigation was within the scope of the standard.

An example of how this presents in the ISO OBP is presented in Figure 11.

¹ CORE-MD received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 965246.

² Study Design Recommendations in ISO Standards for High-risk Medical Devices, a Systematic Review of the Horizon2020 CORE-MD Project, a poster is available at https://www.ispor.org/docs/default-source/euro2022/studydesigncardiovascularisoispor2022v03-psi-pdf.pdf?sfvrsn=b7319a1f_0

Figure 11. Search results from the ISO OBP

ISO 5910:2018(en)
Cardiovascular implants and extracorporeal systems – Cardiac valve repair devices

2 Normative references
...the referenced document (including any amendments) applies. ISO 10993-1 , Biological evaluation of **medical devices** – Part 1: Evaluation and testing within a risk management process ISO 10993-...

3.5 adverse event
untoward **medical** occurrence, unintended disease or injury, or untoward **clinical** signs (including abnormal laboratory findings) in subjects, users or other persons, whether or... ..repair **device**...

See 5 more

Where this was the case, the standard was selected for retrieval and further extraction. Standards were retrieved from the SAI Global i2i Platform. This is a platform which allows access to ISO standards, and it was available to reviewers via the library service of TCD.

Where the retrieved standards had normative or informative content relating to clinical investigation, the “online view” tool on the SAI Global i2i Platform was used to complete an initial review of the standard to verify the content.

The full text of the standards were retrieved and analysed using the Extraction Template developed internally. The selected standards were grouped into device types. Standards relating to biocompatibility, health informatics, risk management, post market surveillance, medical laboratories were excluded. Where references to Standards within the text of the standard were deemed to have relevance, they were also extracted. These standards are identified within the text.

The interrogation of the Online Browsing Platform for all of searches was completed by one researcher. The n = 43 standards were also extracted by one researcher, using the extraction template. Where a standard was excluded, this decision would be validated by a second researcher.

To ensure completeness of inclusion relating to EFS or associated terms, an additional interrogation of the ISO OBP was completed using the terms listed below. These terms align with WP1, where these search terms were used to interrogate clinical trial registries for information on EFS. The inclusion/exclusion criteria used was the same as that for the first search, however, an additional criterion for exclusion was implemented if the standard had already been retrieved in previous searches. From the terms searched, a total of 428 standards were identified. There were no records removed prior to initial screening. From the screening, there were no additional standards identified for extraction (see PRISMA diagrams below).

Figure 12. PRISMA flow chart of the ISO Standards selection Search 1

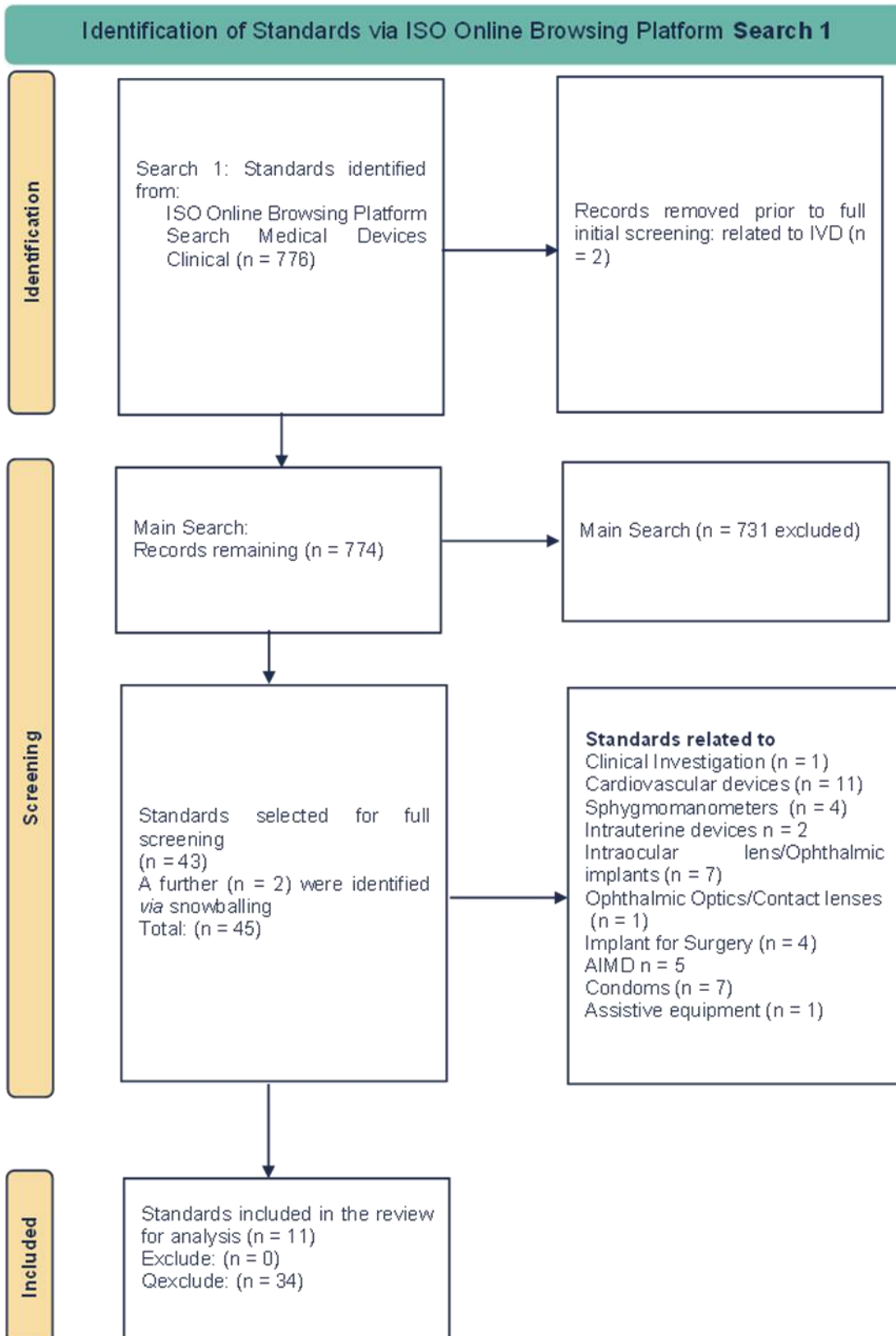


Figure 13. PRISMA flow chart of the ISO Standards selection Search 2

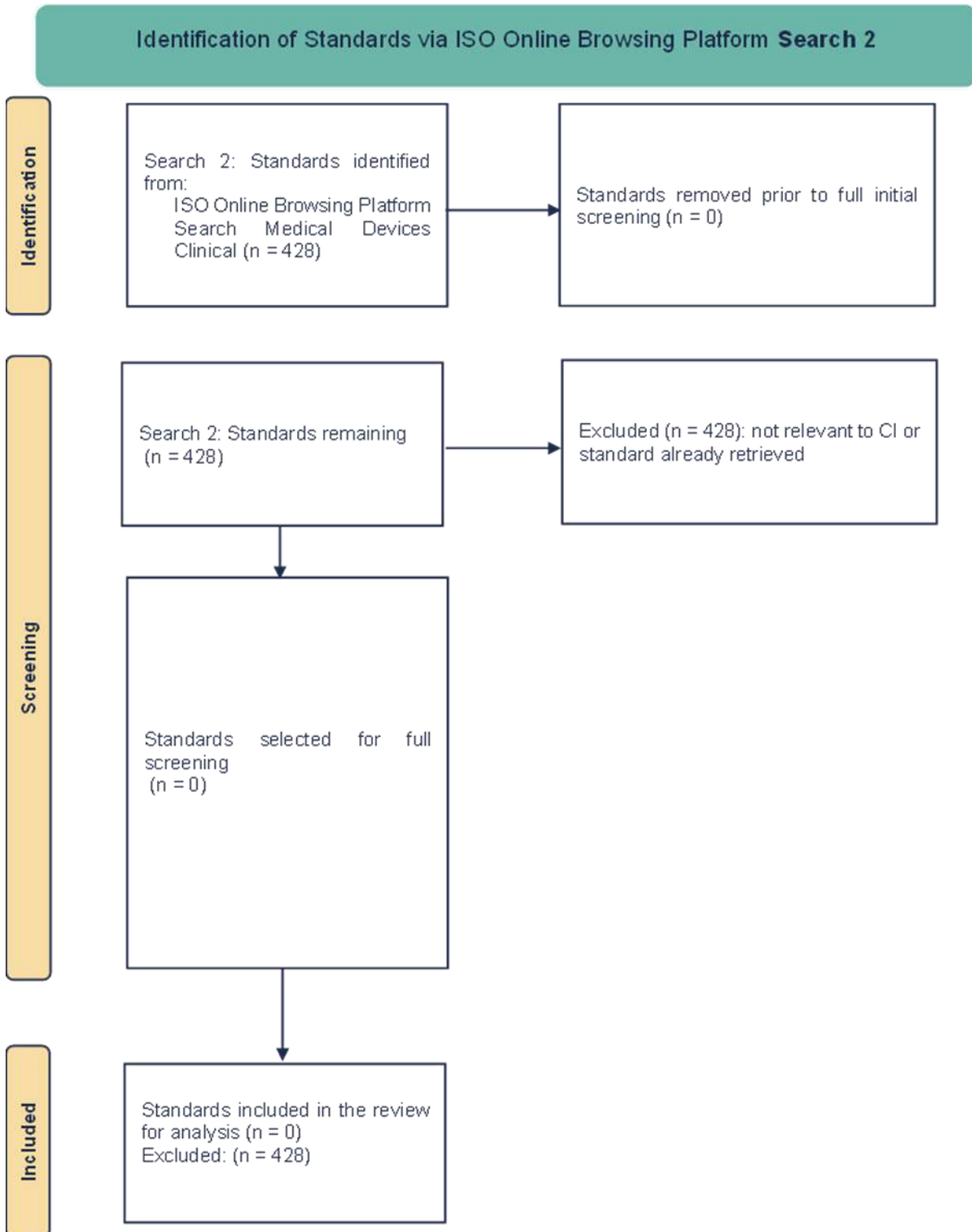


Table 7. List of Standards under the scope from Search 1 and Search 2 Standards Search

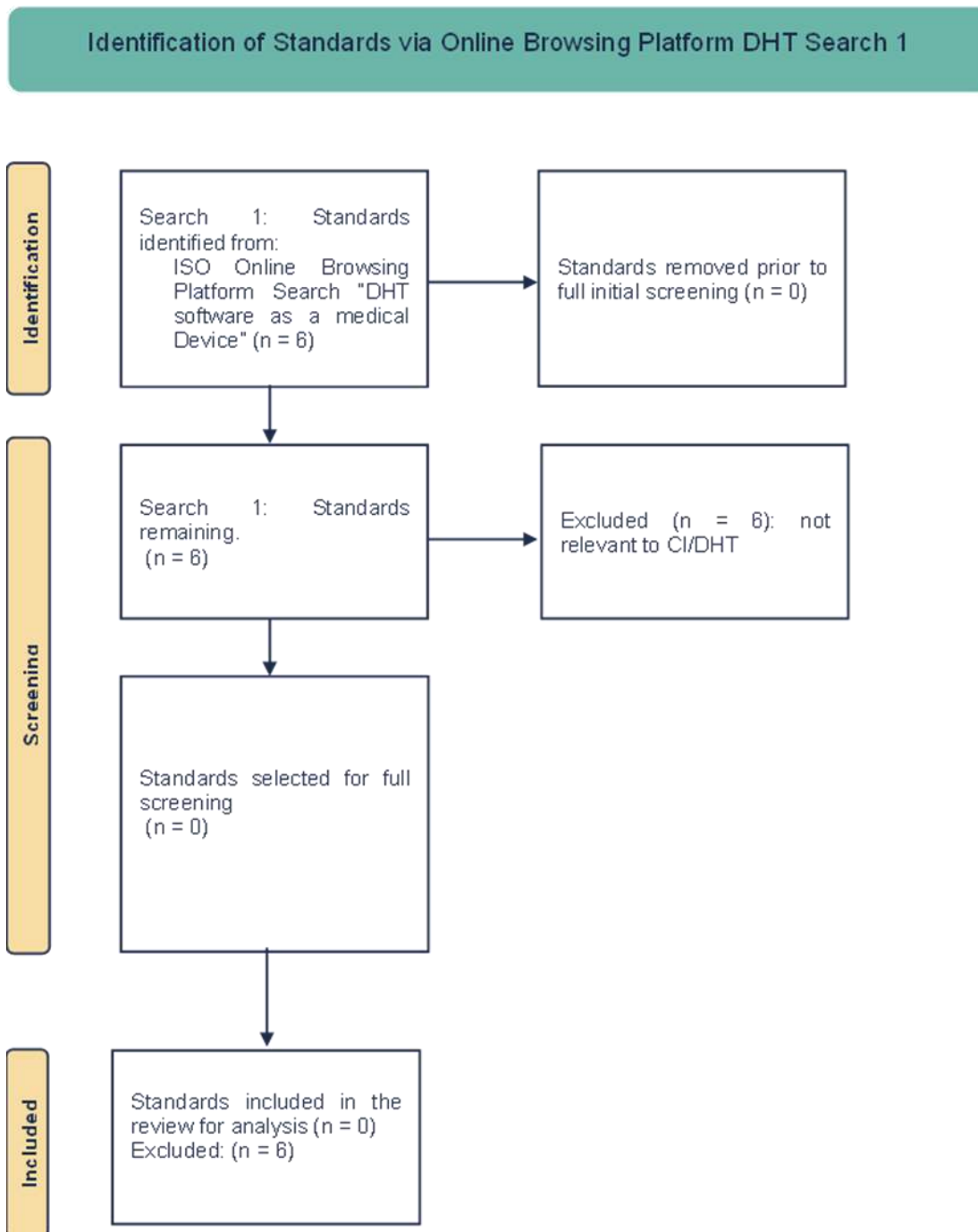
Standard	Standard Title
ISO 14155:2020	Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2020)
ISO 5840-2:2021	Cardiovascular implants — Cardiac valve prostheses — Part 2: Surgically implanted heart valve substitutes
ISO 5840-3:2021	Cardiovascular implants — Cardiac valve prostheses — Part 3: Heart valve substitutes implanted by transcatheter techniques
ISO 5910:2018	Heart Valves Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices.
ISO 22679:2021	Cardiovascular implants: Transcatheter cardiac occluders
ISO 21535:2023	Non-active surgical implants — Joint replacement implants — Specific requirements for hip-joint replacement implants
ISO 21536:2023	Non-active surgical implants — Joint replacement implants — Specific requirements for knee-joint replacement implants
ISO 29943-1:2017	Condoms — Guidance on clinical studies — Part 1: Male condoms, clinical function studies based on self-reports
ISO 29943-2:2017	Condoms — Guidance on clinical studies — Part 2: Female condoms, clinical function studies based on self-reports
ISO 11980:2012	Ophthalmic optics - Contact lenses and contact lens care products - Guidance for clinical investigations
ISO 11979-7:2024	Intraocular lenses — Part 7: Clinical investigations of intraocular lenses for the correction of aphakia
ISO 11249:2018	Copper-bearing intrauterine contraceptive devices — Guidance on the design, execution, analysis and interpretation of clinical studies

Appendix 2.3 PRISMA flow diagram for ISO Standards relating to DHTs review

The ISO online browsing platform was interrogated using 5 independent searches.

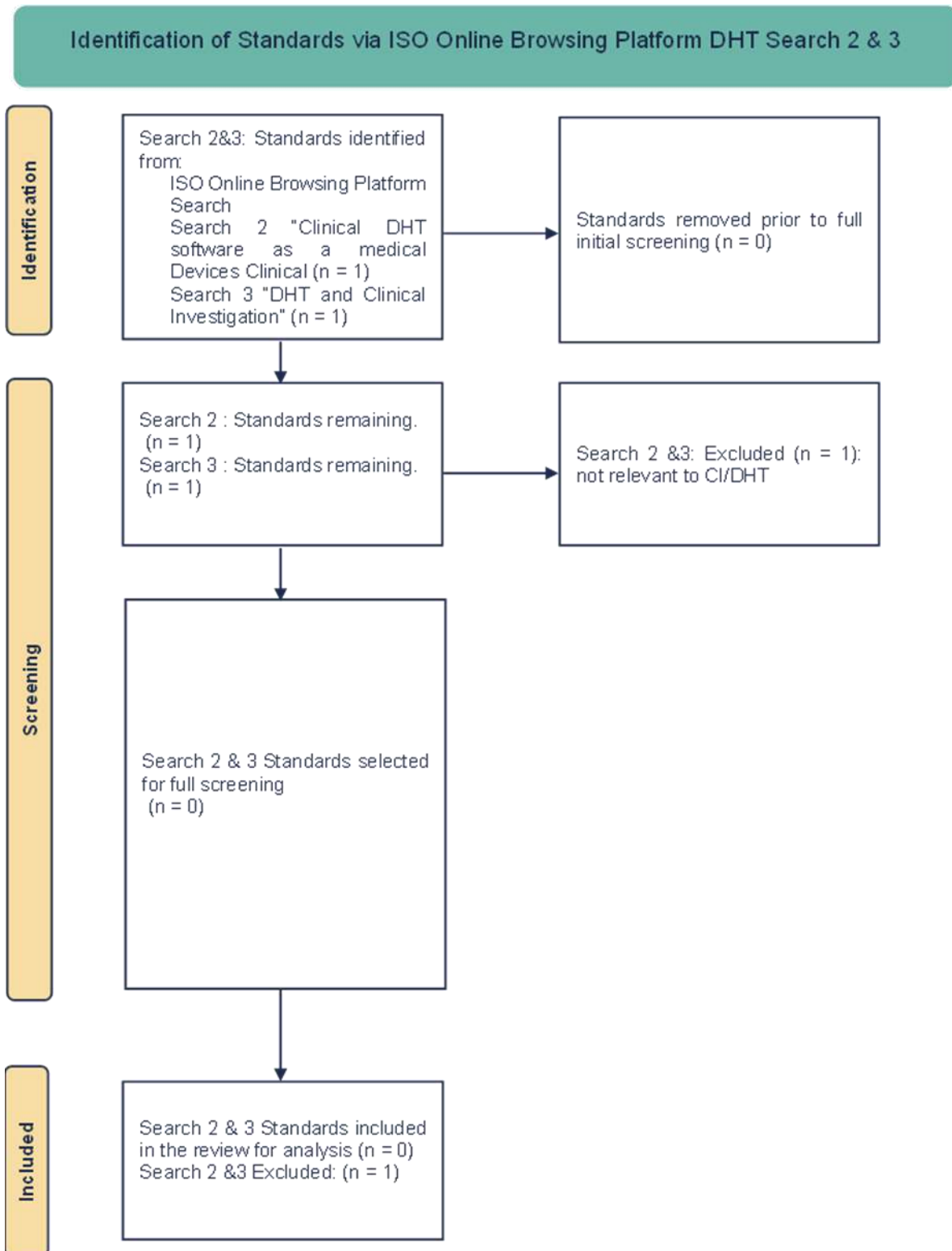
Search 1: The terms “DHT software as a medical device” yielded a total of 6 standards, of which 5 were excluded based on a review of the title and 1 by review of the scope:

Figure 14. PRISMA flow chart of DHTs ISO Standards selection Search 1



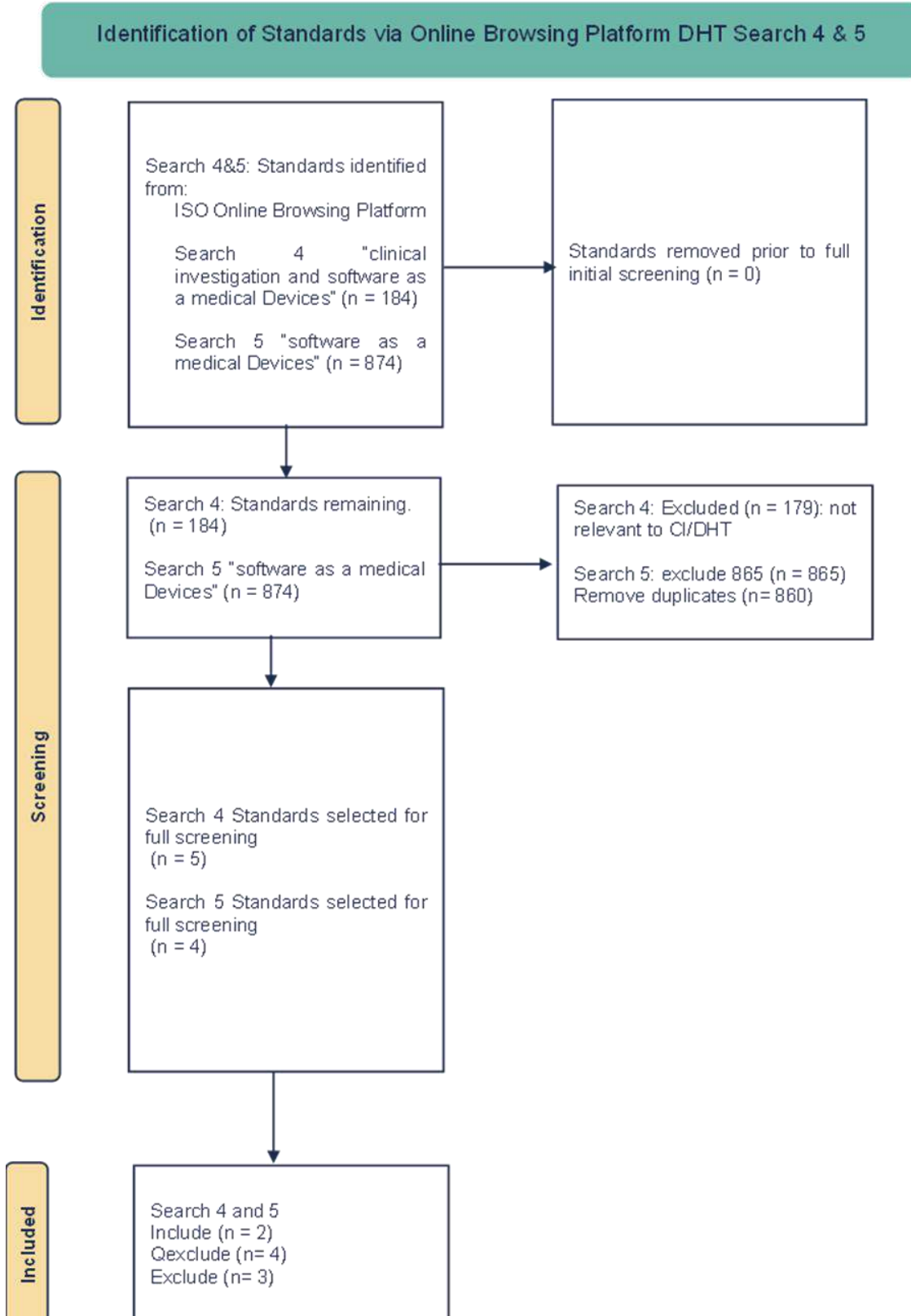
Search 2 and Search 3: The terms “Clinical DHT software as a medical device” and “DHT and Clinical Investigation” yielded a total of 1 standard. The scope of this standard was reviewed and excluded as it did not include DTx market pathways for medical devices.

Figure 15. PRISMA flow chart of DHTs ISO Standards selection search 2 & 3



There are some commonalities related to Search 4 and Search 5 and the results of both of these searches are documented in Figure 16.

Figure 16. PRISMA flow chart of DHTs ISO Standards selection Search 4 & 5



Search 4: The terms “Clinical Investigation and Software as a medical device” yielded a total of 183 standards. Using the exclusion criteria, a total of 5 standards were identified as being relevant.

Search 5: The terms “Software as a medical device” yielded a total of 874 standards. A total of 5 standards were identified as being relevant.

These 9 standards from Searches 4 and 5 were reviewed and discussed for relevance with WP2 reviewers. The initial inclusion criteria used was that the standard included reference to Software/DHT and any reference to clinical/ clinical investigation/clinical evaluation. The inclusion criteria were re-evaluated, and standards were selected that also described the lifecycle and the quality and reliability of health applications, that did not exclude medical devices.

Using this approach, 9 standards were selected for screening and documented in Table 8, of which 2 were included

Table 8. Two included standards of the nine selected for screening

Standard	Title
ISO 14155:2020	Clinical investigation of medical devices for human subjects - Good clinical practice
ISO 82304-2:2021	Health and wellness apps - Quality and reliability

Appendix 2.4 Justification for selection of sources of Regulatory Guidance documents

Medical Device Coordination Group (MDCG)

The MDCG comprises national experts appointed by EU Member States, who typically work for national competent or designating authorities. Its primary aim is to facilitate the efficient and effective implementation of the EU MDR and the EU IVDR. To do so, MDCG has issued more than 100 guidance documents tailored for medical device manufacturers, notified bodies, and relevant parties. These guidance documents offer detailed explanations and insights into different facets of the EU MDR and IVDR, proving indispensable for anyone engaged in the EU market for medical devices. Including MDCG guidance for clinical investigations on medical devices in the regulatory review is essential, as it ensures compliance with the EU MDR, provides clarity on requirements, shares best practices, and highlights how to perform risk management.

Guidance produced for the Medical Device Directives (MEDDEVs)

The MEDDEVs were guidance documents produced for the Medical Device Directives. These documents were developed by national competent or designating authorities in collaboration with all stakeholders including industry associations, health professionals' associations, notified bodies and European standardisation organisations. These guidelines aimed to help manufacturers and notified bodies understand and comply with the requirements of the EU Medical Device Directive 93/42/EC (MDD) and Active Implantable Medical Devices Directive 90/385/EC (AIMDD). Because medical devices certified under the MDD or AIMDD can, subject to conditions, continue to be marketed until specific deadlines (until 31 December 2027 for high-risk devices and until 31 December 2028 for the others), our rationale was to thoroughly examine the MEDDEVs to ensure that no crucial information on EFS was overlooked.

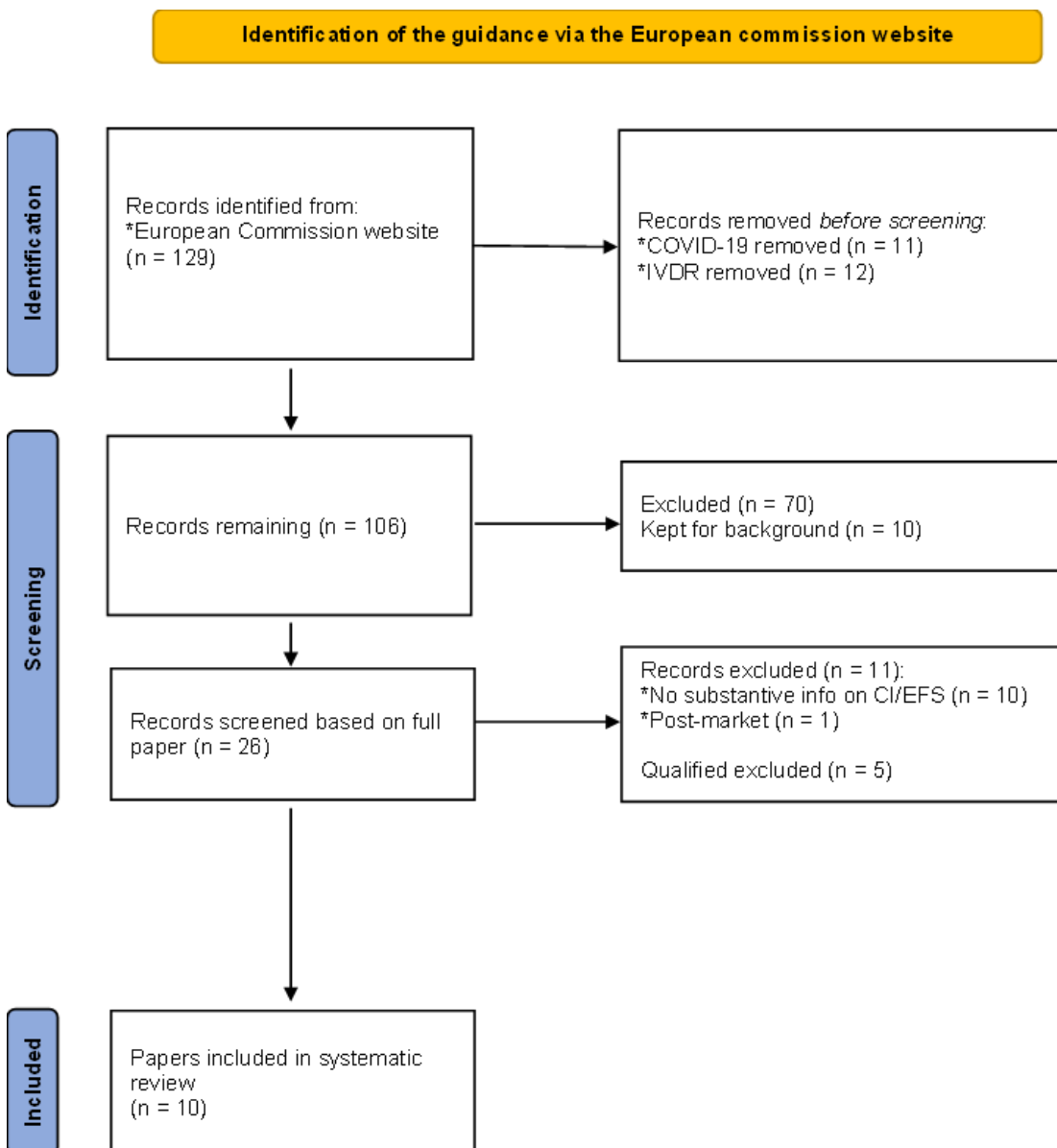
International Medical Device Regulators Forum (IMDRF) Guidance

The International Medical Device Regulators Forum (IMDRF) is a voluntary group comprising medical device regulators from around the world, who collaborate to harmonize the regulatory requirements for medical products that vary from country to country. The aim is to accelerate international medical device regulatory harmonization and convergence. IMDRF develops internationally agreed-upon documents addressing a wide range of topics relevant to medical devices. For this reason, we decided to review the documents available on the IMDRF website to ensure that no crucial information on EFS was overlooked.

Appendix 2.5 PRISMA flow diagram for MDCG review

For the MDCG guidance review, the documents were sourced from the European Commission's site. Initially, 129 guidance documents were identified; after the first screening, 26 were included and 103 were excluded. The reasons for exclusion included 12 relating to IVDRs, 11 relating to COVID-19 and the remaining 80 documents not related to clinical investigations. A full-text screening of the previously included guidance was then conducted. At the conclusion of the screening, 10 guidance documents were included, 5 were classified as qualified exclude, and 11 were fully excluded (Figure 17).

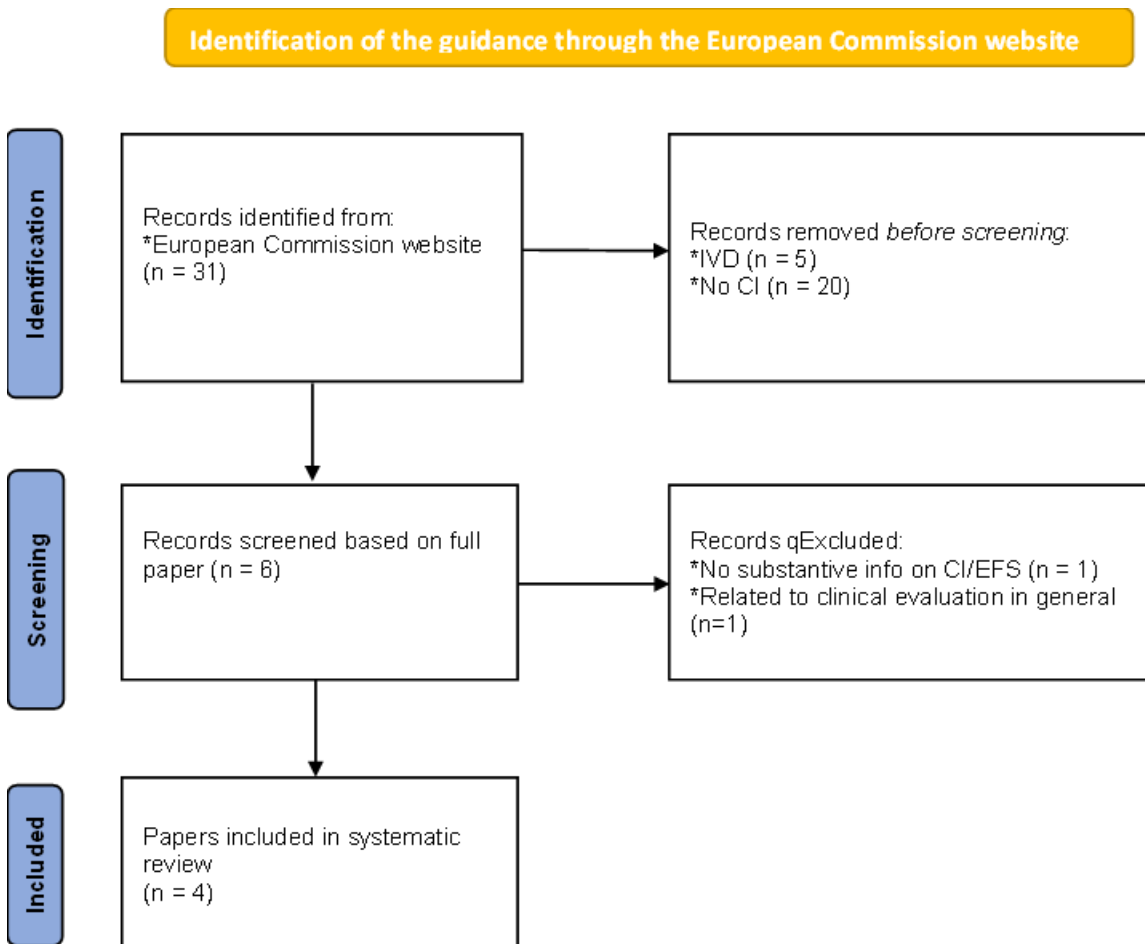
Figure 17. PRISMA flow chart of MDCG guidance selection



Appendix 2.6 PRISMA flow diagram for MEDDEV review

For the MEDDEVs guidance review, the documents were sourced from the EC's site. Initially, 31 guidance documents were identified; after the first screening, 6 were included and 25 were excluded (Figure 18). The reasons for exclusion included 5 relating to IVDs, with the remaining documents not related to clinical investigations. A full-text screening of the previously included guidance was then conducted. At the conclusion of the screening, 4 guidance documents were included, 1 was classified as qualified exclude, and 1 was fully excluded. The primary reason for exclusion was that the document was not pertinent to CI as initially assumed (Figure 18).

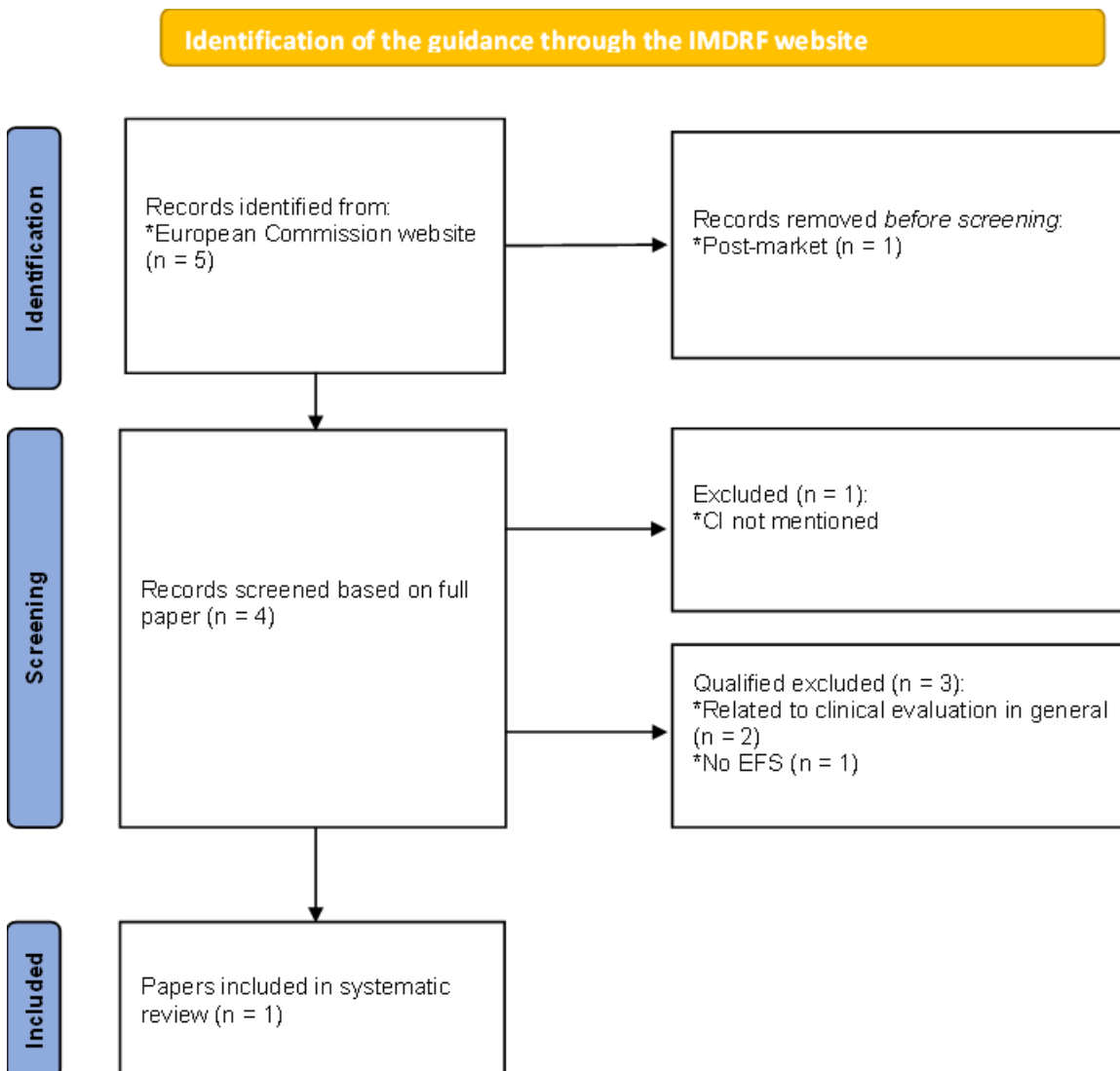
Figure 18. PRISMA flow chart of MEDDEV guidance selection



Appendix 2.7 PRISMA flow diagram for IMDRF review

From the IMDRF website, we sourced five documents that potentially related to CI on MDs (Figure 19). One document was excluded during the initial screening because it was related to post-market considerations. Of the four documents included, we conducted a full-text screening and data extraction based on the extraction table. At the conclusion of the screening, one document was ultimately included, and the remaining three were classified as qualified exclude because they either pertained to clinical evaluations in general or contained no specific information on EFS (Figure 19).

Figure 19. PRISMA flow chart of IMDRF document selection

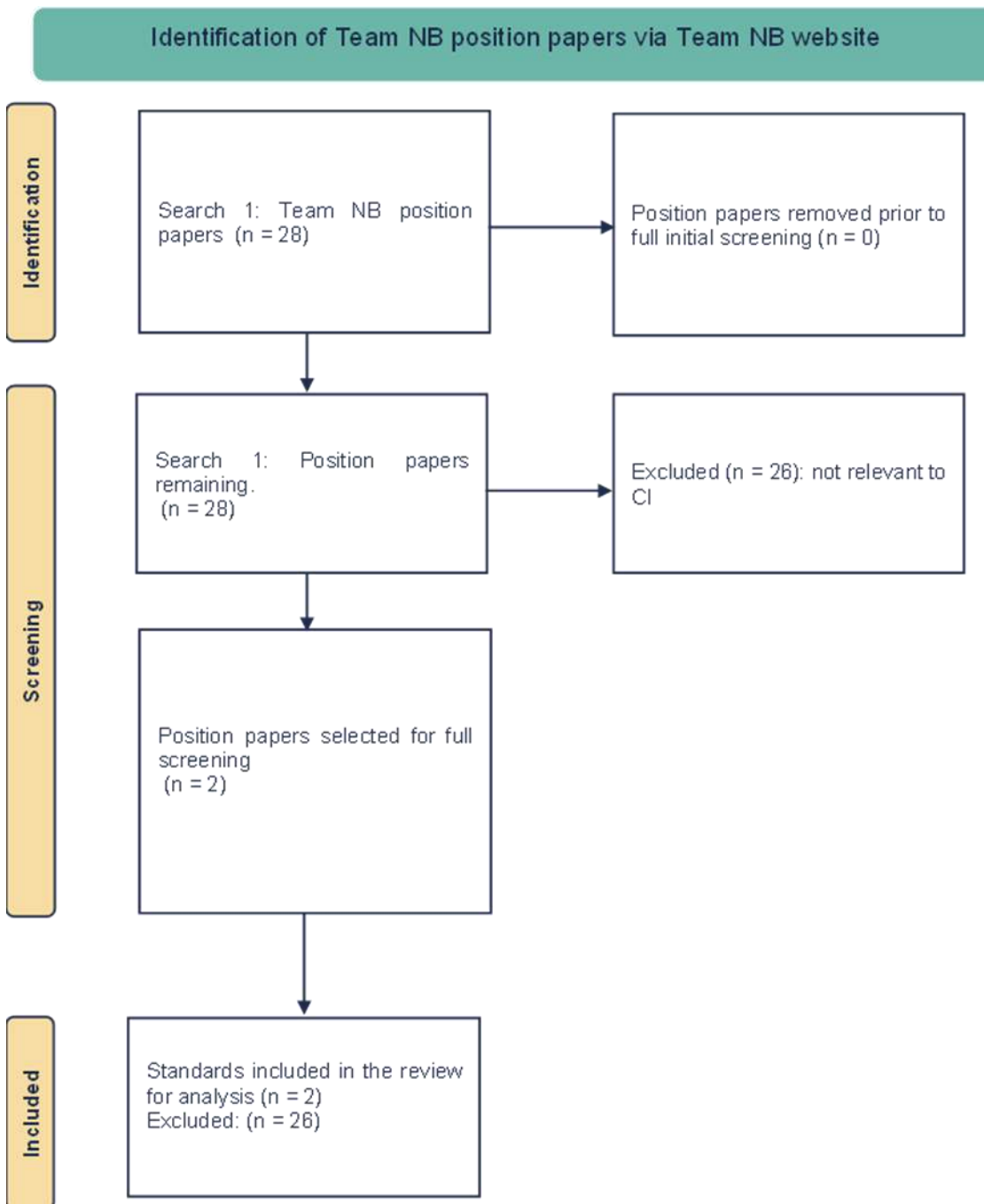


Appendix 2.8 Team NB and NBCG Guidance Documents

Team NB Position Papers

There were 2 position papers identified that had information of relevance to manufacturers. The selection is detailed in Figure 20. The position paper(s) were screened by name and by Scope/Description and content and is documented in the PRISMA diagram below.

Figure 20. PRISMA flow chart of Team NB document selection



We will discuss each in turn

- 1) Best Practice Guidance for the Submission of Technical Documentation under Annex II and III of Medical Device Regulation (EU) 2017/745) Information to be supplied by the manufacturer – a collaborative notified body approach; (V2) noting that this document is currently under revision (73).
- 2) Data generated from ‘Off-Label’ Use of a device under the EU Medical Device Regulation 2017/745.

Best Practice Guidance for the Submission of Technical Documentation under Annex II and III of Medical Device Regulation (EU) 2017/745) Information to be supplied by the manufacturer – a collaborative notified body approach

This technical documentation submission guidance is aligned to the requirements of Medical Devices Regulation [MDR] (EU) 2017/745, described in detail in Annexes II and III of Regulation (EU) 2017/745. This document is a position paper that describes a consensus regarding notified body expectations for technical documentation submissions from manufacturers. The paper addresses, clinical evaluation (and associated documents such as the summary of safety and clinical performance, and labelling), where the requirements of the clinical development plan for device are addressed.

The text provides a reference to Annex XIV Part A where the clinical development plan should describe “the progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a PMCF”.

The clinical development plan is required to be provided for the clinical evaluation assessment, and if not “a suitable justification” should be provided for the absence.

If clinical investigations are performed, a list of required documentation is provided. There is no specific reference to EFS. The Clinical evaluation (Includes Summary of Safety and Clinical Performance labelling) part of the document discusses requirements for the final report where a pre-market clinical investigation has been conducted. The final report should demonstrate the following:

“A. requirements for all safety and performance endpoints have been met;

B. no open clinical investigations relevant to the devices with endpoints related to safety or performance claims;

C. study locations are included in the pre-market clinical investigation”.

This information is important for developers and manufacturers to be aware of as failure to meet these requirements may result in delays in processing the technical files. This information would ideally be documented in the manufacturers quality management system (QMS) documentation.

Data generated from ‘Off-Label’ Use of a device under the EU Medical Device Regulation 2017/745

The position paper *Data generated from ‘Off-Label’ Use of a device under the EU Medical Device Regulation 2017/745*, describes requirements for “off label use” as mentioned in (MDR) in Annex XIV Part B (74).

The position paper states that foreseeable misuse may be identified through usability studies or pre-market clinical investigation reports, but it is often difficult for manufacturers to predict areas of future misuse and without the manufacturer having direct supervision over the use of each individual device, it is inevitable that in off-label use may occur.”

The position paper describes the options that manufacturers have when they identify systematic off-label use of the device and describes the possible need to set up a clinical investigation. Reference is made to the specifics of the EU MDR 2017/745 Article 74 Clause 2, conducted outside of the scope of the intended purpose of a CE marked device must follow the same requirements of a pre-market clinical investigation. Again, this information is important for manufacturers to be aware of and have identified and documented in the QMS documentation.

The necessity for study phasing and early-stage studies such as EFS is not addressed, however manufacturers need to undertake a pre-market clinical investigation, despite the device already being CE marked.

NBCG position papers

In addition to guidance, the notified body groups have engaged in training on clinical aspects. This training is not open to the public, and there is limited information available via the respective websites for Team NB or NBCG (75,76).

The following statement was provided by a member of the NBCG, indicating that the focus is not on early-stage studies or EFS “*TEAM-NB and NBCG have arranged expert sessions for notified body clinical assessors to discuss challenging clinical topics collectively. TEAM-NB have also provided a number of training sessions concerning clinical data. As the notified body assessments concern clinical data presented for conformity assessment and marketing, this does not have a focus on early stage or EFS studies.*”

The main finding of relevance to this report is that there is limited information available in notified body guidance documents of relevance to EFS.

One of the key challenges that manufacturers face when seeking CE marking for their devices is the failure to provide the required documentation to comply with the EU MDR 2017/745 Regulation. Team NB has provided guidelines to manufacturers which help developers and manufacturers to understand application requirements, and how to submit the clinical data derived from EFS and clinical investigations generally. These guidelines include the identification and documentation of both the clinical development plan and off-label uses, along with a clear strategy for addressing them.

Using these guidelines is essential for maintaining compliance with the regulations. Adhering to these recommendations helps manufacturers avoid legal and regulatory repercussions and ensures the highest standards of patient safety are upheld. Proper documentation and a proactive approach are critical components of a compliant QMS.

By following Team NB's guidelines, manufacturers can better navigate the complexities of the CE marking process, ensuring their devices meet all necessary regulatory requirements and are safe for patient use under all intended and potential off-label scenarios.

Appendix 2.9 PRISMA flow diagram for the systematic literature review (EFS and DHTs reviews)

The EFS and DHT literature review is part of two broader systematic reviews that encompasses Pre-Market Approval Pathways.

Search 1: Pre-market approval pathways in the EU and other relevant jurisdictions

The study selection retrieved a total of 1,025 records, of which 295 were duplicates. Following the initial screening of 730 records by title and abstract, 343 were excluded in the first round, and 290 conflicts were resolved through discussions among five reviewers, leading to a further 182 exclusions. Ultimately, 523 records were excluded and 207 were included based on title and abstract. The included papers were then categorized into three groups for full-text screening: PMP (139 papers), EFS (24 papers), and DHTs (44 papers).

Search 2: EFS-focused search – Early Feasibility Studies and MDs, digital health technologies

The study selection retrieved a total of 3,612 records, of which 1,627 were duplicates. Of the remaining 1,985 records, 112 were included as the digital health technology subset based on title (inclusion criteria – the words: digital, software or artificial intelligence). Ultimately, 82 records were excluded and 30 were included based on title and abstract.

EFS review

The scientific literature review on pre-market approval pathways programs (PMAP), including EFS in the search terms was then conducted to gather relevant publications outlining the history, objectives, salient features, performance, challenges and barriers encountered since the first pilot EFS projects in 2011. Of the 270 papers identified for full paper screening from the PMAP search, we separated out the papers with specific mention to EFS for screening and data extraction.

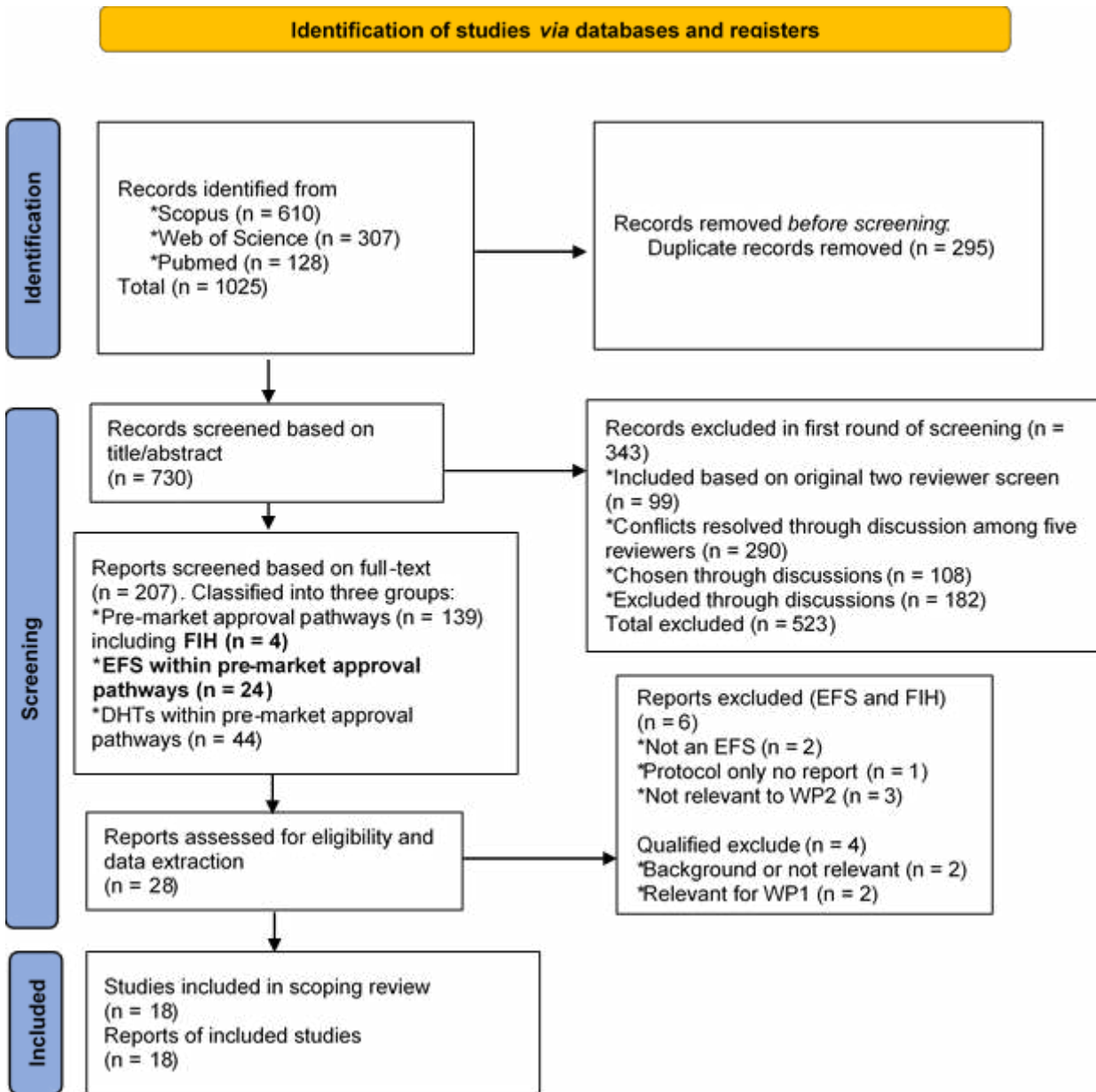
In our review, we identified 24 papers with specific mention of EFS. After full paper screening, 17 were included as relevant to a future EU EFS program. Four additional papers were identified in the larger PMAP search as possibly related to EFS (though not specifically mentioned) or first-in-human clinical investigations. One paper from this list was included as relevant to this theme. The 18 papers were then analysed according to different themes outlined in the proposal related to Work Packages 3-6 to inform tasks related to identifying EFS characteristics, planning, criteria, role of patients, performance, monitoring, ethical and legal aspects, for example, to formulate eligibility criteria, inform clinical investigation plans, evaluate and improve the program over time, and address patient consent and protection needs.

From the scientific literature review of PMAPs, a selection of 18 papers related to EFS were included for data extraction (Figure 21). In particular, 13 studies focus on the US (Brooks, 2017; Ghebremichael

et al., 2017; Herrmann *et al.*, 2022; Holmes, Califf, *et al.*, 2016; Holmes *et al.*, 2020, 2021, 2022; Holmes, Shuren, *et al.*, 2016, 2016; Ibrahim *et al.*, 2020; Leipheimer *et al.*, 2019; Weiss & Farb, 2023; Zahr *et al.*, 2022), 3 on Europe (Callea *et al.*, 2022; Grohmann *et al.*, 2016; Guerlich *et al.*, 2023), and 1 on China (Long *et al.*, 2023), while the additional included paper describes the idea, development, exploration, assessment, long-term follow-up for clinical evaluation of device innovation, or IDEAL-D framework, particularly as it relates to the preclinical stage of development (Marcus *et al.*, 2022). Most (of the included US studies provide insights on the establishment and functioning of the US FDA EFS program and/or key issues related to EFS (Brooks, 2017; Herrmann *et al.*, 2022; Holmes, Califf, *et al.*, 2016; Holmes *et al.*, 2020, 2021, 2022; Holmes, Shuren, *et al.*, 2016, 2016; Ibrahim *et al.*, 2020; Weiss & Farb, 2023), one was an EFS (Zahr *et al.*, 2022), and two were EFS-like studies (Ghebremichael *et al.*, 2017; Leipheimer *et al.*, 2019). Among the EU-based papers, Callea *et al.* (Callea *et al.*, 2022) thoroughly examine the issues related to establishing an EU EFS program, describing the FDA EFS program, eliciting perceptions from stakeholders regarding the desirability of establishing an EU EFS program, and offering recommendations towards the development of the same. Guerlich *et al.* (Guerlich *et al.*, 2023), though not specifically focused on EFS, provides some insights into developing clinical evidence for high-risk MDs for special populations (pediatrics) under the new MDR, touching on design, while Grohman *et al.* (Grohmann *et al.*, 2016) was included as an EFS-like study conducted in Germany on four infants. Finally, a study in China was included as a potential EFS-like study (Long *et al.*, 2023).



Figure 21. PRISMA flow diagram for the systematic literature review (EFS reviews)



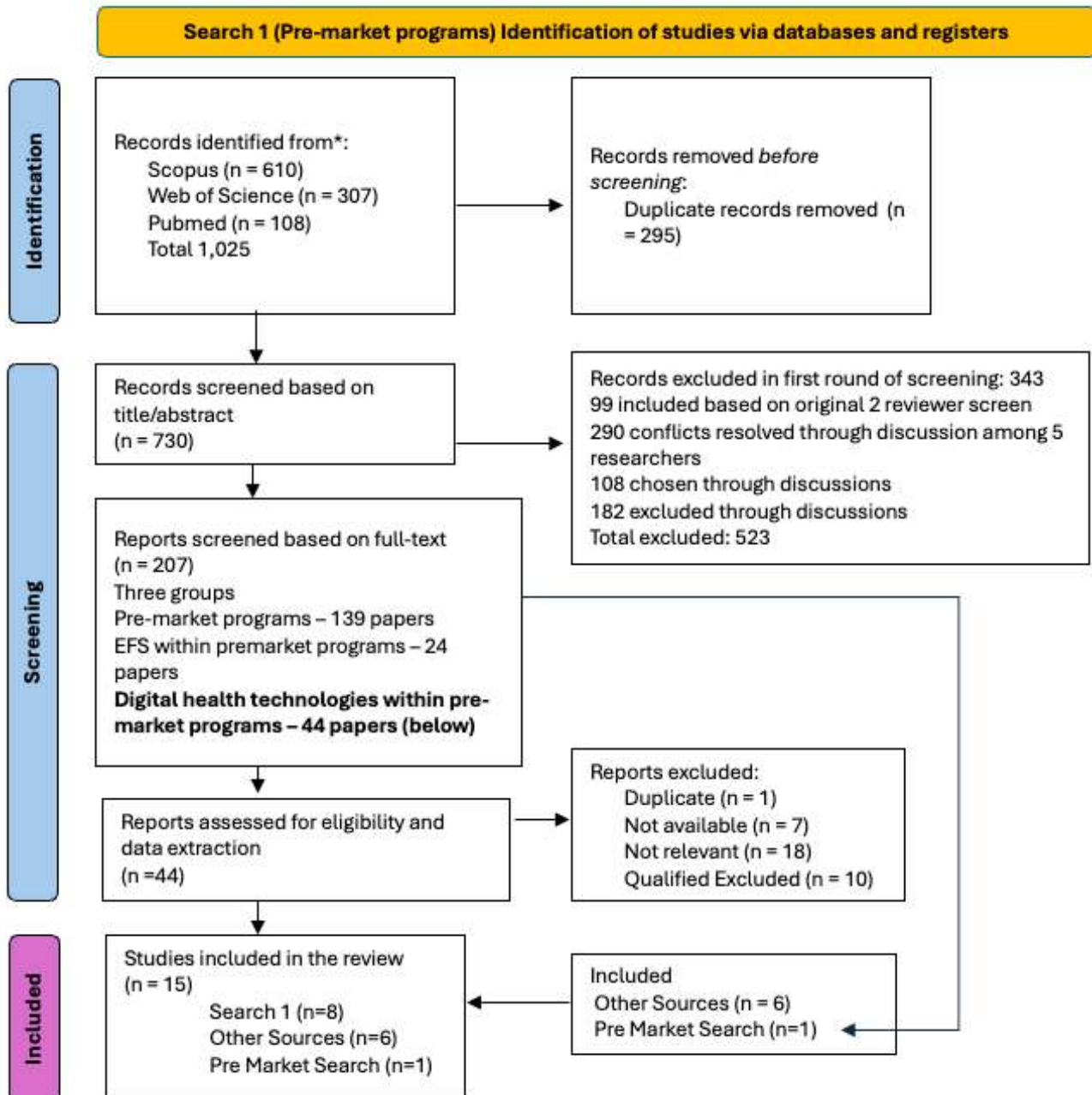
DHTs review

Search 1: Pre-market approval pathways in the EU and other relevant jurisdictions (DHT subset)

Among the 44 DHT papers, one was excluded as duplicate, seven were not retrievable, 18 not relevant and 10 were qualified excluded mainly because the papers bear no reference to an EFS program but provide overviews and supporting information for subsequent work packages (Figure 22).

At the conclusion of the full-text screening process, within the DHT paper group, 8 papers were selected for inclusion in the review. 5 papers were added through snowballing and other sources, 1 additional paper from Search 1 was included, which was not covered under the 44 identified DHT papers. The total inclusion in the review is 15.

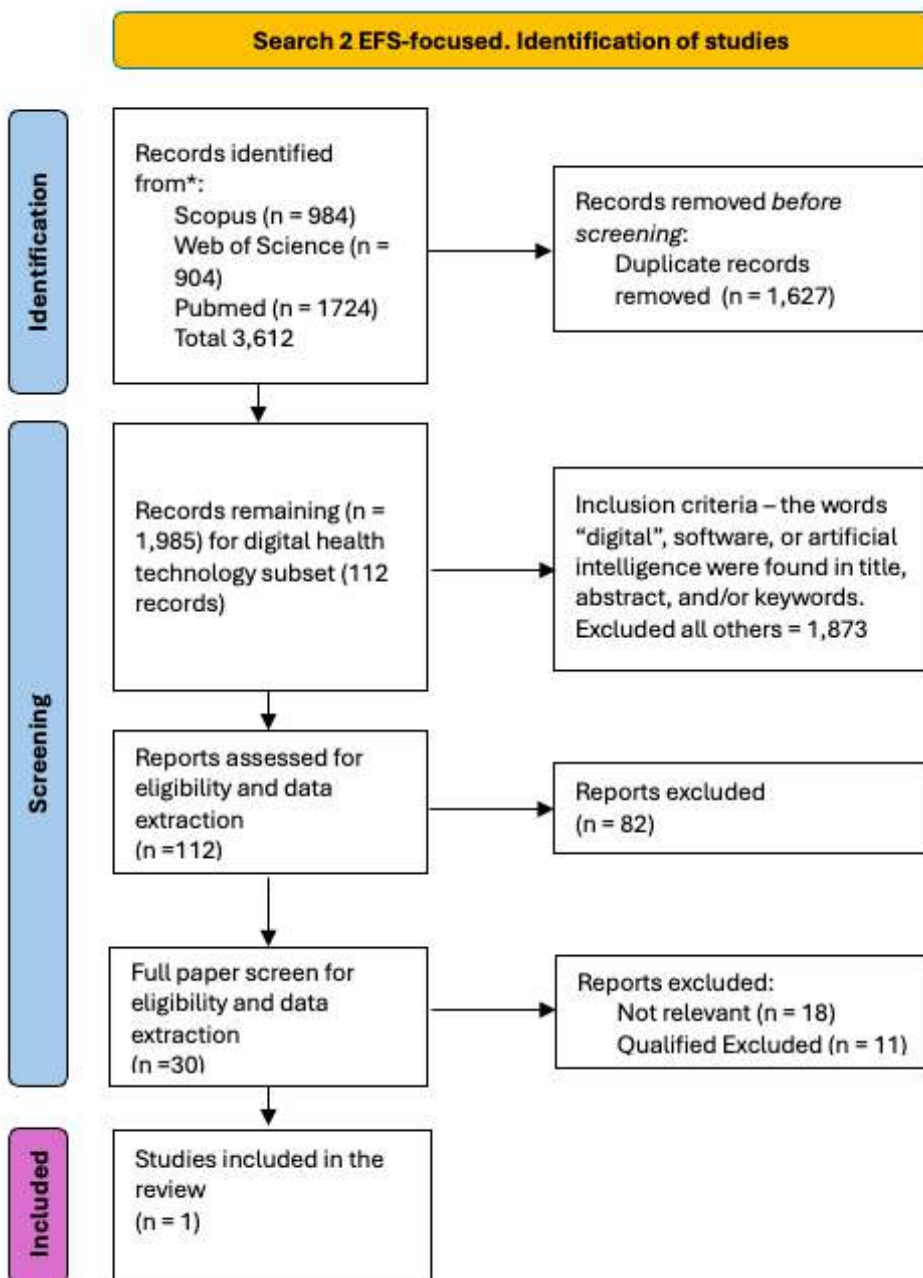
Figure 22. PRISMA flow diagrams for the systematic literature review (Pre-market-programs)



Search 2: EFS-focused search – Early Feasibility Studies and Medical Devices, DHTs

Among the 30 DHT papers, 18 were not relevant and 11 were qualified excluded mainly because the papers 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 paper group, 1 paper was selected for inclusion in the review (Figure 23).

Figure 23. PRISMA flow diagrams for the systematic literature review (EFS-focused)



Appendix 3.1 MDR/MDCG guidance concerning clinical development plans

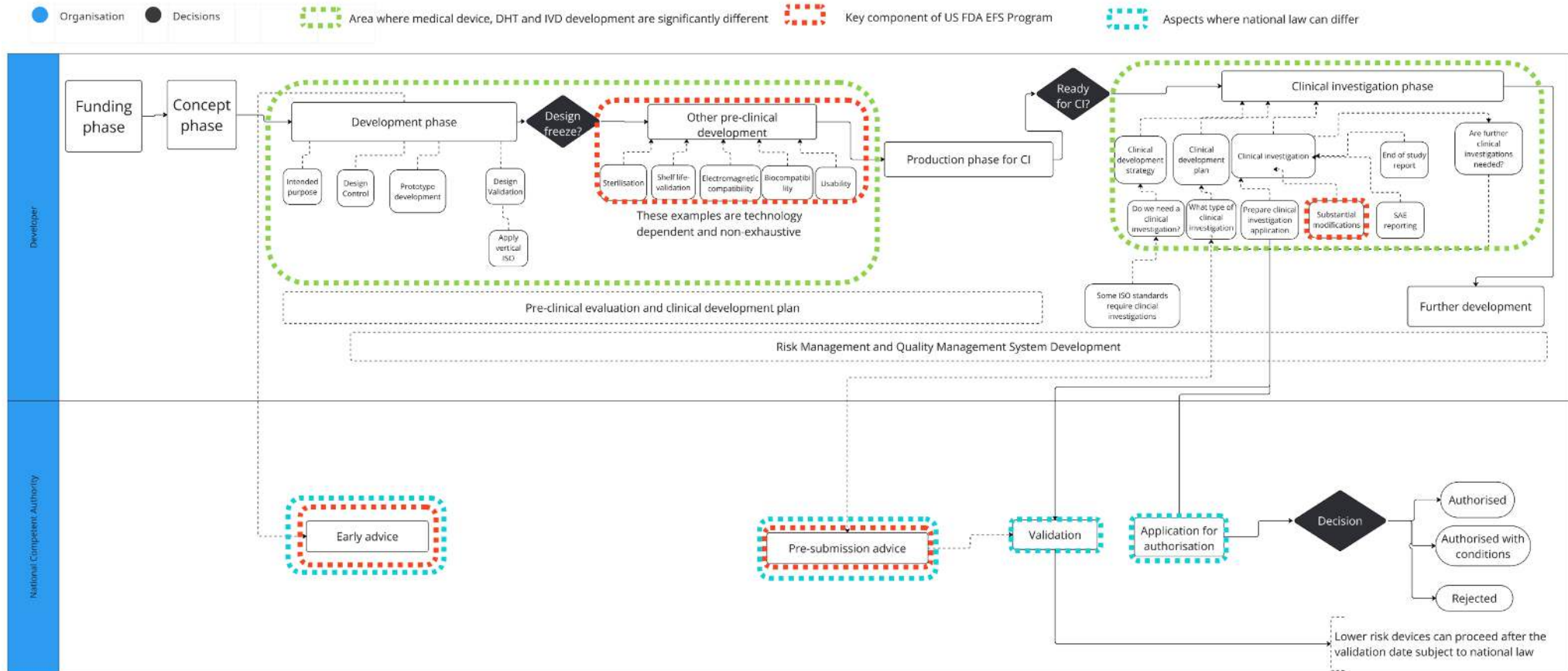
MDR introduced a requirement for the first time to prepare a ‘clinical development plan’, in addition to a ‘clinical evaluation plan’. The clinical development plan is described in MDR as follows:

a clinical development plan indicating progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a PMCF as referred to in Part B of this Annex with an indication of milestones and a description of potential acceptance criteria;³¹

The expected content for a clinical development plan is not subject to detailed guidance, for example the way in which the milestones or acceptance criteria should be described has not been further defined in MDR or associated MDCG guidance. MDCG 2024-3 (concerning the clinical investigation plan) notes that sponsors should consider how a proposed study such as an EFS fits into the overall development plan:

Describe where the clinical investigation fits into the clinical development of the device (i.e., is this a pilot study, a pivotal study or a post-market clinical investigation?). The informative Annex I in ISO 14155:2020 has information on clinical development stages.³²

Appendix 3.2 Schematic of early-stage development



Appendix 3.3 Regulatory review – MDR/MDCG in regard to DHTs

The following section examines the current legal framework (MDR and MDGC) from the perspective of the special features of DHTs. It is undisputed that DHTs face special considerations and challenges in their iterative development and (early) clinical evaluation.

In the EU MDR, DHTs are hardly mentioned, apart from the definition in Article 2 (1) of the MDR that software is also classified as a medical device under the MDR. The main finding from the targeted review of the MDR framework is that there is very little information that could be directly relevant to EFS for DHTs. The most specific aspects of the MDR that relate to DHTs generally concern the assignment of a software to a risk class and in terms of interoperability, compatibility and cybersecurity requirements.

Similar to the EU MDR, the MDCG guidance documents contain only a few references to a possible EFS for DHT. In principle, the clinical evaluation of DHTs should be considered as an ongoing process in the product life cycle. Like the EU MDR, the MDCG 2024-5 defines the specific requirements for the reliability, interoperability and compatibility, cybersecurity and software verification and validation of DHTs in more detail.

DHTs and MDR

a. Document selection

There are particular considerations and challenges when developing DHTs. From a regulatory perspective, part of this challenge arises from the fact that DHTs are broadly treated in the same way as general medical devices, and there is little mention of separate provisions in the EU MDR. Apart from the mention that software is also a medical device and a specific classification rule, there are few specific requirements. The central Articles 61 to 82 of the MDR, which cover clinical evaluation and investigations, do not specifically address the unique requirements for DHTs, including EFS for DHTs.

Article 2(4) defines software as an active device. According to Rule 11 of Annex VIII of the EU MDR, software is classified as a class IIa device if it provides information used for medical diagnostic or treatment decisions. However, if these decisions could have serious implications, the classification changes: to class IIb if there is a potential for serious health deterioration or surgical intervention, and to class III if the decisions could potentially lead to death. These statements make it clear that software will no longer be assigned to risk class I only and that more clinical studies will therefore be required in the future.

Annex XIV of the MDR refers to the clinical evaluation and clinical follow-up after an MD has been placed on the market. These sections specify exactly which data must be collected and how the documentation must be carried out. The clinical evaluation does not generally refer to EFS, but it

could serve as a basis for an EFS for DHT, as DHTs must undergo a conformity assessment after an EFS. In Annex XIV, Part A, Section 3 refers to the claim of equivalence of MD. In simple terms, this is a manufacturer's claim that product X is equivalent to product Y so that the clinical data for that product can be used. To demonstrate equivalence, clinical, technical, and biological characteristics must be considered. Specifically, for DHT, the "technical" characteristic can be, for example, "similar ... software algorithms" can be accepted for the purpose of claiming equivalence. Although this does not directly relate to the performance of an EFS for DHT, it could be used by manufacturers to avoid the need for further clinical investigations in this area and would be the simplest solution in the complex certification process.

As another part of the technical documentation requirements in particular, described in Annex II of the MDR, section 6.1.b. specifies the detailed information that must be recorded for DHTs (e.g. description of the software design and development process and evidence of validation of the software as used in the finished device). In this context, Article 2(26) defines the term "interoperability" in terms of the ability of two DHT devices to interact, exchange information or work together, where their compatibility is secure (protected from unauthorized access) and reliable. Interoperability, cybersecurity and software verification and validation are specific aspects of DHT that must be considered from the outset.

b. Key Findings

The key finding from this MDR focused review of MDR is that there is very little information of relevance to EFS directly. The most specific aspects of MDR relating to DHTs generally relate to interoperability, classification, and clinical evaluation. Summaries of these are provided below.

- **Interoperability and Compatibility:**

- **Article 2, 26:** Defines interoperability as the ability of two or more devices, including software, from the same or different manufacturers, to exchange information and work together as intended.
- **Chapter II, 14.5:** Devices intended to operate with other devices or products must be designed for reliable and safe interoperability and compatibility.
- **Chapter II, 18.8:** Devices should be protected against unauthorized access that could interfere with their intended function.

- **Classification of Software:**

- **Annex VIII, 6.3 (Rule 11):** Software intended for diagnostic or therapeutic decision-making is classified based on the impact of the decisions. It ranges from Class I to Class III depending on the severity of the potential impact on health.
- **Clinical Evaluation and Pre-Clinical Testing:**
 - **Annex XIV, 3:** Clinical evaluation can be based on clinical data showing equivalence to a similar device, considering technical, biological, and clinical characteristics.
 - **Annex XV, 2.3:** Pre-clinical evaluation should include relevant testing and experimental data, such as in vitro tests, animal tests, mechanical or electrical tests, reliability tests, sterilization validation, and software verification and validation.

DHTs and MDCG

a.) Document selection

Similar to the MDR (EU) 2017/745, the MDCG guidelines contain only a few references to a possible EFS for DHTs. In general, the MDCG 2019-11 describes the qualification, classification and clinical evaluation of software. The MDCG 2020-1 Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software describes the clinical evaluation of DHT as an ongoing process and explicitly points out on page 10 that proof can also be provided by the manufacturer as part of a proof of concept. Even if DHTs are not specifically addressed in Articles 61 to 82 "Clinical evaluation and clinical investigations" of the (EU 2017/745 - MDR), the requirements of the MDR must also be observed for DHT as part of a clinical evaluation. In particular, MDCG 2024-5 "Guidance on the content of the Investigator's Brochure for clinical examinations of medical devices" contains specific requirements for DHTs that further specify Annex XV - Clinical investigations - Chapter II "Templates for the clinical investigation application documentation" of the EU MDR to support sponsors in the preparation of their Investigator's Brochure (IB) and serve as a checklist for submission. Specifically, the MDCG 2024-5 defines requirements for the reliability (2.3.2.2.2.), interoperability and compatibility (2.3.2.2.3.) of DHTs. It also deals with cybersecurity (2.3.2.3.4.) and software verification and validation (2.3.2.3.3.). These requirements are particularly relevant for DHT. Furthermore, it is also crucial for DHTs that they fulfill their intended purpose and that a detailed description of the DHT is provided.

In addition, MDCG 2020-5 - "Clinical evaluation - Equivalence: A guide for manufacturers and notified bodies" describes the specifications and characteristics of the technical features when assessing equivalence with another device for DHTs. Section 3.1 Technical characteristics states: "Note that the MDR explicitly requires that the software algorithms in the device considered equivalent must be similar. This applies both to software algorithms in software that controls or influences the use of a

device and to software intended for stand-alone use. When proving the equivalence of a software algorithm, the functional principle of the software algorithm as well as the clinical performance(s) and the intended purpose(s) of the software algorithm must be considered. It is not appropriate to require proof of equivalence of the software code if it has been developed in accordance with international standards for the safe development and validation of software for medical devices. Software that is used solely to configure a device (e.g. display on a graphical user interface, etc.) and is not associated with a medical purpose (e.g. diagnosis, treatment, etc.) does not need to be similar when assessing equivalence as long as it can be demonstrated that it does not affect usability, safety or clinical performance."

However, after investigation, it can be stated that a precise MDCG guideline for conducting a clinical evaluation or EFS to fulfill a certification process of DHT is not available. The other MDCG guidelines (MDCG 2019-16 Rev.1 Guidance on Cybersecurity for medical devices; MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 - MDR and Regulation (EU) 2017/746 - IVDR; MDCG 2023-4 Medical Device Software (MDSW) - Hardware combinations Guidance on MDSW intended to work in combination with hardware or hardware components; MDCG 2019-15 rev.1 - Guidance for manufacturers of Class I medical devices; MDCG 2021-24 - Guidance on classification of medical devices; MDCG 2020-3 Rev.1 Guidance on Significant Changes Regarding the Transitional Provision Under Article 120 of the MDR with Regard to Devices Covered by Certificates According to MDD or AIMDD; Guidance on the Information Required for Conformity Assessment Bodies' Personnel Involved in Conformity Assessment Activities; MDCG 2018-5 UDI Assignment to Medical Device Software; MDCG 2019-14 Explanatory Note on MDR Codes) provide implementation guidance for the MDR, but without reference to clinical evaluations or EFS for DHT.

b.) Key findings

- **Proof of Concept Studies for Medical Device Software (MDSW):** The MDCG 2020-1 guidance emphasizes conducting proof of concept studies to validate the clinical performance of MDSW. These studies should test the software under intended conditions, including target populations, usage scenarios, and environments, to demonstrate its effectiveness in real-world settings.
- **Clinical Evaluation and Data Acquisition:** Clinical data for MDSW can be acquired through various methods as outlined in relevant documents. Compliance with MDR Articles 62(1), 74, and 82 is essential, especially for pre-market retrospective studies of MDSW under MDR jurisdiction. The clinical evaluation is an ongoing process throughout the DHT's life cycle.
- **Usability and Software Design:** According to MDCG 2024-5, usability testing is crucial and includes evaluating the user interface in the intended environment. The guidance also requires a

comprehensive description of the software design and development process, including validation, verification, and testing performed both in-house and in simulated or actual user environments.

- **Technical Specifications and Reliability:** The guidance emphasizes the need for detailed technical specifications of the device, including variants, configurations, and accessories. Reliability tests are also crucial, assessing durability, stability, and performance, especially for devices with a measuring function or those that incorporate electronic programmable systems.
- **Cybersecurity and Interoperability:** Cybersecurity must be considered from the beginning of EFS, with comprehensive testing for verification and validation of security, including methods like fuzz testing and vulnerability scanning. Interoperability and compatibility tests are essential when the device is intended to operate with other devices or products, ensuring reliable and safe performance in combination with other systems.

Appendix 3.4 The role of ISO standards in the MDR framework

Recital 22 of MDR, emphasises the important role of standards and harmonised standards to the MDR framework generally, stating that “[t]o recognise the important role of standardisation in the field of medical devices, compliance with harmonised standards as defined in Regulation (EU) No 1025/2012 of the European Parliament and of the Council should be a means for manufacturers to demonstrate conformity with the general safety and performance requirements (GSPR) and other legal requirements, such as those relating to quality and risk management, laid down in this Regulation”. As we describe in the structural description part of this report, compliance with standards is not mandatory, it is ‘a means’ of compliance, however developers and manufacturers can apply other means to meet MDR requirements directly.

The importance of the harmonised standards for clinical investigations are first referenced in Recital 64 of the MDR which notes:

The rules on clinical investigations should be in line with well-established international guidance in this field, such as the international standard ISO 14155:2011 on good clinical practice for clinical investigations of medical devices for human subjects, so as to make it easier for the results of clinical investigations conducted in the Union to be accepted as documentation outside the Union and to make it easier for the results of clinical investigations conducted outside the Union in accordance with international guidelines to be accepted within the Union. In addition, the rules should be in line with the most recent version of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

Article 8 of MDR contains specific reference to the application of harmonised standards by the actors involved in clinical investigations noting that requirements in standards can apply to clinical investigations, in addition to other regulatory requirements such as quality or risk management. Further reference to the role of harmonised standards relating to the design of the clinical investigations is contained in Article 71(3) of MDR, which concerns the assessment by competent authorities (referred to as ‘Member States’ in MDR) of applications to conduct clinical investigations (and hence EFS). Article 71(3) notes that ‘*Member States shall assess whether the clinical investigation is designed in such a way that potential remaining risks to subjects or third persons, after risk minimization, are justified, when weighed against the clinical benefits to be expected. They shall, while taking into account applicable CS or **harmonised standards**, examine in particular ...*’

From this introduction, we can surmise that the MDR highlights the important role of standards generally, and also with specific reference to clinical investigations and clinical investigation design.

Appendix 3.5 Glossary of ISO terminology

Horizontal and vertical standards

Standards can be categorised into horizontal and vertical standards.³

Horizontal standards (sometimes referred to as ‘basic’ standards) tend to indicate fundamental concepts, principles, and requirements with regard to general safety and performance aspects applicable to all, or a wide range of, products and/or processes.

Vertical standards (also sometimes known as a product standard) relate to specific products indicating safety and performance aspects.

Informative versus normative language in standards

Standards contain clauses and annexes which are either normative or informative.

Normative elements are those that are prescriptive, typically using the word “shall”, meaning that the requirements must be followed.

Informative clauses/annexes are those that provide useful or interesting information or are descriptive and offer help to apply/understand concepts within the normative text. They can also include recommendations or interpretations of the normative clauses, however, there is no requirement to comply/apply these parts of the standard.

Normative references within standards

A *normative reference* in a standard means that the standard cannot be applied correctly without applying the requirements of another standard.

As such a normative reference is different to normative and informative clauses / annexes. When included in the standard, normative references are typically documented in Clause 2.

³ Ref. Role of Standards in the Assessment of Medical Devices, Global Harmonization Taskforce, Study Group 1 Final Document GHTF/SG1/N044:2008

Appendix 3.6 Terminology used for different types of clinical development stages related to EFS studies in ISO 14155 and vertical standards

Table 9. Terminology used for different types of clinical development stages in ISO standards

Standard	Name	Terms
ISO 14155:2020	Clinical investigation of medical devices for human subjects — Good clinical practice	“Pilot stage. Exploratory clinical investigation first in human, feasibility clinical investigations.
ISO 5840-2:2021	Cardiovascular implants — Cardiac valve prostheses — Part 2: Surgically implanted heart valve substitutes	“Pilot phase studies, first in human, feasibility clinical investigations”
ISO 5840-3:2021	Cardiovascular implants — Cardiac valve prostheses — Part 3: Heart valve substitutes implanted by transcatheter techniques substitutes	Pilot phase studies, first in human, feasibility clinical investigations”
ISO 5910:2018	Heart Valves Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices. substitutes	: “Pilot phase studies, first in human, feasibility clinical investigations”
ISO 22679:2021	Cardiovascular implants: Transcatheter cardiac occluders studies	Pilot Stage, exploratory clinical investigation, first in human, feasibility clinical investigations
ISO 11249:2018	Copper-bearing intrauterine contraceptive devices — Guidance on the design, execution, analysis and interpretation of clinical studies	“early clinical investigation(s), e.g. feasibility clinical investigation(s)
ISO 29943-2:2017	Condoms — Guidance on clinical studies — Part 2: Female condoms, clinical function studies based on self-reports	Terms: “ Pilot clinical studies, Pilot clinical investigation clinical feasibility study

Standard	Name	Terms
ISO 29943-1:2017	Condoms — Guidance on clinical studies — Part 1: Male condoms, clinical function studies based on self-reports	“Pilot clinical studies, Pilot clinical investigation clinical feasibility study”
ISO 11979-7:2024	Ophthalmic implants — Intraocular lenses — Part 7: Clinical investigations of intraocular lenses for the correction of aphakia	“Pilot phase study”
ISO 21535:2023	Non-active surgical implants — Joint replacement implants — Specific requirements for hip-joint replacement implants	“premarket clinical investigation”
ISO 21536:2023	Non-active surgical implants — Joint replacement implants — Specific requirements for knee-joint replacement implants	“premarket clinical investigation”
ISO 11980:2012	2012 Ophthalmic optics - Contact lenses and contact lens care products - Guidance for clinical investigations	“premarket studies”

“Pilot studies” is the term that is most commonly used in vertical standards, however it is noted that there are variations of the terms used, ISO 29943-2:2017 and ISO 29943-1:2017 both using terms “pilot clinical studies”, “pilot clinical investigation”. The term “first is human” is common to all of the cardiovascular standards.

ISO 21535 and ISO 21536 favour the use of umbrella term “premarket clinical investigation” from the regulatory status and do not provide any additional references to the clinical development stages. Whilst ISO 11980 Annex A (informative) outlines requirements for Elements of a Clinical Investigation, which are referred to in Annex A. 2.1 refers to “contact lens investigations” or “contact lens clinical investigations” and reference is made to specific requirements for “premarket studies”.

The terms “early feasibility CI” and “traditional feasibility CI” are not called out in any of the vertical standards, instead these studies are grouped collectively and referenced as “feasibility clinical investigations” in the n = 4 cardiovascular standards and also the n = 1 intrauterine standard (Table

5) Similarly, the term “clinical feasibility study” is called out in the n = 2 condom standards. There is no reference to “feasibility studies”, in the remaining standards.

Although ISO 14155 states that early feasibility clinical investigation can also be called proof of concept clinical investigation, there is no reference to “proof of concept studies” in the vertical standards that have been assessed in this review.

Appendix 3.7 Summary of findings concerning the requirement to conduct EFS

Clause 7.4.1 of three of the cardiovascular standards (5840 -2, -3 and 5910) documents requirements on pilot phase studies. These pilot studies provide “initial” information on the clinical safety and device performance and also “may be used to “optimize” the system and “patient selection prior to initiation of a larger clinical investigation following further pre-clinical testing”

Whilst the considerations for pilot phase studies in the cardiovascular standard ISO 22679 are documented in clause 7.4.6, it is stated that “exploratory clinical investigation(s) will evaluate the limitations and advantages of the medical device and is commonly used to capture preliminary information on a medical device (at an early stage of product design, development and validation) to adequately plan further steps of device development, including needs for design modifications or parameters for a pivotal clinical investigation.”

The importance of the pilot phase studies is highlighted by the statement that “A scientific justification shall be provided if pilot phase studies are not to be undertaken”. However, there is no guidance documented as to what this scientific rationale should be based on.

There are variations in the requirements noted in the non-surgical implant standards, (ISO 21535 and 21536) where the mandatory requirements for “pre-market clinical investigation” are documented in Clause 7.3 Clinical Investigation. The indications for when a pre-market clinical investigation is necessary are broadly related to a lack of or inadequate performance requirements/parameters that are documented in Clause 7.2, pre-clinical evaluation.

It is important to note the provision documented in Clause 7.2.1.1, where the requirements are “not intended to require the re-design or re-testing of implants which have been legally marketed and for which there is a history of sufficient and safe clinical use”

The requirements for pilot studies in the condom standards, ISO 29944-1 2017 and -2 are documented in Clause 4 and Clause 5 respectively, Pilot Clinical studies and Annex B (informative).

ISO 29943-1 The pilot study “should” be done for two reasons, both relating to risk. It is required to characterize and quantify the risk in undertaking a larger scale investigation.

ISO 29943-2, where a pilot study helps to identify and evaluate the different types of acute failure events and risks prior to initiation of a larger clinical investigation. The information that is collected on acute failure rates, will influence the statistical calculation for the pivotal study. The pilot study can also identify potential safety concerns.

The requirement to consider a pilot phase study for the ISO 11979-7:2024 is documented in *Annex F (informative) Clause F.4.3.1 Contrast sensitivity, General*, where pilot studies to validate the proposed testing conditions are recommended.

However, Annex A (informative) of ISO 11980 outlines requirements for Elements of a Clinical Investigation. Specifically, A.2.1 refers to "Contact Lens Investigations" or "contact lens clinical investigations." Table A.1 provides the requirement for the number of subjects per group that must complete the trial for "premarket studies" involving "all materials and designs."

Appendix 3.8 Summary of design characteristics relating to study subjects and statistical considerations for EFS from ISO standards.

ISO 14155 does not specify the actual number of subject to be enrolled in the study. With respect to statistical considerations, Annex I.7 (informative) of ISO 14155, notes that all principles of the ISO 14155 apply, with the exception “that no mandatory (pre-)specification of a statistical hypothesis is required” for an EFS.

Vertical standards demonstrated variability in the references to the number of subjects, the need for a statistical hypothesis and the detail required for the study population.

Clause 7.4.2 of ISO 5840-2, -3, ISO 5910 and ISO 22679 identify considerations for *pilot phase studies*, noting a small sample size for study subjects. These standards also include a consideration of the number of “clinical investigators” which can help to understand inter-operator variability. The considerations also include the exploratory nature of the pilot phase studies and “may not require pre-specified statistical hypothesis”. These standards also outline the limitations of a “robust” interpretation of the use of such limited numbers.

ISO 22679 has an additional consideration, that reflects the guidance in Annex I.7 Statistical design and analysis which states “For exploratory and observational clinical investigations (see Annex I), in which the sample size is not required to be derived by calculation, the scientific rationale for the chosen sample size shall be provided”,

ISO 22679 states that “Exploratory clinical investigations might not require pre-specified statistical hypotheses, although the design of the clinical investigation and the interpretation of the outcome can be more straightforward if statistical considerations are provided in the CIP”.

ISO 11249:2018, mentions “special reasoning and sample size(s) might apply for the early clinical investigation(s), e.g. feasibility clinical investigation(s)”.

Appendix 3.9 Other considerations relating to EFS design from vertical ISO documents

Informed Consent

From the 11 vertical standards relevant to EFS, informed consent is addressed in 6 standards. The consent process for ISO 5840-2, 3 and ISO 5910, require the subject to be made aware of both the nature of the study and also alternative options, including other approved devices.

ISO 22679 standard, has the same requirements with respect to the nature of the study and availability of alternative options, however, specifics are documented such as the use of “clear language stating that the device together with the procedure has not been evaluated for safety or effectiveness and that the patient is among the first in the world to be treated with this device”.

Informed consent is documented in Annex B5 (informative) of ISO 29943-1 and -2, stating that “Participating study subjects should be given appropriate informed consent”.

Monitoring Plan/Oversight

From the 11 vertical standards relevant to EFS, 4 standards address safety monitoring and oversight by data safety monitoring boards (DSMBs). These are all cardiovascular standards - ISO 5840, -2 -3 and ISO 22969. These standards reference a DSMB or an independent medical reviewer. ISO 5910 requires oversight of the study safety by a clinical events committee (CEC) and/or a DSMB. The adjudication of adverse events by a clinical events committee (CEC) is specifically called out in for ISO 5840-2 and -3 and ISO 22679 where a clinical events committee “should” be used.

The use of External Organizations / Core laboratories

ISO 5840-2, -3, Clause 7.4.2 states that core laboratories are *recommended* for outcomes that might be prone to inter-laboratory variability for pilot phase (at multiple sites) studies. Similarly, in ISO 22679, “the use of imaging or other appropriate core labs should be considered”. These core laboratories are a requirement for pivotal studies. The requirement for core laboratories is not defined for pilot studies in ISO 5910.

Rate of Enrolment

The 4 cardiovascular standards had requirements for limitations on the rate of enrolment, documented in ISO 22679, 5910, 5840-2 and -3. Limitations on the rate of enrolment (e.g. evaluation of acute outcomes after each patient and before treating the next patient) is described in ISO 5840 and ISO 5910, whereas in the ISO 22679 standard, it states that limitations on rate of enrolment may be applicable based on risk assessments.

Patient Selection

2 standards (ISO 22679 and ISO 5840-3) outline requirements for patient selection. ISO 22679 addresses *the patient values and preferences* stating:

“Patient selection shall be a shared decision process between physician and patient that takes into account the best scientific evidence available, as well as the patient’s values and preferences”.

However, the ISO 5840-3, has an *additional* requirement, when compared to ISO 5840-2, relating to patient selection, where a “heart team approach with “at least” one non-conflicted physician, “according to the criteria of the relevant ethical committee”.

Subject follow up

2 cardiovascular standards had documented normative requirements for follow up.

ISO 5840-2 notes that for surgical mitral valves, a TEE study “shall be performed” on all patients within the first 4-6 weeks. ISO 5840-3 also notes that for transcatheter aortic valves, “an enhanced CT imaging study of the prosthesis shall be performed for all patients or a well-defined and scientifically justified subset within the first 3 months”. This standard also notes that for transcatheter mitral valves, a TEE study “shall be performed” on all patients within the first 4-6 weeks.

ISO 5910 notes that the pre-market and post-market cohorts shall be analysed and reported separately and in aggregate and also that the “principles of long-term post-market follow-up apply to the pre-market patient cohort” (Clause 7.4.10 Post-market clinical follow-up).

Ethics Committee

4 standards that had specific requirements documented for ethics approval. These were all cardiovascular standards.

ISO 5840-2, -3 and ISO 22679, state that: “Ethics Committee/Institutional Review Board approval shall be obtained and documented for both pilot phase and pivotal studies.” Despite being one of the three standards with documented ethical considerations, ISO 5910 does not specifically include the requirement that “Ethics Committee/Institutional Review Board approval shall be obtained and documented for both pilot phase and pivotal studies. This summary highlights the inclusion and specific requirements for ethics approval in certain ISO standards, while also noting the inconsistency in ISO 5910 regarding the explicit statement of these requirements.

Compensation and additional health care

5 standards referenced compensations. ISO 22943-1 and -2, note that requirements for compensation, confidentiality of individuals and their record and the use of local ethics committees would not be addressed and refers back to ISO 14155. However, Annex B.2 Study does make the

recommendation that “financial payment to panellists should be made at the end of the study”. Whilst in the 5840 -2 and -3 compensation in EFS are indirectly addressed in a general statement in Clause 7.4.4, stating that “Compensation of patients for the costs for participating in the clinical investigation shall be limited to an appropriate amount based on national regulations and, in line with ISO 14155, shall not be so large as to encourage patients to participate”. This theme is followed through in Clause 7.4.8 of ISO 22679.

Appendix 3.10 Summary of EFS and DHTs Considerations from ISO Standards

The main challenges identified include the lack of specific standards for conducting clinical investigations and Early Feasibility Studies (EFS) for Digital Health Technologies (DHTs) and Software as a Medical Device (SaMD). Existing standards like ISO 14155, ISO 82304-2, and EN 62304 do not explicitly cover these processes.

Key findings revealed that while ISO 14155 acknowledges its relevance to SaMD, there are no software-specific references within it. ISO 82304-2 outlines safety and quality requirements but lacks detailed guidance for clinical investigations. EN 62304's safety classification could be adapted to streamline the EFS process by tailoring requirements based on the potential harm severity. Monitoring new standards development, indicates ongoing efforts to address these gaps and enhance regulatory guidance for DHTs.

ISO 14155 and Its Application to SaMD

From the extensive searches that were completed, ISO 14155 brings clinical investigations and DHT into direct context: Reference is made in Clause 1 Scope, Note 2 in the document explains that for SaMD, the standard's requirements for proving analytical validity, scientific validity, and clinical performance are applicable as relevant (referencing IMDRF/SaMD WG/N41FINAL:2017). It allows for exemptions based on the unique indirect interaction SaMD has with subjects, provided these exemptions are justified. There are no references to any standards relating to Software/DHTs in the Normative references of ISO 14155: Similarly, there was no reference to ISO 14155 in the software standards.

ISO 82304-2: Framework for Safety and Quality

ISO 82304-2 provides a framework for the safety and quality requirements for health software products, ensuring they are reliable and safe for use. However, ISO 82304-2 does not detail specific processes for conducting clinical investigations or EFS, the requirements for ensuring safety, effectiveness, and performance imply that manufacturers must conduct appropriate testing and validation, which could include clinical investigations where necessary to substantiate the software's clinical claims and performance (5.2.1.6, 5.2.1.7, 5.2.2.1, 5.2.2.2, 5.2.2.3, 5.2.2.5, 5.2.4.1, 5.2.4.2, 5.2.4.5, 5.2.4.5.2).

Pre-development Guidance from ISO 82304-2

ISO 82304-2 provides an accessible entry point into the subject matter during the pre-development and early development stages of DHTs. Notably, chapters 5.2.2 (Health Risks) and 5.2.4 (Health Benefits) offer clear and structured guidance and should be considered in WP3 and WP4. They have

the potential to guide the planning and execution of early pilot studies for software as a medical device (SaMD).

Principal Findings and Future Directions

The principal finding from the review of the standards relating to digital health technology/software, is that they do not document requirements for clinical investigations or Early Feasibility studies. However, the standards EN 62304 and ISO 82304-2 focus on providing structured frameworks for software development processes, risk management, and lifecycle maintenance, ensuring the software is robust, reliable, and safe. These standards are designed to be comprehensive in guiding the development, which are critical precursors to any clinical investigation.

Potential Role of EN 62304 in EFS Guidelines

Given the nature of the technology, however, EN 62304 has the potential to play a pivotal role in the context of creating guidelines for EFS for SaMD. The software safety classification within EN 62304, which categorizes software based on the potential severity of harm from failures (Classes A, B, and C), could be adapted to streamline the EFS process. By tailoring the requirements and rigor of EFS activities to these classifications. This adaptation would facilitate a more efficient and targeted approach to developing and testing digital health technologies, ultimately enhancing their safety and effectiveness while expediting their path to market.

Additional remarks:

The qualified excluded standards do not mention clinical investigations or Early Feasibility Studies (EFS). However, they do outline principles and set standards that can be considered for WP3 and WP4. Notably EN 62304 contains a Software Safety Classification based on the potential impact of software failures on patient safety which in turn determines the rigor of the software development and maintenance process. It uses a predefined classification system (Classes A, B, and C) to categorize software based on the severity of potential harm.

Signals of future standards developments relevant to EFS studies for DHTs

In addition, a further search of the ISO platform was completed to identify standards under development that may be relevant to the DHTs.

From this search, one standard under development was identified as having potential relevance, ISO/AWI 24051-2 Medical laboratories Part 2: Digital pathology and artificial intelligence (AI)-based image analysis and will be monitored.

The report “International Standards in process” CD registered “Committee Draft” (period from April 01 to 01 May 2024) was reviewed for relevant standards. There were 2 standards that will be kept

under surveillance. ISO 11073 series and ISO 27599 will be kept under surveillance. Many of the software standards for medical devices are developed by IEC TC 62. This platform, [IEC - TC 62 Dashboard > Projects / Publications: Work programme, Up-to-date Project Plans, Publications, Stability Dates, Project files](#) will continue to be monitored for content relevant to DHTs.

Appendix 3.11 Mapping of EU-funded and International Digital Health Technologies (DHTs) Projects

International Projects

Development and harmonisation of methodologies for assessing digital health technologies in Europe (ASSESS-DHT)

Status: Open (2024 - ongoing)

ASSESS-DHT aims to boost the adoption of trustworthy and effective Digital Health Technologies (DHT) across Europe, creating a cohesive digital market for health systems and patients, and providing industry with a European market. The consortium plans to develop a new assessment framework beyond existing models for uniform HTA adoption across Europe, addressing challenges in Digital Therapeutics, AI, and telehealth. They will co-create this framework with specialized pathways for different DHT categories, using a novel evidence-based typology. The plan includes phased adoption, complex life-cycles, iteratively developed AI, and comprehensive HTA assessment manuals plus guides on topics like cybersecurity. They aim to establish a sustainable repository with the ASSESS-DHT framework, pathways, criteria, a searchable evidence library, checklists, tools for evidence generation, health system value evidence from DHT, and online practice communities.

Coordinating Research and Evidence for Medical Devices (CORE-MD)

Status: Closed (2021 - 2024)

The CORE-MD (Coordinating Research and Evidence for Medical Devices) project, funded by the European Union's Horizon 2020 program, spanned from April 2021 to March 2024. Its primary objective was to review and enhance the methods used for evaluating high-risk medical devices. The project aimed to translate expert evidence into actionable advice for EU regulators and to recommend an appropriate balance between fostering innovation and ensuring safety and clinical effectiveness in the medical device sector. The outcomes of CORE-MD are expected to contribute significantly to the refinement of regulatory processes, thereby enhancing patient safety and promoting the development of innovative medical technologies. The CORE-MD group is expected to provide guidance or suggest a framework related to clinical evaluation, which will assist stakeholders in navigating the complexities of the Medical Device Regulation, potentially also DHTs.

Reinforced market surveillance of medical devices and in-vitro devices (JAMS 2.0)

Status: Open (2023 - ongoing)

The Joint Action on Reinforced Market Surveillance of Medical Devices and In Vitro Medical Devices (JAMS 2.0) aims to strengthen the market surveillance of medical devices (MDs) and in vitro devices (IVDs) among EU Member States, promoting harmonized approaches across the European Union.

This initiative lays the groundwork for increased dialogue and future coordination between Competent Authorities (CAs) by adopting aligned and consistent work methods.

By enhancing coordination, JAMS 2.0 aims to improve the safety of medical devices, ensuring they are safe, perform as intended, and comply with existing regulations, thereby effectively contributing to public health protection. The project encompasses eight work packages, offering collaboration opportunities for 24 CAs through joint inspections, signal detection operations, and harmonized market surveillance campaigns.

Co-funded by the European Health and Digital Executive Agency (HaDEA) through the EU4Health program, JAMS 2.0 will facilitate the sharing of best practices and the development of training programs for market surveillance of MDs/IVDs. Due to its potentially high regulatory implications, the project will also impact digital health medical devices, ensuring their compliance and safety within the regulatory framework.

European Taskforce for Harmonised Evaluations of Digital Medical Devices

Status: Open (2022 - ongoing)

The European Taskforce for Harmonised Evaluation of Digital Medical Devices (DMDs) was launched in April 2022 with the aim of integrating technology with clinical evidence into healthcare procedures, thereby enhancing patient access and acceptance across the European Union (EU).

The taskforce's mission is to establish a European-level blueprint for DMD assessment procedures and methodologies. This harmonized approach will support national appraisal and reimbursement by statutory health insurance organizations for various categories of DMDs.

The taskforce will provide guidance to the HTA Coordination Group (HTAR), national authorities, agencies, innovators, and policymakers, in alignment with EU medical device regulators. Their efforts will focus on developing a joint DMD assessment framework and common procedures, including defining DMDs based on their application purpose and establishing mutually acceptable evaluation categories.

Digital Health Regulatory Pathways (DHRP)

Status: Open (2022 - ongoing)

Digital Health Regulatory Pathways is a collaborative initiative of the Digital Medicine Society with FDA and other organizations including industry partners to support the development of high-quality digital health products. Focuses on building tools and resources that support innovators in developing digital health products and clarify regulatory approaches for emerging technologies.

National Initiatives

DHTs presenting unique regulatory and reimbursement challenges at EU national levels. Within the EU, there is a dynamic landscape of DHT assessment frameworks, ranging from advanced national frameworks in pioneering countries like Germany, France and Belgium, to less developed or non-existent frameworks in other Member States. This national approach for harmonization of Health Technology Assessment is further driven by the upcoming HTAR, aimed at standardizing comparative evaluations across the EU. However, significant gaps remain, particularly in integrating pre-market and post-market evaluations and leveraging real-world data for continuous assessment. The progress in pioneering countries is expected to guide and accelerate similar advancements in other nations, and also for a EU-wide consistency in DHT regulation.

Prise en Charge Anticipée Numerique (PECAN)

Status: Open (2023 - ongoing)

The PECAN (Prise en Charge Anticipée) program was established by the Social Security Financing Act of 2022. It encompasses two categories of medical devices and digital health technologies (MD-DHT). The first category, intended for inclusion in the List of Products and Services Reimbursed (LPPR), comprises therapeutic MD-DHTs. The second category, designated for the List of Medical Telemonitoring Activities (LTAM), includes MD-DHTs designed solely for patient monitoring purposes. To qualify for PECAN, an MD-DHT must be CE-marked and demonstrate innovation. The device can be in any risk class. This innovation can manifest either in terms of clinical benefits, supported by ongoing studies that enable the French National Committee for the Evaluation of Digital Medical Devices (CNEDiMTS) to provide an opinion on LPPR inclusion within 6 months or LTAM inclusion within 9 months. Alternatively, innovation can be demonstrated through advancements in care organization while maintaining care quality. Since PECAN came into force in 2023, only one telemonitoring health solution has been approved for patients undergoing radiotherapy or systemic treatment. Regarding this particular application, current studies are expected to yield ample data for the Haute Autorité de Santé (HAS) to make a decision on permanent coverage within the designated timeframe.

Digitale Gesundheitsanwendungen (DiGA)

Status: Open (2019 - ongoing)

The Digitale Gesundheitsanwendungen (DiGA) which is the Fast-Track Process for Digital Health Applications (DiGA) has fundamentally changed the evaluation and reimbursement of digital health applications in Germany. Enacted on December 19th, 2019, the Digital Healthcare Act introduced the "app on prescription," enabling approximately 73 million insured Germans in the statutory health insurance (SHI) system to access digital health applications listed in the DiGA directory. These apps can be prescribed by healthcare providers and are reimbursed by insurers.

The DiGA Fast Track process, established by the Digital Healthcare Act, facilitates the swift evaluation, approval, and reimbursement of lower-risk digital health apps (Class I and IIa). This process, outlined in the Digital Health Applications Ordinance (DiGAV), sets comprehensive requirements for data protection, information security, interoperability, consumer protection, ease of use, support for healthcare providers, quality of medical service, and patient safety. Apps must also demonstrate a positive impact on patient care, such as medical benefits or improved healthcare access.

Manufacturers must prove compliance with these requirements to the BfArM, which has up to three months to assess applications. If sufficient evidence is provided, a direct permanent listing can be obtained; otherwise, a preliminary listing for 12 months (extendable to 24 months) is possible, requiring a supporting trial for permanent listing. Current regulatory reforms under discussion include a 14-day free trial period for patients to address poor adherence. In 2024, the Digital Law (DigiG) will further evolve the DiGA process, allowing for higher risk classes (up to IIb) and integrating telemonitoring and disease management programs.



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