innovative health initiative

HEU EFS
HARMONISED APPROACH TO EARLY FEASIBILITY STUDIES FOR MEDICAL DEVICES IN THE EUROPEAN UNION

Harmonised approach to **E**arly **F**easibility **S**tudies for Medical Devices in the **E**uropean **U**nion **(HEU-EFS)**

WP1 Research and analysis on the state of play of pre-market programs and implementation barriers to EFS

DELIVERABLE 1.1

Characteristics, gaps, and best practices of pre-market programs

COCIR efpia EuropaBio MedTech Europe Vaccines Europe

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Disclaimer:

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ABBREVIATIONS

CDRH	Center for Devices and Radiological Health
CEP	Clinical Evaluation Plan
CER	Clinical Evaluation Report
CI	Clinical investigation
CIP	Clinical investigation plans
CTA	Clinical trial agreements
EC	European Commission
EFS	Early Feasibility Studies
EU	European Union
FDA	Food and Drug Administration
FIH	First in Human
GSPR	General Safety and Performance Requirements
HDE	Humanitarian Device Exemption
HEU-EFS	Harmonized Approach to Early Feasibility Studies for Medical Devices in the European Union
HTA	Health Technology Assessment
HTACG	HTA Coordination Group
HTAR	HTA Regulation
IDE	Investigational Device Exemption
IEC	Internal Ethics Committee
IHI	Innovative Health Initiative
IRB	Institutional Review Board
MCTA	Model Clinical Trial Agreement
MD	Medical device
MDCG	Medical Device Coordination Group
MDIC	Medical Device Innovation Consortium
MDR	Medical Device Regulation
MS	Member State
NB	Notified Body
OPEQ	Office of Product Evaluation and Quality
PAG	Patient Advisory Group
PMAP	Pre-Market Approval Pathways
PMAP-DB	Pre-Market Approval Pathways Database

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
PROM	Patient Reported Outcome Measurements
SM	Small and Medium Enterprise
UB	Bocconi University
UK	United Kingdom
US	United States
WP	Work Package

EXECUTIVE SUMMARY

An overarching goal for medical device (MD) regulation is to provide timely access to innovative technologies that are safe and effective. Approval processes for MDs necessarily affect both how the devices are developed and how clinical evidence to support their use and guarantee their safety is generated and regulated. By extension, these same approval processes impact exchanges between stakeholders, including regulatory bodies, clinicians, patients, payers, and producers. Though the ultimate goal is shared, in Europe, the United States (US), and elsewhere, regulations and guidance for evidence generation and pathways to approval for MDs differ, sometimes considerably.

The aim of this report "Characteristics, gaps, and best practices of pre-market programs" is to identify aspects that would both facilitate the establishment of a harmonized European Union (EU) Early Feasibility Studies (EFS) Program and provide strategies to overcome any barriers. To achieve this goal, we provide a comprehensive analysis of the current state of pre-market approval pathways (PMAPs) for MDs in the EU and other relevant jurisdictions, and describe their distinguishing characteristics, gaps, barriers, and challenges, as well as best practices and performance monitoring systems currently in place. The report highlights the differences in regulatory frameworks between the EU and the United States (US) that are most relevant to an EU EFS Program and synthesizes evidence gathered from approximately 12 years of experience from the US Food & Drug Administration (FDA) EFS program.

A mixed-methods approach was employed to gather comprehensive data on the characteristics, challenges, and performance of PMAPs in various jurisdictions. Methods included a scoping review of peer-reviewed literature, grey literature analysis, and surveys and interviews with stakeholders.

The overview of the US FDA Program, established in 2013, highlighted several facilitating factors: incorporation of EFS into the existing regulatory framework; a formalized process to obtain early and ongoing advice from FDA regulators organized into dedicated therapeutic-areas; standardized resources, including guidance specific to the program in a dedicated area of the FDA website; greater flexibility related to non-clinical testing requirements, provisions to address the increased risk posed to patients for these early-stage studies; and FDA participation in a public-private partnership (the Medical Device Innovation Consortium, MDIC) dedicated to facilitating the program and measuring its performance.

The overview of the EU regulatory landscape identified significant gaps and opportunities for improvement necessary for an EU EFS program. Among those factors facilitating an EU EFS program are provisions in the new EU Medical Device Regulation that have strengthened and

standardized clinical evidence generation, providing common guidance on processes and documents needed across the EU. Key challenges include a lack of specific guidance and frameworks for EFS, less flexibility regarding non-clinical testing, and no formal process for dialogue between sponsors of clinical investigations (CIs) and regulators to guide device development and clinical testing. In addition, sponsors planning and conducting clinical studies in the EU must navigate a unique process for approval and oversight of clinical studies in each country.

The analysis of current approval pathways for pre-market CIs allowed to define and describe elements important in designing and implementing an EU EFS program, including criteria for innovation, eligibility criteria for MDs and patient conditions, pre-clinical testing requirements, product and protocol modifications, patient engagement, the role of clinical sites, interactions and dialogue between stakeholders, as well as financial barriers, timelines and performance of EFS studies.

As far as barriers are concerned, the broad discussion with stakeholders (i.e., technology developers, sponsors of CIs, trialists, HTA agencies, ethics committees, notified bodies (NBs), FDA,) involved in pre-market CIs of MDs highlighted that, among the main challenges, lie study design, endpoints, enrolment targets, and timelines. Risk-benefit analysis and device risk assessment are deemed the major hurdles by sponsors, together with aspects related to clinical sites (e.g., experience, capacity to enrol patients, timelines required for first patient enrolment), management of CI amendments, and regulators closure to dialogue. Team-NB, representing NBs, emphasized the importance of structured dialogue to minimize delays and improve data accuracy, whereas ethics committees highlighted the complexity of the regulatory framework and the need for better training and clearer instructions. Regulatory complexities have been widely discussed by trialists too, underlying how this is a major hurdle in light of the new and more stringent MDR, in an EU landscape where support for research is lacking. Professionals from clinical sites highlighted the increased difficulties in finding qualified investigators, as well as meeting regulatory requirements. To meet these needs, HTA agencies and SMEs stressed the importance of early collaboration among stakeholders more clarity and less fragmentation of the system. Taking a further perspective, the main barriers encountered by patients during clinical trials were represented by fragmented information about the study as well as insufficient time and information to carefully assess the risks and benefits of participating as part of the informed consent process. All these barriers and challenges have been considered by the FDA which, in turn, shared insights on their EFS program, aiming to balance risk-benefit considerations and streamline processes to, in fact, solve barriers that are recognised and faced by various stakeholder groups.

Drawing from the US experience, this report outlines best practices for implementing an effective EFS program in the EU. Key recommendations include establishing dialogue between regulators and manufacturers starting from the early development phases, adopting a risk-based approach to

device modifications, and enhancing patient involvement in the research process. The report concludes that a harmonized EFS program in the EU could significantly improve the efficiency of pre-market approval pathways for medical devices and leverage European expertise in developing and clinically testing innovative devices. By addressing the identified gaps and barriers, the EU can foster innovation while ensuring the safety and effectiveness of new medical technologies.

1. Introduction

An overarching goal of medical device (MD) regulation is to **ensure timely access** to innovative technologies that are **both safe and effective**. Approval processes for MDs influence not only how devices are developed but also how clinical evidence supporting their use and assessing their safety is generated and regulated. These approval processes also shape interactions among key stakeholders, including regulatory bodies, clinicians, patients, payers, and manufacturers. While the ultimate goal is shared, **regulatory frameworks** and evidence-generation pathways differ significantly across regions, including Europe and the United States (US).

This report evaluates the **strengths, weaknesses, and opportunities** inherent in the current pre-market evidence generation and approval pathways for MDs in EU. It aims to provide a comprehensive analysis of the current state of such pathways, identify gaps and barriers, and explore monitoring systems for pre-market performance across the EU and other relevant jurisdictions.

To achieve these objectives, the following tasks were undertaken:

1. **Scoping Review of Literature.** A scoping review of both scientific and grey literature was conducted, covering the EU, the UK, the US, Canada, Latin America and Asia. This analysis provided a comparative evaluation of pre-market programs, including Early Feasibility Studies (EFS). Relevant grey literature included the US FDA, the Medical Device Innovation Consortium (MDIC) and websites of national competent authorities (NCA).
2. **Dedicated Surveys.** Surveys were designed and disseminated to gather insights from developers of new technologies, internal ethics committees (IECs) or institutional review boards (IRBs), professional associations of clinicians and biomedical engineers, NBs, HTA agencies, contract research organizations (CROs), and member of the Patient Advisory Group (PAG), a group of patients with different health conditions directly involved in the project.
3. **Stakeholder Interviews.** Interviews with stakeholders across jurisdictions will be designed and conducted to identify and discuss **critical success factors for EFS**. These interviews will enrich the findings with real world perspectives from diverse actors involved in pre-market evidence generation.

These activities contribute directly to the ongoing work packages (WPs):

- **WP3** *Methodology development: rationale, processes and procedures to develop and validate a sound, widely applicable, and harmonized EU EFS Program, compliant with EU regulations*;

- **WP4** *Methodology development: evidence requirements, data and statistical tools to develop a standard protocol for conducting EFS studies in the EU*;
- **WP5** *Methodology development: to design and implement a Dashboard to monitor the performance of the EU EFS Program;*
- **WP6** *Methodology development: ethical and legal aspects*.

All WPs will ultimately support **WP7** *Testing the methodology through pilot use cases* and the final outputs and recommendations of the HEU-EFS project as a whole.

Report Structure

The report is organised into three main sections:

1. **Methodologies and Activities.** This section details the mixed methods applied, including the scoping literature review, the grey literature searches, and survey and interview processes with MD industry stakeholders.
2. **Comparative analysis**. This section provides an overview of the US EFS program, the EU regulatory landscape and their implications for conducting EFS. Key differences between the US and EU systems are analysed, highlighting their structures, similarities and variations.
3. **Findings and Conclusions**. The final section focuses on findings from the literature review, surveys and interviews. Topics include initiation factors for EFS, pre-clinical testing requirements, clinical sites and patient selection, quality aspects, risk management, regulatory engagement, financial barriers and timing. Based on these findings, the report outlines recommendations for developing an EU EFS program, emphasizing key barriers and success factors.

Conclusions

The findings presented in this report provide actionable insights to inform the design, implementation and monitoring of an effective EFS program in Europe, addressing both current challenges and opportunities for alignment with global best practices.

2. Methods

To support the development of the future EU EFS Program, we sought to build a robust understanding of the strengths, weaknesses, and opportunities inherent in current pre-market clinical evidence generation approval pathways, using different approaches, involving three main components: a scoping literature review, a grey literature review, and survey and interviews activities with a broad and diverse range of stakeholders.

2.1. Scoping literature review

A scoping literature review covering the characteristics, challenges and performance of pre-market clinical investigations (CI) approval pathways (PMAPs) was undertaken between January and February of 2024 by the project's academic partners. The literature review aimed to:

1) Map and identify the characteristics of current PMAPs for MDs, including digital health technologies (DHTs), in the EU and other relevant jurisdictions to inform WP3, 4, and 6;
2) Outline impacts, gaps, barriers, and challenges in pre-market clinical research investigated in the literature to inform WP3;
3) Identify performance monitoring systems currently in place for PMAPs, including the US Food and Drug Administration (FDA) EFS Program to inform WP5.

Search terms were combined into four parts, joined by AND, and searched for title and abstract in Pubmed; title, abstract and keywords in Scopus; and in all fields in Web of Science (**Box *1***). In this search, no date restriction was used since it covers pre-market programs and not just EFS (the program started in 2013). Final results for the included papers from the main search are summarized in the PRISMA flow diagram (

Figure *1*). In total 1,025 records were identified (610 from Scopus, 307 from Web of Science, and 128 from Pubmed), for a total of 730 after duplicates were removed.

Box 1*: Search terms used in the literature review*

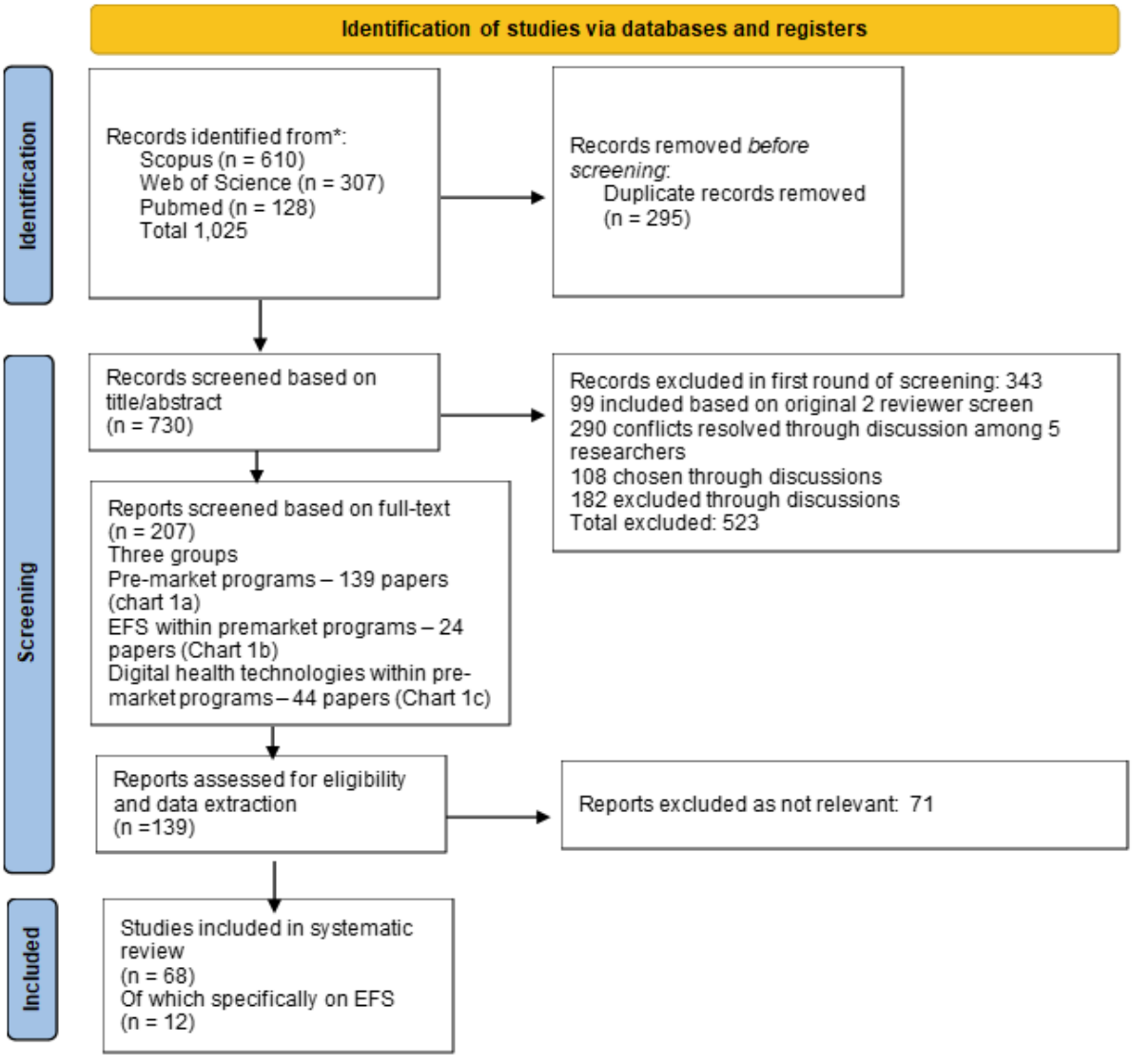
(("early feasibility stud*" OR "clinical feasibility" OR "first in human" OR "iterative development" OR (("premarket" OR "pre-market") AND "clinical") OR (("preapproval" OR "pre-approval") AND "clinical") OR "clinical investigation" OR "clinical evaluation")

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*"))

Figure 1: PRISMA 2020 flow diagram of scoping literature review for pre-market approval pathways (PMAP), including EFS



The resulting 730 records covering characteristics, features, challenges and performance of PMAPs, were all screened by title and abstract by a team of 6 experienced researchers so that at least two independent researchers screened each record. From these, 163 were earmarked for full paper screening by at least two independent experienced researchers; 24 of these papers specifically mentioned EFS. At the conclusion of full text screening, 68 papers were included in the scoping review covering PMAPs, including 12 papers specifically related to EFS (please see the first 68 papers in the reference list,).[1–68] The settings covered in the included papers were geographically distributed according to **Table 1**. For those papers specifically related to EFS, 10 studies focus on the US, and two on Europe.

Table 1: Geographical distribution of selected papers

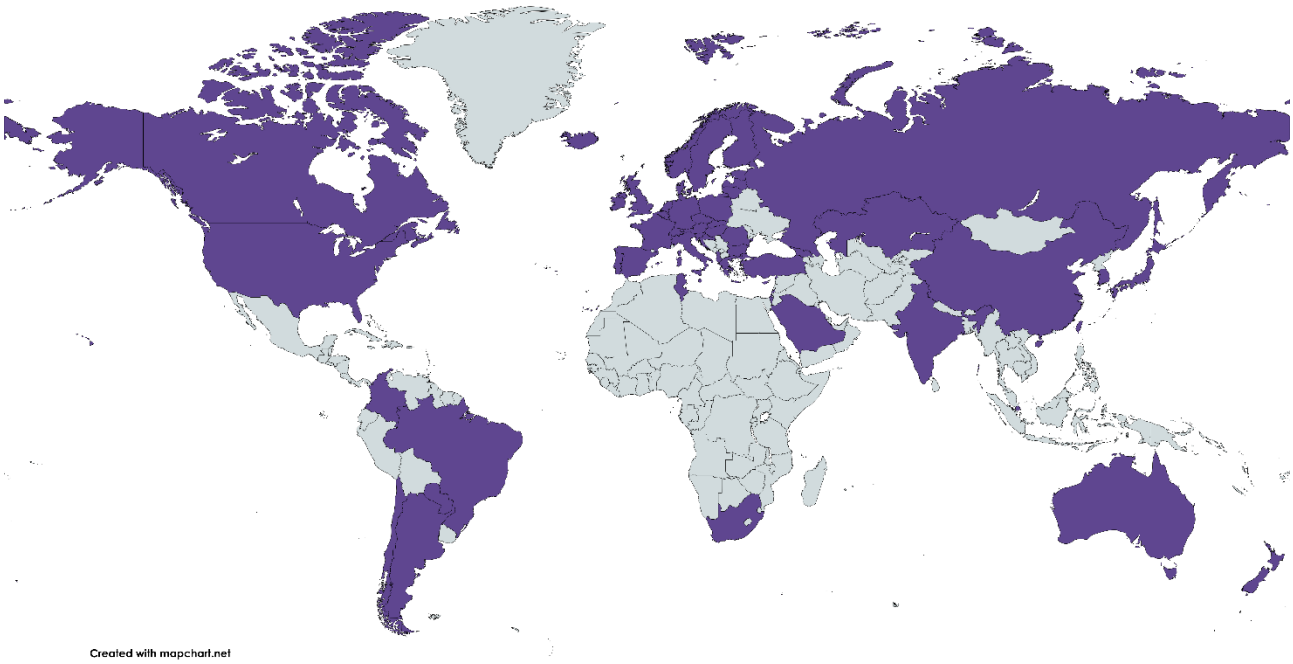
Setting	N.	%
EU only	25	36,8%
US only	30	44,1%
EU-US (and/or other countries) comparisons	7	10,3%
Asia (China, India, Japan)	6	8,8%
TOTAL	68	

2.2. Grey literature

The scoping review of the scientific literature was supplemented by grey literature searches including non-peer reviewed documents as well as other relevant documents found in websites (e.g., the US FDA EFS Program and the Medical Device Innovation Consortium (MDIC) website).[1] Websites of national competent authorities (NCA) and/or bodies in charge of authorizing the initiation of CI for MDs were screened to obtain information and documents regarding how evidence generation is regulated in the European Union and other key worldwide jurisdictions (56 countries in all, **Figure 2**). The information gathered on procedures for the submission of pre-market CI of MDs applications fed into an ad hoc database called Pre-Market Program Database (PMAP-DB). Details on the methodology and results are provided in deliverable D1.2 *Pre-Market Program Database*.

[1] The Medical Device Innovation Consortium (MDIC) is a public-private partnership created in 2012 to promote advancing medical device regulatory science for patient benefit. It brings together representatives of the FDA's Center for Devices and Radiological Health (CDRH), the National Institutes of Health (NIH), the Centers for Medicare & Medicaid Services (CMS), industry, non-profits and patient organizations to improve the processes for development, assessment and review of new medical technologies.

Figure 2: Countries included in the PMAP-DB (in purple)



2.3. Surveys and interview activities

The results of the scientific and grey literature review informed the discussion with stakeholders. A survey was run in October-November 2024 among sponsors of CIs to identify the challenges they experience when planning, monitoring, and conducting pre-market studies for MDs. The survey, developed by several members of the consortium, is made up of four sections and comprises 20 questions overall. The first section focuses on the study submission processes to NCAs and includes questions around the criteria for countries' selection as well as the main challenges sponsor face when preparing the required documentation. The second section focuses on the Clinical Investigation Plan (CIP), followed by a section on the CI conduct in the EU and a final one on challenges specific to EFS. The survey was implemented on Qualtrics^{XM} platform and tested across project partners, before ethics approval by Bocconi University Ethics Committee and publication on the project's website and social media. To ensure high response rate, European life science industries trade associations MedTechEurope (European trade association representing the medical technology industries), COCIR (European trade association for medical imaging, radiotherapy and electromedical industries), and EFPIA (European Federation of Pharmaceutical Industries Associations) supported the dissemination of the survey among their associate companies covering a wide range of profiles (large, medium, and small enterprises, including start-ups and university spin-offs) and clinical sectors of interest (such as cardiology, neurology, diabetology, orthopaedics).

Project's industry partners were also asked to share the survey among their networks, including national representative associations, to collect as many opinions as possible on whether current pre-market programs present any barriers or challenges that would need to be overcome to successfully implement an EU framework for the implementation of EFS. We reached a total of 83 complete surveys. Descriptive statistics are presented in **Table 2**.

Table 2: Descriptive statistics of the survey for clinical investigation sponsors

	n	%
Number of respondents	83	
Company size		
Large enterprise: ≥250 employees	48	57.8%
Medium enterprise: 51 - 249 employees	11	13.3%
Small enterprise: 11 - 50 employees	13	15.7%
Micro enterprise: ≤10 employees	10	12.0%
Not applicable or not provided (NA/NP)	1	1.2%
Country of the respondent		
Austria	1	1.2%
Belgium	4	4.8%
Denmark	1	1.2%
Finland	1	1.2%
France	14	16.9%
Germany	10	12.0%
Greece	1	1.2%
Hungary	0	0.0%
Ireland	1	1.2%
Italy	12	14.5%
Norway	0	0.0%
Spain	5	6.0%
Sweden	1	1.2%
Switzerland	3	3.6%
The Netherlands	14	16.9%
United Kingdom	1	1.2%
United States	10	12.0%
NA/NP	4	4.8%
Experience designing or conducting EFS in the EU		
Yes	42	50.6%
No	29	34.9%
NA/NP	12	14.5%
Experience designing or conducting EFS in the US		
Yes	20	24.1%
No	51	61.4%
NA/NP	12	14.5%

Ethics approval was obtained for conducting one-to-one interviews with those respondents who stated in the survey that they were available to be contacted to further expand on their direct experience with EFS applications (17 so far). The interviews are scheduled in January 2025 and the results will feed into WP1 final recommendations as part of deliverable D1.4.

A survey involving the PAG was also developed and conducted in November 2024, with the aim to collect input on patient perspectives and experiences with clinical investigations. The aim was to identify key gaps and challenges currently faced by patients. The survey questionnaire was shared with all 11 PAG members and those with relevant experience were invited to complete it. The results were further complemented and validated in a workshop with nine PAG members in December 2024.

To better understand the challenges faced in pre-market clinical research in the EU from different perspectives, during December we run interviews with HTA agencies, NBs, clinical sites, trialists, and national ethics committees.

The findings from these activities are presented in details in Section 4 of the report.

3. Early Feasibility Studies within the framework of pre-market approval pathways

In this section, we provide an overview of the US EFS program, incorporating, where illustrative, a larger discussion of pre-market approval pathways and issues surrounding non-clinical testing and clinical evidence generation in various jurisdictions, focusing primarily on the EU and the US. We highlight the distinguishing features of each system, outlining similarities and differences, performance measures, as well as key challenges and barriers for each, particularly as they relate to the design and eventual implementation of an EU EFS program. Following this section, we present the findings directly related to the components necessary to build an EU EFS program, divided into sections relevant to various issues necessary for building the program, including eligibility criteria and underlying principles, risk mitigation, non-clinical and clinical phases, dialogue with regulators, clinical centres, patient consent and ethical issues, and patient feedback and involvement.

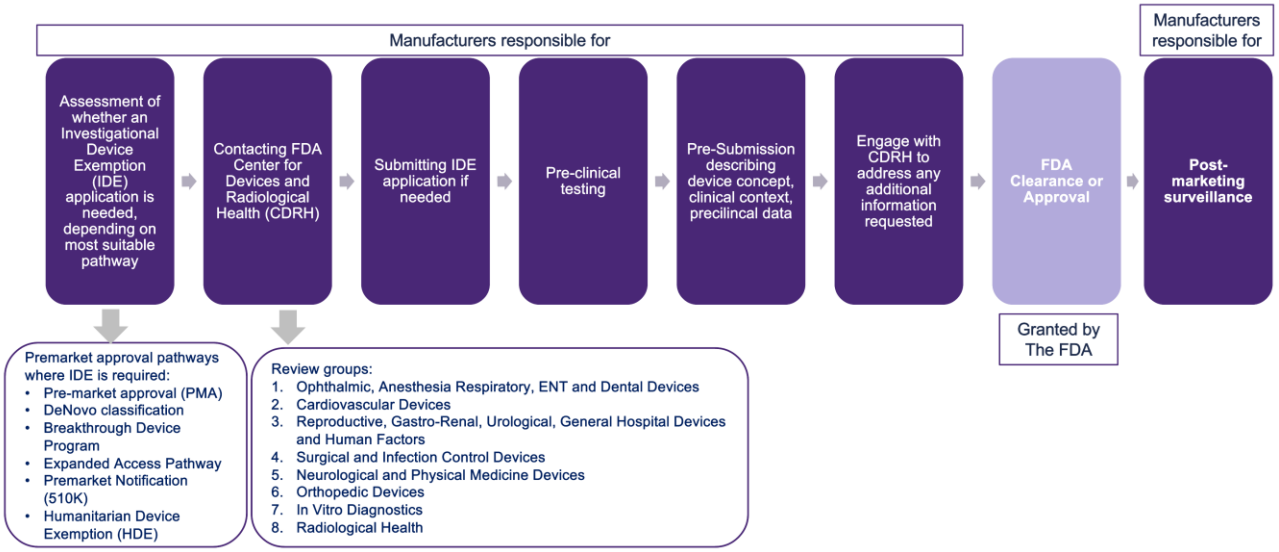
3.1. Overview of the US FDA EFS Program

The FDA's CDRH regulates MDs for the US, setting requirements for clinical investigation and approval pathways of MDs according to their risk-based classification (I, II, III), which reflect the potential risk the device poses for use in humans, as established by federal law through the Federal Food, Drug, and Cosmetic Act, section 513.[1,69–71] In 2013, the CDRH launched the EFS program, which represented an opportunity to incentivise research, attract investments, and ensure early access for US patients to new technologies.[30,72] Once established, the US EFS program became part of the regulatory approval pathway for medium and high risk MDs.[73] In the same year, the FDA published a guidance titled "*Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Clinical Studies, Including First in Human (FIH) Studies*", intended to support FDA staff, clinicians, innovators and the industry with the development and review of IDE applications for EFS of "significant risk devices".[73,74] This guidance defines an EFS as: "a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication".[74] EFS are suitable when further non-clinical 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 adequate non-clinical tests are unavailable.[74] Conducting an EFS can be helpful not only in optimizing design or function when non-clinical testing is not sufficiently informative, but it may also serve to optimize operator technique or refine the patient population for the technology's

intended use.[28] As devices eligible for EFS are early in their development, the EFS program is characterized by a higher degree of uncertainty compared to other clinical investigations and, as for other studies, it must be justified by a risk-benefit analysis, along with preclinical evidence.[28] As it brings greater risks, FDA guidance refers several times to conducting EFS on a "small number" of patients, without ever specifying a limit,[74] though other documents and several publications usually refer to numbers of patients as less than 15.[27,29,35,72]

Clinical evidence is generally required for novel devices and for all high-risk (class III) devices in the US, which follow one of several regulatory paths, depending on the degree of innovation and level of risk.[1] As such, MDs can follow different regulatory pathways, including: the pre-market approval (PMA) pathway (for high risk devices, requiring extensive clinical data); the premarket notification (510(k)) pathway (usually for Class II device that are substantially equivalent to another predicate (other) devices already on the market); the de Novo classification (for lower risk novel devices, without a predicate), and the humanitarian device exemption (HDE) pathway (for novel devices meant to treat rare conditions) (**Figure *3***).[73]

Figure 3: Pre-market approval pathway for high-risk medical devices in the US



Finally, a related but somewhat different pathway is the Breakthrough Devices Program, previously known as the Expedited Access Pathway, which is a voluntary program for devices that promise to provide "more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions".[75] Criteria for the Breakthrough MD designation are summarized in **Table 3** below. The assumption is that the device will eventually follow one of the established pathways, and the Breakthrough designation facilitates interaction between manufacturers and the FDA during the premarket review phase and promises prioritized review of their eventual submission.

Table 3: Criteria for the US FDA Breakthrough Devices Program, (Source75)

Criteria	Description
First criterion	The device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions
Second criterion	The device also meets at least one of the following:
	a. represents breakthrough technology
	b. no approved or cleared alternatives exist
	c. offers significant advantages over existing approved or cleared alternatives
	d. device availability is in the best interest of patients

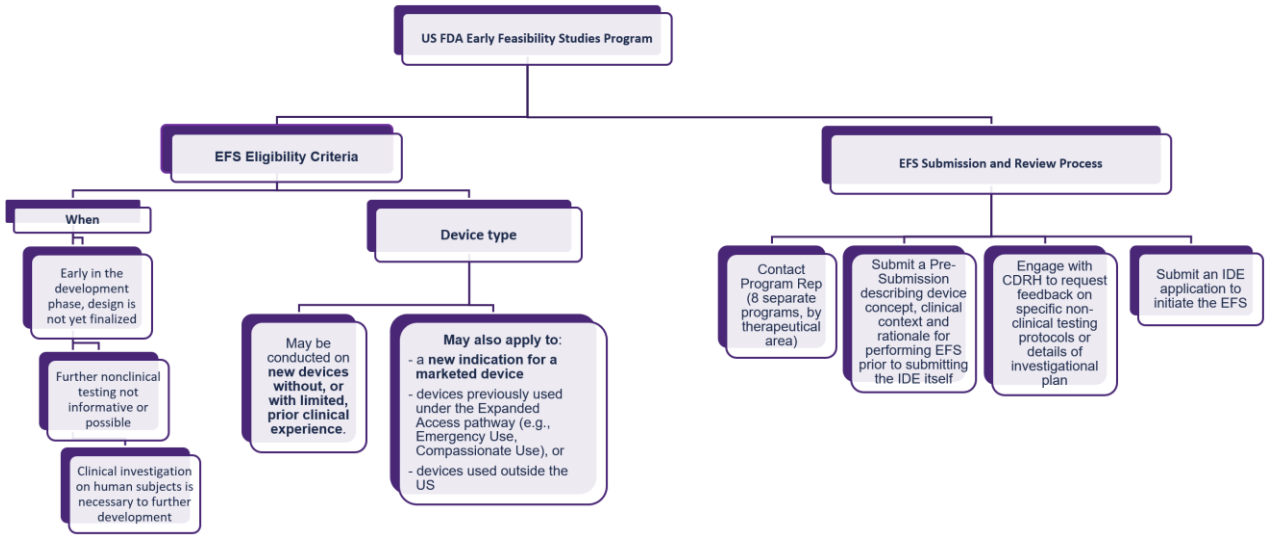
The clinical investigations undertaken as part of the EFS program are regulated by the EFS IDE. This guidance for IDE for EFS is distinct, but related to the standard IDE, which allows an investigational device to be used in a clinical study that has not been cleared for marketing, which normally aims to collect both safety and efficacy data (see **Box 2** for details on the FDA IDE process).[76] For EFS, instead, the alternative IDE for EFS application guidance accounts for the need to clinically test the device in a small number of subjects, to inform initial clinical safety and device functionality when the device design is not yet finalized, at this earlier stage in development.[74]

Box 2: The US FDA Investigational Device Exemption (IDE) process for clinical evaluations of investigational devices

In the US, clinical evaluation is governed by the Investigational Device Exemption (IDE) process. An IDE allows an investigational device to be used in a clinical study in order to collect safety and efficacy data. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before a clinical study is initiated. The assumption underlying an IDE (whether for pre-market approval studies or for EFS – as explained above) is that of a significant risk device. Significant risk is defined in the U.S. Code of Federal Regulations (CFR), Title 21,[77] as an investigational device that is: i) "intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject"; ii) "purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject"; iii) "for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject"; or iv) "otherwise presents a potential for serious risk to the health, safety, or welfare of a subject". Clinical studies are most often conducted to support a PMA, as only a small percentage of 510(k)s require clinical data to support the application. [76] Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. The information required to accompany an IDE process requires a clinical investigation plan (CIP) approved by an IRB – the IDE must also be approved by the FDA if it involves a significant risk device, and informed consent from all patients, as well as appropriate labelling of the device as investigational, study monitoring and required documentation.[76,77]

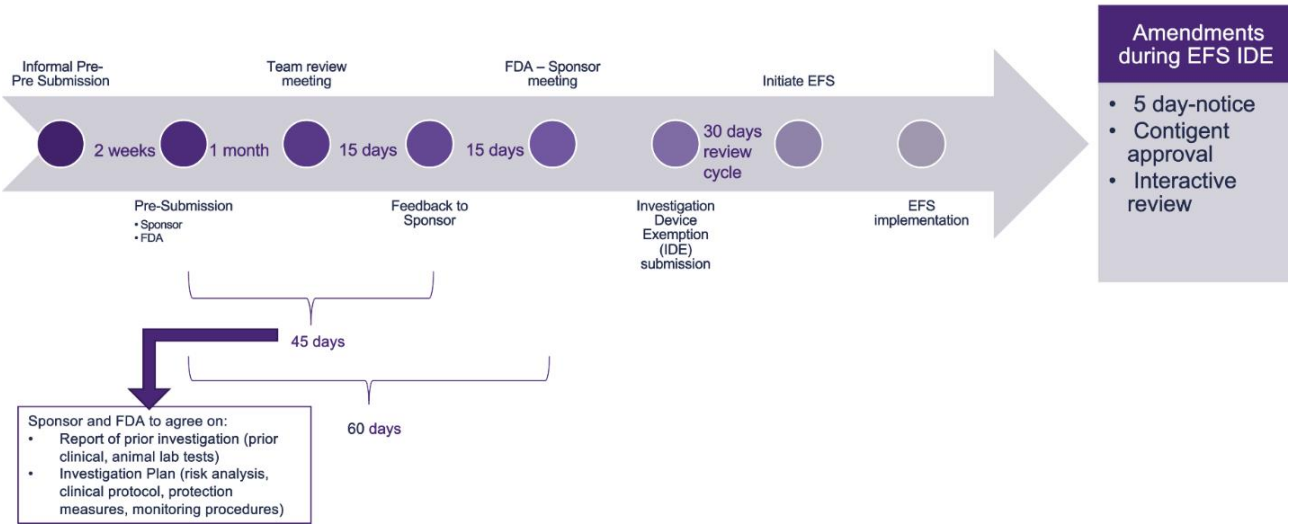
A schematic representation of general eligibility criteria and processes to follow for entry into the EFS program is provided in **Figure 4** .

Figure 4: Schematic representation of the USFDA EFS program



To initiate an EFS in the US, the sponsor contacts the 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. orthopaedics or cardiovascular, (**Figure *3*Error! Reference source not found.**), 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 *3***, **Figure 5**).[78] During this process, the FDA becomes more familiar with the device and may provide feedback or advice to the sponsor, upon request, on the information to be included in the Report of prior investigation (including any prior clinical, laboratory and animal testing previously run) and the Investigational Plan (reporting risk analysis, clinical protocol, protection measures and monitoring procedures).[78] At this stage, the sponsor should obtain approval from the IRBs responsible for assuring the study is ethical and participants' rights and welfare are protected. Once the FDA and the sponsor reach an agreement, 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. 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.[78] Once IDE approval has been obtained the EFS study can begin, provided, as for all clinical investigations, the IRB approval from the study site has also been obtained.[74,78]

Figure 5: FDA EFS Submission and Review Process Timelines



Source: [78], p. 25.

Since "changes to the device design and, materials, procedure, instructions, and even patient population are to be expected",[79] continued interaction with the FDA is encouraged and serves to lower the risk of regulatory delays. Given that the aim of conducting an EFS is to gather data to help optimize the device design, its function or deliverability, there are different approaches that sponsors can take to make **changes** to the device or the clinical protocol 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 cycle.[74]

Once an EFS is completed, the sponsor 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, the EFS could **evolve** into a traditional feasibility study or a pivotal study, depending on whether the preliminary safety and efficacy data is adequate or further safety and efficacy data is needed (**Table 4**).[27] In this case, a new IDE is not necessarily needed, and the same IDE code can accompany the device through the subsequent stages of clinical investigation. This decision must be reached in conjunction with the FDA.

Table 4: Comparison between EFS, traditional feasibility, and pivotal study

	EFS	Traditional Feasibility	Pivotal
Design	Not final	Near final	Final
Data	Less non-clinical data available	More non-clinical data available	Non-clinical data completed
Aims	Provide initial insights regarding clinical safety and performance, design, and / or functionality	Collect safety and efficacy information for a near final or final device design, in a small number of subjects, used to plan pivotal study	Collect safety and efficacy information to support marketing application

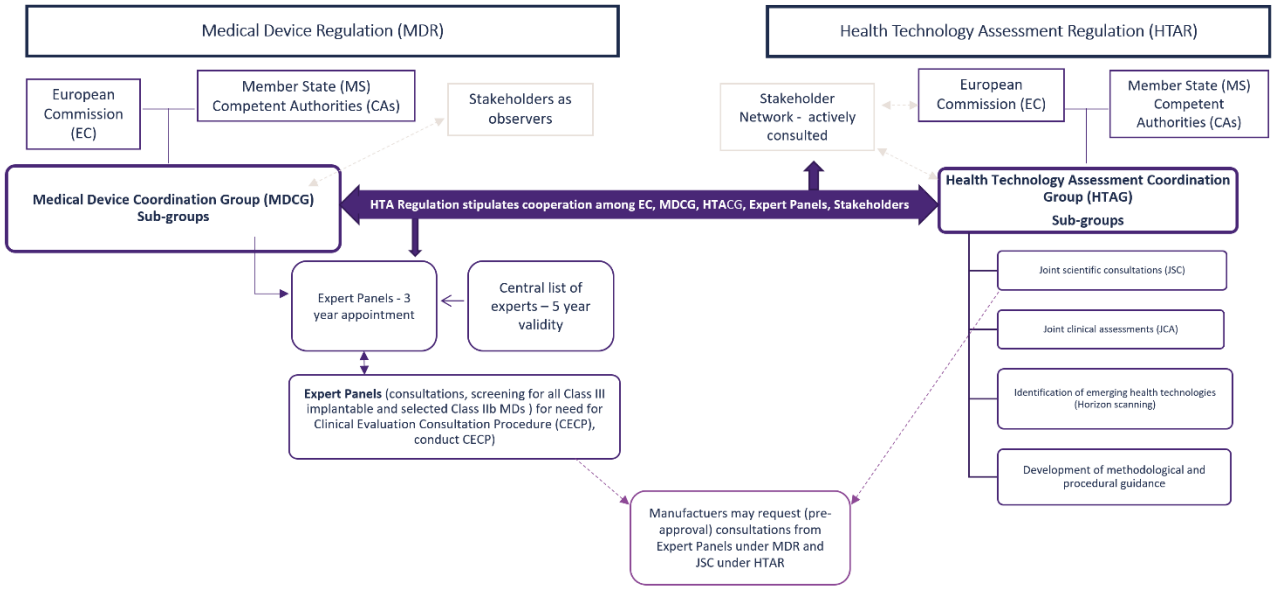
3.2. EU Regulatory Landscape and EFS Implications

A complete overview of the EU regulatory landscape and its implications for EFS is provided in Deliverable 2.1 *EU regulatory framework and international standards* from this project. For completeness, and to offer a full comparison between the US and European regulation, a summary of the EU regulatory landscape is provided below.

In the EU there is currently no program specifically addressing EFS and therefore, to understand what is needed for a future EU EFS Program, a brief overview of the current state of regulatory processes follows. The EU regulatory landscape has evolved over time from a system governed by Directives to the passage of a Regulation providing the regulatory framework for MDs, where clinical investigations are authorized under the Regulation and subject to conformity assessment for market access, with the European Commission (EC) setting legal policy and helping to coordinate Member States (MSs).[1,21,62] NCAs in MSs designate independent commercial organizations known as Notified Bodies (NBs) to assess the conformity of an MD to the requirements of relevant standards regarding safety and performance. From the 1990s to 2017, the EU Medical Device Directives provided overall objectives for regulation of MDs but allowed some variance among MS in how they were implemented.[21,46] In 2017, the Medical Device Regulation 745/2017 (MDR) entered into force (with an initial date of application set for May 2020,[80] subsequently extended and still not fully implemented at this writing), which governs the regulatory pathway to market approval for the European Economic Area (i.e., 27 MSs with EEA members Iceland, Liechtenstein, and Norway) and dictates that all legal requirements must be applied equally in all countries. The impetus behind the MDR was the need to address previous gaps in clinical evidence requirements, place more stringent controls on NBs, increase transparency of information for stakeholders, establish Expert Panels to provide formalized opinion and medical advice, and increase post-marketing requirements and introduce new reporting requirements for manufacturers, thus introducing greater standardization in the process but maintaining the decentralized structure.[20,21,46,61,62,81] Additionally, at the end of 2021, the Health Technology Assessment (HTA) Regulation (HTAR)[82] was adopted to harmonize, improve, and foster cooperation in HTA processes across the EU and MSs for health technologies, including

medicines and those MDs in the highest risk classes that have been subject to Expert Panel review.[62,82] The HTAR contains, among others, provisions for joint clinical assessments of health technologies. **Figure 6** provides a schematic representation of the regulatory process and stakeholder involvement for MD marketing approval under MDR and HTA processes under HTAR, highlighting key features and where the two regulations may interact. In particular for MD regulation, while there is no equivalent to the FDA's CDRH, the Medical Device Coordination Group (MDCG) established under the MDR performs important functions, and provides opportunities for MS collaboration as well as guidance and advice within the expert areas of the 12 subgroups. There is a similar structure for the HTAR, through its HTA Coordination Group (HTACG).

Figure 6: Schematic representation of the regulatory process for MD marketing approval under MDR and HTAR



Although the MDR aims to provide a robust and shared regulatory framework for MDs in the EU, it lacks methodological guidance which has resulted in great variability between MSs, hence the recent push for a more centralized and harmonized approach to make device approval faster and more streamlined.[20,21,83] Within the EU, the MDCG guides the clinical evaluation of MDs by issuing documents about clinical evaluation processes.[1,84] To provide specialized guidance, the MDCG includes several groups, ranging from the Notified Bodies Oversight subgroup, overseeing their work, to the Market Surveillance subgroup, coordinating activities of surveillance across MSs.[84] A more detailed overview of the MDCG subgroups is provided in **Table 5**. By providing guidance that standardizes clinical evaluation across MSs (including performance aspects and data requirements), the MDCG fosters harmonization across the EU and makes sure that clinical data are in line with EU standards.[1,21] While the MDCG guides clinical evaluation at the EU level, at the national level, each

NCA is responsible for overseeing and enforcing compliance with the EU Commission under the MDR.[1,20,80]

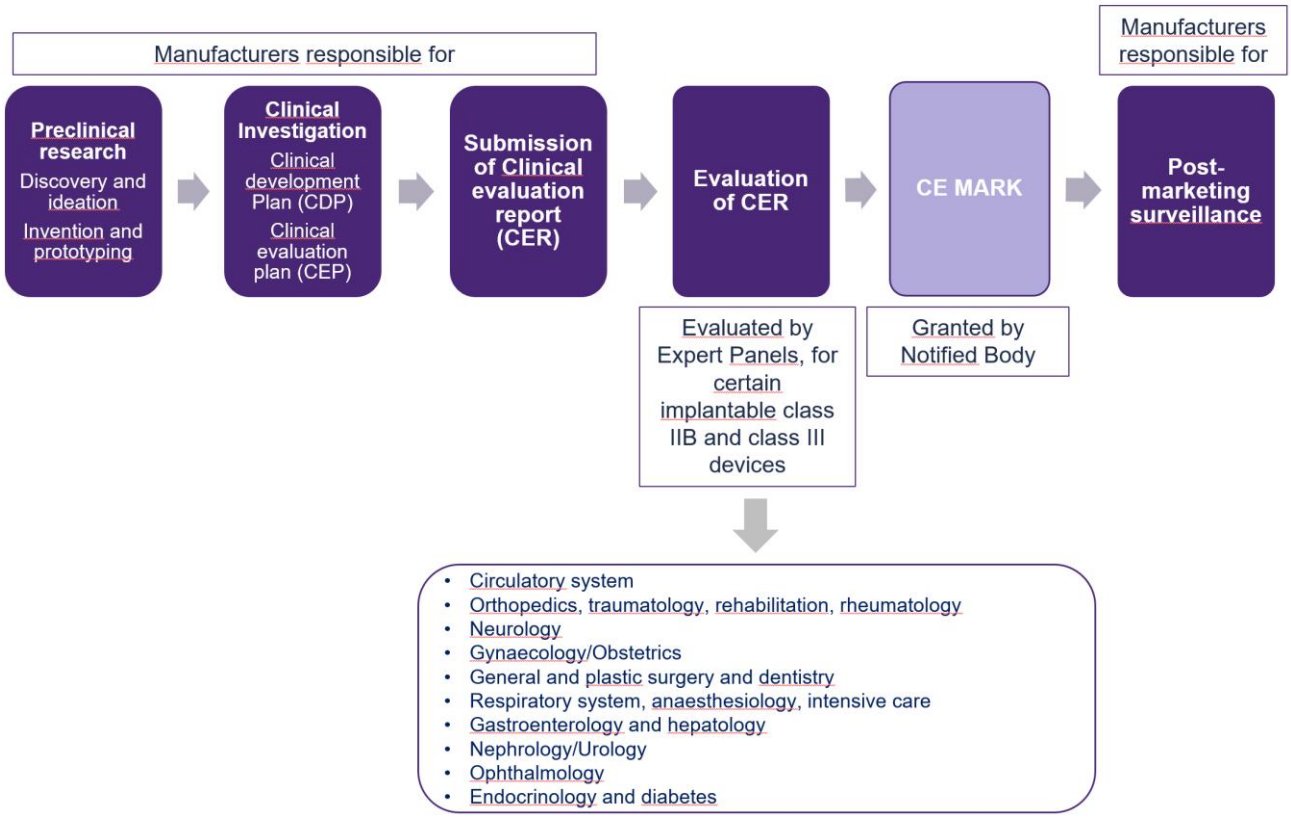
Table 5: The Medical Device Coordination Group (MDCG) subgroups (source [84])

Subgroup	Main task
Notified bodies oversight (NBO)	Oversee operations of NBs to ensure consistency in conformity assessment
Clinical Investigation and Evaluation (CIE)	Focus on clinical evidence requirements
Post-market Surveillance and Vigilance (PMSV)	Aid on post-market issues, incident reporting and vigilance
Market Surveillance (MS)	Focus on surveillance activities and control of devices across MSs
Borderline and classification (B&C)	Assist with issues about product's qualification as a medical device and classification
New Technologies	Focus on new and emerging technologies and their applications
Unique device identification (UDI)	Implement UDI requirements
Standards	Discuss issues related to standardization and coordinate proposals about development and use of standard documents, when necessary
EUDAMED	Aimed at facilitating the implementation of the platform
International matters	Discuss medical device regulations and international issues relate to MDs
In vitro diagnostic medical devices (IVD)	Promote common implementation of IVD MDs
Nomenclature	Help with any issues related to MDs nomenclature
Annex XVI products	In charge of developing guidance for products with no intended medical purpose, listed in Annex XVI of the MDR

Figure 7 illustrates the pre-market approval pathway for high-risk medical devices under the EU MDR, where manufacturers are responsible for pre-clinical/non-clinical (see also the glossary from Deliverable 2.1 *EU regulatory framework and international standards*) and clinical evaluation to support their submission for marketing approval. According to the MDR, Annex I, the technical file is a comprehensive document that demonstrates a MD's conformity with general safety and performance requirement (GSPRs).[80] The manufacturer's technical documentation (including the clinical evaluation documentation, described in Annex II/III),[80] among other documents, comprises the Clinical Evaluation Report (CER), referring to the Clinical Development Plan (CDP) and the Clinical Evaluation Plan (CEP), that goes to the Notified Body for conformity assessment. The Notified Body's conformity assessment procedure includes evaluation of the CER and produces the Clinical Evaluation Assessment Report (CEAR). The CEAR (along with the manufacturer's CEP and CER) is subject to Expert Panel review (known as the Clinical Evaluation Consultation Procedure, see also Article 54))[80] for certain Class III and Class IIb high-risk devices (specified in the MDR as "class III implantable devices (and) class IIb active devices intended to administer and/or remove a medicinal product").[80] A Screening panel decides whether the opinion of one of the thematic expert groups is needed.[85] The Expert Panels may issue a scientific opinion (within 60 days) that Notified

Bodies may or may not consider in making the final conformity assessment, but any refusal to consider the opinion must be justified.[20,21,62,80] The key feature of the EU market is that once an MD has been approved for marketing, i.e., obtained a Conformité Européenne (CE) mark, it may be commercialized throughout the EU.

Figure 7: Pre-market development and approval pathway for high-risk (implantable and class III) medical devices in the EU



3.3. EFS in EU regulatory documents

As mentioned above, Deliverable 2.1 *EU regulatory framework and international standards* from this project provides a complete overview of the EU regulatory landscape; for convenience, we have extracted some elements from that report to provide some of the key elements and definitions that provide context here and for the sections that follow. At present in the EU, reference to EFS in the above-described regulatory landscape is limited to non-specific text in Annex XIV, Part A, of the MDR related to the manufacturer's "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…"[80] Other than this, EFS are only defined in reference to the International Organization for Standardization (ISO) system of standards, where they are defined in ISO 14155:2020, entitled, *"Clinical investigation of medical devices for human*

subjects — Good clinical practice". ISO 14155:2020 includes these types of studies among possible pre-market clinical investigations, and defines them in Annex I.5.3 as:

> "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 efficacy (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."[86]

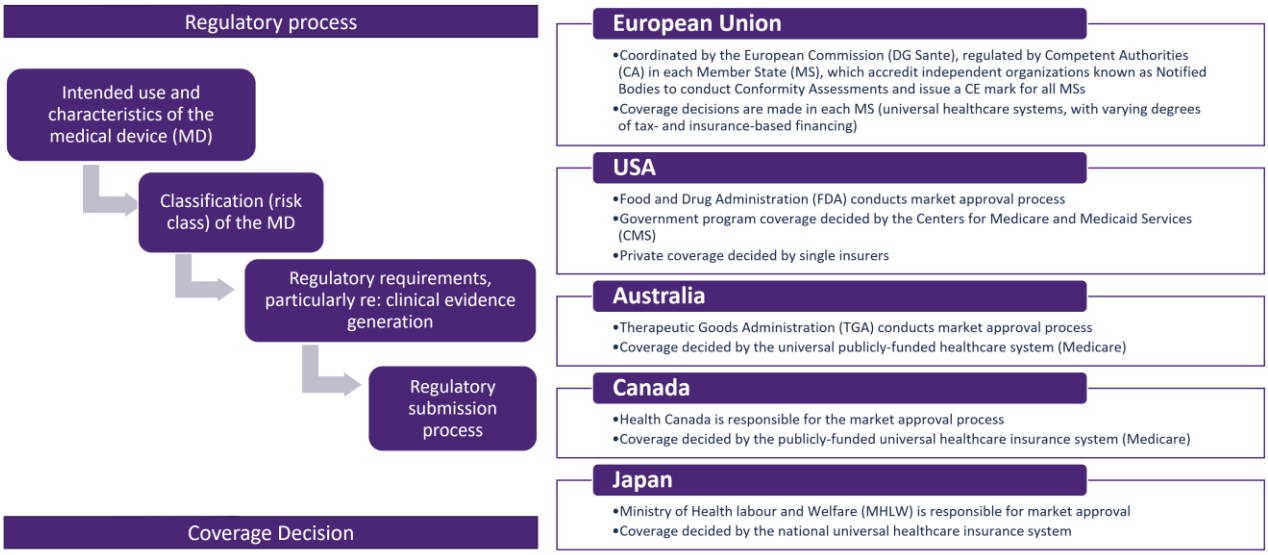
Finally, because indications directly from the MDR may need explanation, clarification, or further information, the MDCG provides a number of guidance documents (over 100 have been issued since the publication of the MDR); though each comes with a disclaimer at the beginning stating that they are not official opinions of the EC and are therefore not legally binding, NBs are expected to follow MDCG guidance, making them important for manufacturers as well. In fact, MDCG guidance 2021-6 rev.1 (revised in 2023) covering clinical investigations to gather preliminary safety and performance data, includes a reference to EFS, where they are described as one of the types of pilot or early-stage clinical investigations (which may also be referred to as a proof-of-concept investigation).[6,87] In addition, though ISO 14155 itself is only referred to once in the MDR in Recital 64[2] its mere inclusion creates an expectation that it be followed as a standard for clinical investigations, which becomes increasingly clear in MDCG guidance documents.[80] For instance, MDCG 2021-6 rev.1 repeatedly references ISO 14155, as does MDCG 2024-3 on the expected content of a Clinical Investigation Plan (CIP).[88] MDCG 2024-3 (in section 3.6.1) also encourages increased safety measures for "early studies of new/high-risk devices", including limiting study participants by using a staggered approach, i.e., test in one patient and evaluate before testing on the next patient.[88]

[2] MDR Recital 64: "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"

3.4. Key US-EU Differences for an EU EFS Program

From the descriptions above, several key similarities and differences between the US and the EU jurisdictions emerge that may be particularly relevant for the establishment of an EU EFS Program. Perhaps most importantly, MDs are centrally regulated in the US as well as in most jurisdictions around the world (**Figure 8**), while they follow a decentralized process in the EU, which has important implications for evidence generation, especially as it relates to processes governing the approval and oversight of clinical studies conducted within each EU MSs.

Figure 8: The regulatory process and coverage decisions for medical devices in selected world regulatory agencies and coverage decision bodies



Both the US and the EU systems have similar definitions of an MD, with similar divisions of MDs into risk classes.[80,89] The table below (**Table 6**) compares the EU and US systems on several key components of their respective MD regulatory systems.

Table 6: Key features of the EU and US regulatory systems for MDs

European Union	United States
Definition of a medical device	
Definition from the EU Medical Device Regulation 2017/745: [87] Any instrument, apparatus, appliance, software, implant, reagent, material or other article intended to be used in human beings for: i) diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, ii) or for an injury or disability, or iii) investigation, replacement or modification of the anatomy or of a physiological or pathological process of state, or iv) providing information by means of in vitro examination of specimens derived from the human body. The	Definition of an MD from the Federal Food Drug and Cosmetics Act of 1992: [89] Instrument, apparatus, implement, machine, contrivance, implant or in vitro reagent that is i) recognized in the official national formulary or pharmacopeia, ii) intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease; iii) intended to affect the structure or function of the human body.

<table>
<tr><th colspan="2">European Union</th><th>United States</th></tr>
<tr><td colspan="2">definition also distinguishes MDs from pharmacological products.</td><td></td></tr>
<tr><td colspan="3">Pre-market regulatory pathways</td></tr>
<tr><td colspan="2">Medical Device Regulation (MDR) 745/2017.
In particular, Articles 62 and 82 for requirements governing clinical investigations, Article 74 (clinical investigations regarding devices with CE marking), and Article 78 (Coordinated assessment procedure for clinical investigations)[80]</td><td>• Premarket approval (PMA)
• DeNovo classification
• Breakthrough Devices Program
• Expanded Access Pathway
• Premarket Notification (510(k))
• Humanitarian Device Exemption (HDE)</td></tr>
<tr><td colspan="3">Risk classification of medical devices and level of regulatory control</td></tr>
<tr><td>Class I
Class IIa
Class IIb
Class III</td><td>MDs are classified from lowest to highest risk, and are governed by specific rules in Annex VIII of the MDR. [1,80] Guidance 2021-24 provides information for manufacturers to determine the correct risk class.[90]</td><td>Class I – low to moderate risk – general controls.
Class II – moderate to high risk – general controls and Special Controls.
Class III – high risk – general controls and Premarket Approval.</td></tr>
<tr><td colspan="3">Non-clinical (or pre-clinical) testing requirements</td></tr>
<tr><td colspan="2">Requirements depend on classification of the device. Requirements under the MDR focus on ensuring health, safety standards and performance, usually including:
• Biocompatibility testing
• Performance testing
• Microbiological testing
• Animal studies
• Bench testing
• Toxicology testing</td><td>Requirements depend on classification of the device. For high-risk devices, more studies are required. Core areas usually refer to:
• Biocompatibility testing
• Performance testing
• Microbiological testing
• Animal studies
• Bench testing
• Toxicology testing
These are primarily regulated by FDA’s 21 CFR Part 820 (Quality System Regulation).</td></tr>
<tr><td colspan="3">Clinical investigations</td></tr>
<tr><td colspan="2">Under MDR: clinical data is required to demonstrate safety and performance for all medical devices unless Art 61(10) applies (where clinical data is “not deemed appropriate”).[80] See also Articles 62, 74, 78, 82.
Sponsors must prepare a clinical development plan (CDP) as well as a clinical evaluation plan (CEP).</td><td>Clinical data is required for novel, high-risk devices on the PMA pathway, but may not be required for all devices or pathways, e.g., often not for 510(k).
All clinical investigations of medical devices must have an approved IDE before any study begins.</td></tr>
<tr><td colspan="3">Dialogue with regulators</td></tr>
<tr><td colspan="2">While MDR allows for consulting Expert Panels for high-risk devices. While there is currently no general, formal process for dialogue between manufacturers and regulators focusing on ensuring compliance with MDR, several pilot projects (Article 61.2) are currently underway for high risk MDs (see also Deliverable 2.1).</td><td>Early engagement with the FDA, including pre-submission process (Q-Sub), ensuring collaborative approach since the beginning of the study. Sponsors considering applying for the EFS program applicants may contact the appropriate office throughout the EFS process, from before application to transition to later stage clinical investigations.</td></tr>
<tr><td colspan="3">Coverage and reimbursement</td></tr>
<tr><td colspan="2">Decided in each MS.</td><td>Medicare, Medicaid and private insurance.</td></tr>
<tr><td colspan="3">Post-marketing surveillance</td></tr>
<tr><td colspan="2">MDR makes specific provisions for post-marketing surveillance on the part of manufacturers, and requires a post-market surveillance plan, Post-Market Surveillance Reports and Periodic Safety Update Reports.</td><td>Mandatory for all Class II and III MDs posing potentially serious health risks.</td></tr>
</table>

4. Pre-market Approval Pathways: key insights for an EU EFS Program

This section presents the findings from the scoping literature review, focusing on the characteristics, challenges and performance metrics of pre-market clinical investigations approval pathways. It also integrates insights from grey literature, with a specific emphasis on how these findings can inform the design, implementation and monitoring an EU EFS Program. Additionally, the results from stakeholder surveys and interviews are analysed to identify the challenges faced by key actors involved in pre-market clinical investigations for MDs in the European Union.

4.1. Defining "innovation" in pre-market approval pathways

4.1.1. Novel vs. Equivalent Devices

The U.S. FDA's Early Feasibility Studies (EFS) program does not outline explicit eligibility criteria but provides detailed guidance on its scope and the circumstances under which an EFS might be conducted. According to FDA resources, EFS are intended for:

- New devices or devices with novel indications that pose significant risks and have limited or no prior clinical data.
- Existing devices in specific scenarios where non-clinical testing is insufficient or non-informative to refine the design, functionality, or deliverability.

Key criteria for pursuing an EFS include:

1. The device design is not yet finalized.
2. Non-clinical testing alone cannot adequately inform further development.
3. Clinical investigation is required to optimize the design and establish proof of principle and/or safety.

EFS are not always part of the clinical evidence supporting final approval but are assumed to target devices eligible for FDA pre-market approval programs (e.g., PMA, 510(k), DeNovo classification, HDE). These studies may sometimes transition directly to pivotal trials, bypassing traditional feasibility studies. EFS primarily focuses on innovative, high-risk devices intended for the PMA pathway and requiring clinical investigation. Devices in the FDA's Breakthrough Device Program, which accelerates approval for transformative technologies, may also be suitable for the EFS pathway.

Differentiating between novel and equivalent devices is an often-discussed topic in the literature, both in general and specific to EFS. A comprehensive list of elements to consider in making the

decision to undertake an EFS for a novel device (see **Box 3**) is provided by Herrmann et al. (2022),[27] who illustrate how EFS can be conducted for those devices that are new, unapproved, or for those already approved but with a different indication.[27]

Suggested preparatory steps for an EFS are proposed by Holmes et al. (2022)[29] who emphasize the need to check the availability of predicate devices. Overgaard et al. (2023)[51] do not specifically address EFS, however, they provide a thorough discussion of the importance of distinguishing between devices which are truly novel and those that are equivalent to others already approved. To make the distinction, the authors suggest analysing technical, biological and clinical features of the device. They further provide five general levels of innovation in implantable orthopaedic devices as they relate to modifications, including genuinely novel devices, that may be useful for classifying devices eligible for an eventual EU EFS program (**Box 4**).[51]

Box 3: Elements to consider in deciding whether to undertake an EFS

Use of novel technology	Reports of prior clinical studies
	Design concept and potential benefit(s)
	Detailed Device Evaluation Strategy (DES), including initiation of the study based on a risk assessment
	Reports of prior bench, laboratory, and non-clinical testing
	Additional computational or virtual modelling
EFS design	Risk analysis and mitigation
	Human subject protection measures
	Increased monitoring
	Use of patient-reported outcomes
	Tracking safety end-points
	Stoppage rules
	Staged study
	Limited enrolment
	Informed consent
	Independent assessor/monitor of data collection
	Caregiver engagement

Source: Herrmann et al (2022)[27]

Box 4: Levels of innovation for implantable orthopaedic devices

Levels of innovation proposed by Overgaard et al (2023) to distinguish between predicate and truly new devices

i) design modifications to optimize existing implants that would not directly influence implant performance, fixation or the patient,
ii) additions to existing implants (e.g., additional sizes),
iii) design changes that directly affect implant performance or extensions to a new patient group,
iv) material changes or changes in the manufacturing process for the same material
v) innovation, as in a "completely new implant design, feature or material"

Level v) devices, including implantable and any other higher risk devices that will require clinical investigation for approval could presumably be candidates for EFS in situations where clinical testing is needed to further the design, delivery or features of the device and nonclinical testing is not sufficient, whereas considering whether modifications to existing devices such as those described in levels i) through iv) would be eligible as candidates for an EFS program would likely require further analysis.

4.2. EFS Eligibility Criteria and Foundational Principles

4.2.1. Significant vs. Not Significant Risk Devices

Explicit eligibility criteria for the US FDA EFS program are not specified; however, the FDA website and guidance provide information on the scope of the program, the when and why an EFS might be pursued.[73,74] Though EFS are not necessarily always included in clinical evidence to support approval, a main assumption is that the device will eventually be eligible for various FDA pre-market approval programs for medical devices (including PMA, 510(k), DeNovo classification, HDE, see also Table 6), [35]The EFS program is not only for innovative, high-risk devices, but it is geared toward investigations of these types of devices where the PMA pathway is indicated and CI is required. Some devices may also be part of (or future candidates for) the FDA Breakthrough Device Program, an expedited approval pathway for highly innovative devices that meet specific criteria for expedited consideration (e.g., significant improvement over existing technologies, no clear alternatives exist), which is referenced on the FDA EFS website.[73,75,91]

To be suitable for an EFS, Herrmann et al (2022),[27] Holmes et al. (2022)[29] and Ibrahim et al. (2020)[35] underline that a device is usually early in its development, before the design has been finalized. Among the steps suggested to determine the need for undertaking an EFS, authors mention gathering background information on alternative treatment strategies,[29] determining the level of novelty of the device by checking availability and use of predicate devices,[29,44] conducting early performance analysis, performing detailed assessment of test results, considering potential iteration of design.[29]

While the study from Callea et al. (2022)[6] highlights two primary principles for EFS eligibility::

- the necessity for human subject testing for further development, and
- a benefit-risk profile that favours patient safety and advancement of medical technology.

Similarly, when discussing new MDs, Marcus et al. (2022)[44] and Overgaard et al. (2023)[51] stress the importance of considering a benefit/risk ratio for the patient involved in the study, as well as the benefits that the new device could bring to a specific group of patients. According to Holmes et al. (2022)[29] and Ibrahim et al. (2020),[35] evaluating the size of the potential population and the clinical need targeted by the device are prerequisites, as also outlined by the FDA and the MDIC.[74,78] Along the same line, Overgaard et al. (2023)[51] state that "new technologies should not be introduced simply for their own sake, and the clinical benefit or clinical issue, that is, a better outcome for the patient or a simplified or faster procedure, must always be at the centre of attention". Herrmann et al. (2022) also discuss the type of patients and suggest the target populations for a new medical device should be patients with serious conditions who lack treatment options.[27]

Though focused on the United Kingdom (UK) regulatory process for devices, Campbell et al. (2018)[7] reflect on the benefits that a new MD could bring to patients. While discussing the value of innovation of MDs, the authors propose a system to check manufacturer claims of benefit of new technologies that can be conducted by the National Institute for Health and Care Excellence (NICE) to decide whether to include the device in the NHS. Although not proposed for EFS, this system considers some aspects worth considering, including the benefits that the innovation could bring to patients (such as quicker recovery, less time spent in hospital) and the benefits to the health system (such as shortening waiting lists, cutting treatment costs).

In summary, eligibility for an EFS hinges on a combination of developmental readiness, clinical need, and potential patient benefit, ensuring that studies contribute meaningfully to advancing medical device innovation while prioritizing patient safety.

4.3. Preclinical Testing

Pre-clinical testing refers to non-clinical testing which is conducted prior to the first clinical use. Although pre-clinical testing is often used as a synonym of non-clinical testing, the latter involves a larger subset of testing, including: "cell-based assays, organ chips and micro-physiological systems, computer modelling, other nonhuman or human biology-based test methods, such as bioprinting, and animal tests".[92]

The FDA EFS IDE guidance contains a chapter for the "Report of prior investigations" covering the design concept, device evaluation strategy, as well as pre-clinical testing and any prior clinical

information, all aimed at showing why an EFS may be warranted to further the development of the device and justify a clinical investigation and the associated risk that poses to patients.[74]

When focusing on pre-clinical testing requirements specifically for EFS, the literature highlights the importance of analysing pre-clinical testing undertaken thus far, to determine whether to undertake an EFS.[74] Bench and animal pre-clinical studies for novel devices may not be sufficient to inform device design, functionality and safety, necessitating early clinical testing to identify "appropriate modifications to the device or the procedure to use the device, to optimize operator technique, to refine the intended use population, and to refine non-clinical testing and development of subsequent clinical study protocols," according to Weiss and Farb (2023).[65] As Holmes et al. (2022)[29] point out, an EFS study is based on less non-clinical data than is usually required for larger or later stage clinical trials.[29] Despite more limited data requirements than other studies, Grohman et al. (2016)[93] and Herrmann et al. (2022),[27] respectively, reiterate the importance of collecting pre-clinical data, which may provide informative data complementing limited clinical evidence and may support basic device and procedure safety for FDA approval.

Zimmerman et al. (2019)[94] describe an EU-based study on 30 patients, providing a useful description of the process from laboratory testing to clinical use, with detailed descriptions of the sequence of pre-clinical to clinical testing (on one patient). The article provides some insights into the transition from pre-clinical investigations to a first-in-human volunteer study in the European environment to define guidance for an EU EFS program and serves as an example of a pathway including an EFS phase in the EU.

Other authors discuss the role of pre-clinical testing for innovative devices in general. According to Brooks (2017),[4] non-clinical laboratory testing encompasses microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf-life, and necessary animal testing. Similarly, Overgaard et al. (2023),[51] in discussing orthopaedic surgeon's expectations in uptake of innovative implants, cite "good pre-clinical documentation (including design and material characterization, biomechanical and bio-tribological testing as well as human donor, usability and animal studies if applicable)".[51]

Also Marcus et al. (2022)[44] discuss the need of pre-clinical testing in an extension of the IDEAL-D framework for medical devices. The authors provide a detailed consideration of clinician, patient and system perspective studies needed before a first-in-human study, stressing that a comprehensive risk assessment, including Failure Modes and Effects Analysis (FMEA), should guide the stratification of device risks. For instance, clinician and patient perspective studies are suggested for medium and high-risk medical devices, whereas system perspective studies are recommended for high-risk devices. By adopting structured, evidence-based approaches, the development of safe and efficacious MDs can better meet both regulatory and clinical expectations.

4.4. Clinical Evaluation

In the EU, article 2(44) of the MDR defines clinical evaluation as a "systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer", and is required for all MDs to demonstrate conformity with the General Safety and Performance Requirements (GSPR) in Annex 1 of the Regulation.[80] The Clinical Investigation Report Template is described in MDCG Guidance 2020-13.[90] Though relevant for EFS, the templates and guidance for clinical investigations under MDR are not necessarily tailored or specific to EFS.

In the US, as mentioned above, the collection of clinical data is governed through the IDE process, and there is a specific IDE for EFS.[1,74] Templates for the clinical trial agreement and for patient informed consent and other resource materials have been developed by the MDIC for the US EFS program, but no specific template for the clinical investigations in an EFS is currently provided.[95]

4.5. EFS Study Conduct

4.5.1. Clinical sites

As described by Holmes *et al.* (2016),[28] there are several key features or qualities to look for in choosing clinical sites for conducting EFS. 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 also 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. Also Overgaard et al. (2023),[51] when discussing the selection of qualified centres for performing clinical studies, mention similar characteristics, including qualified personnel, the availability of required infrastructural network and the centre's experience of conducting clinical, well-designed studies. These same points are widely described in the MDIC guidance,[78] stressing the relevance of having an experienced investigator and staff, as well as the availability of facilities with proper equipment. Several papers also comment on the number of sites that should be engaged in the study. According to Holmes et al (2022), EFS studies usually engage three to five centres, which work closely with the sponsor in designing the protocol, collecting data, and evaluating procedural aspects.[96] Furthermore, Callea et al.[6] 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.

To facilitate the identification of suitable sites for EFS and address some of the challenges stemming from lengthy IRB/IEC approval, administrative inadequacies or lack of experience, difficulties in contracting and obtaining reimbursement, and inadequate access to the targeted patient population,[28] the MDIC provides a map of EFS sites around the US and outlines a list of key characteristics that clinical sites should possess to conduct an EFS. These include:

- Experienced investigators: clinical sites should rely on investigators who have experience of EFS studies, first-in-human trials, and who understand the risk mitigation strategies needed for novel devices.[74]
- Robust IRB protocols: because of the high risks that patients could face when enrolling in an EFS, clinical sites should have the ability to handle patient consent processes as well as ethics reviews.[97]
- Access to patient population: a clinical site should be able to recruit the patient population for testing new, high-risk devices.[79]
- Ability to handle financial aspects: clinical sites must be able to handle financial aspects, including budgeting and contracting, which are often responsible for delays in EFS studies.[79]

To support sponsors in the selection of clinical sites, the MDIC has developed a matrix to compare and rank clinical sites before initiating an EFS. The Pugh Matrix (**Figure 9**) uses a quantitative approach to rank sites according to criteria which should be considered for selecting clinical sites.[95]

Figure 9: Example of Pugh Matrix for sites selection (MDIC) (Source74)

Site Pre-Selection			Site A	Site B	Site C	Site D	Site E	Site F	Site G	Site H	Site I	Site J
	Definition for criterion's score	Weight										
Investigator's expertise in the field	1=Poor, 3=Fair, 9=Strong (Elite)	9	3	9	9	9	1	9	9	3	9	9
Commitment of Investigator/Passion	1= None, 3= Dedicated, 9=Partner	9	3	9	9	1	9	1	3	3	1	3
Availability of the Investigator	1=Limited , 3=Fair , 9=Available when needed	9	9	9	9	1	9	1	9	3	1	3
Site's research staff	1=≤2 people , 3=3-4 people, 9=>5 people	1	9	3	1	9	1	3	9	3	1	3
IRB's experience with EFS	1= None/poor; 3= modest; 9= multiple reviews/year	3	1	3	3	9	1	9	9	3	1	9
Volume of precedure/month	1= <3/mo (low), 3=8-12/mo (medium), 9= > 12/mo (high)	3	9	3	9	9	1	1	3	3	3	3
Proximity of the site (travel time)	1= F>4hours (poor), 3= 2-4 hrs (fair), 9= <2 hours	3	9	1	9	9	9	3	3	9	3	1
Notoriety of the site	1=Limited, 3=Fair, 9=Prestigious (High)	1	9	1	1	9	1	3	9	3	9	9
Record for Site Start-up time	1=>6months; 3=4-6months; 9=<4months	3	1	9	9	1	9	3	9	3	9	1
Total Score			240	298	362	228	260	162	288	168	166	192
Ranking			5	2	1	6	4	10	3	8	9	7

4.5.2. Study participants and patient involvement

As for the number of participants to be involved in the study, numerous authors agree on limiting the study to a small group of subjects (15 or fewer), with the possibility of expanding the study to include

more participants once a satisfactory safety profile has been maintained during the study.[27,29,35] The US FDA EFS program does not set a minimum or maximum number of patients, but highlights in the IDE guidance that it be limited, suggesting a small number (usually fewer than 10), though subsequent presentations and frequently-asked-questions mention fewer than 15.[74]

A guiding principle to govern involvement and protection of patients in EFS is embodied in the concept of Participatory Research (PR), a research-to-action approach that emphasizes direct engagement of local priorities and perspectives through systematic inquiry in collaboration with those affected by the issue being studied, ultimately aimed at producing actionable change.[98] PR emphasizes using research methods that foster genuine and meaningful participation of various stakeholders in a democratic manner, prioritizing shared decision-making and collaboration to ensure the research is relevant and impactful.[99]

PR refers to research conducted 'with' patients rather than 'to', 'on', or 'about' them, and actively involves patients at core stages of research design, development, and delivery, distinguishing it from merely recruiting participants or having patients complete surveys.[100] The terms 'participatory research' and 'patient and public involvement' (PPI) are often used interchangeably to describe this collaborative approach. Despite differing definitions and sub-definitions in the literature, the common goal is to involve patients actively, ensuring that their insights and experiences shape the research. To that end, several papers from the scientific and grey literature search provide insights on overall goals as they relate to patients, how to actively involve patients, ensure that they are adequately informed regarding the increased risks associated with EFS, and how to gather patient preferences and feedback.[2,5,12,40,50,51,61]

Patient experience data, encompassing patient reported outcome measures (PROMs),as well as other types of patient inputs, should be incorporated to ensure that benefits and risks be balanced for new technologies.[12,24,51,61] For instance, patient-reported outcomes can provide additional insights into clinical outcomes that may be relevant to the patient population under an EFS study.[27] Benz et al. (2020) describe how patient preference information can be incorporated into the research process and cite resources and guidance from the FDA on patient preference information studies and the patient centred benefit-risk framework and catalogue of patient preference methods based on regulatory and health economics research from the MDIC as useful resources.[101,102,2] In their summary of an FDA virtual public workshop on spinal device clinical review, Devlin et al. (2022)[12] address PROMs, but also clinician reported outcomes and performance outcomes and provide strategies to increase enrolment of under-represented groups and diversity in spinal device trials.

Regarding the stage at which the incorporation of patient preferences could be most beneficial, a literature review assessing the benefits and barriers to implementation of user involvement in medical devices found that involvement of users at all stages of product development was beneficial;

however, it was most beneficial if implemented during the early stages (e.g., design concept), design and development, prototype testing, and clinical trials.[40] In their IDEAL-D Framework, Marcus et al. (2022)[44] recommend patient preference testing before proceeding to first-in-human clinical investigations.

Brown et al. (2021)[5] stress the importance of informing patients of risks that may be unknown in first-in-human studies and also address equal access and protection of vulnerable groups, all of which is of particular relevance to EFS given the greater uncertainty related to the benefit-risk and safety profile. Among the papers focused on EFS, several authors cite the need to improve informed consent forms to better account for increased risk for patients in EFS and consider criteria for selecting investigation centres and patients, particularly focusing on cultural and clinical expertise and patient risk profiles.[6,27] Holmes et al. (2016)[30] counsel that patient groups should provide input on study protocols and informed consent forms to encourage development and investment in clinically meaningful device innovation by highlighting the needs associated with their specific clinical conditions and advocating for appropriate protocols and devices to meet these demands.

Finally, some papers focus on ethical issues in medical device development.[34,50,53] In particular, Páez et al (2021)[53] highlight the importance of considering ethical aspects when evaluating the need to conduct clinical trials and consider the adoption of an ethical system for device evaluation, that could be an efficient and cost-effective measure. Olimid et al (2018),[50] instead, reflect on the impact that the new MDR could have on ethical principles. According to the authors, the new stringent requirements could enhance patient dignity, informed consent and ethical governance.[50]

4.5.3. Medical liabilities

EFS can pose increased risk for patient harm and injury and as such, medical liability needs to be addressed.[30] Holmes et al. (2020)[28] list contractual agreements to manage liability risk in conducting EFS, noting that responsible parties should be identified at the outset to avoid delays or even discourage pursuing EFS at all. Holmes et al. (2020) also refer to medical liabilities when discussing patient involvement, as in most sponsored clinical research trial participants typically seek indemnification for subject injuries from the sponsor of the device being studied.[103] Callea et al. (2022),[6] in interviews with European experts on the feasibility of a European EFS program, note a lack of a comprehensive insurance system as well as clear guidelines regarding the specific medico-legal responsibilities associated with conducting these early-stage investigations, represent significant challenges for sponsors, clinical centres and regulatory bodies. Additionally, under the MDR, Annex XV mandates that sponsors provide proof of insurance or equivalent indemnification for participant injuries during clinical investigations, further emphasizing the need for robust liability frameworks and adequate patient protection mechanisms to address these challenges effectively.[104]

4.6. Device Modifications During EFS

4.6.1. Iterations of the device

As described by Ibrahim et al. (2020), guidance provided by the US FDA EFS program specifically addresses and facilitates "device iteration during the study", espousing a "just-in-time" testing approach for the type and timing of nonclinical tests to justify initiation of an EFS.[35] This approach "focuses on addressing the highest risk failure modes prior to initial clinical use, and allows for deferring some nonclinical tests, when appropriate, until the device has been finalized." [35] Herrmann et al. (2023)[27] also highlight aspects of the FDA EFS IDE guidance that facilitate making changes to the device during an EFS study as an integral part of the often iterative process of device development.

The MDR distinguishes between changes that are substantial or non-substantial. According to art. 75 of the MDR, application and approval is required before implementing substantial changes.[105] The timeline for assessing the degree of change is 38 days, with an additional 7 days if expert 'consultation is required.[106] Despite that a list of substantial changes is provided by the MDCG, this is non-exhaustive, and distinguishing between substantial and non-substantial changes and identifying the right regulatory response to apply is not always clear.[107] According to Overgaard et al. (2023),[51] since it is quite difficult to understand in advance the effects that changes could have on a device, any modification should be evaluated in line with a risk-based approach.

Three additional papers not specific to evaluation of the EFS program refer to post-market device design or process modifications that are approved through the Supplements program of the US FDA that may have relevance to EFS studies on devices with a new indication of use.[8,14,49] The FDA allows manufacturers to submit a supplement to the original PMA application to make modifications to previously approved devices that are aimed to incrementally improve safety and efficacy, specifying five types of supplements, which include: panel track, 180-day track, real-time, special (immediate) track, 30-day notice, and 135-day track.[14,49] The modifications can cover changes to "device indication, manufacturing, labelling, packaging, or design," with only a "panel-track supplement" (significant design changes) requiring additional clinical testing.[8] Analysis of supplements by Dubin et al. (2023)[14] concluded that devices associated with supplement applications were associated with a 30% increased risk of recall.

4.6.2. Quality and risk management

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.[74] In quality and risk management, devices enrolled in the US FDA EFS program are often classified as Category A (experimental) devices by the

Centers for Medicare & Medicaid Services (CMS), indicating unresolved safety and efficacy questions and uncertain potential, according to the FDA.[65] Therefore, emphasis should be placed on justifying the suitability for EFS participation, conducting comprehensive risk analyses, and implementing mitigation strategies with contributions from specialized experts on patient safety.

Suggestions by Herrmann et al. (2022)[27] to mitigate risk include EFS protocols that may include guidelines for pausing or terminating the clinical study when specific safety events occur; restricting the number of participants in the EFS to help minimize overall risk to subjects during the initial stages of the investigation (e.g., staged enrolment of 1-2 subjects with evaluation before enrolling others); fully informing participants in an EFS of all risks related to the study. In the EU, MDCG 2024-3 guidance also provides some measures to evaluate and reduce risk, particularly in relation to early clinical studies of high-risk devices, including limiting patient numbers and testing and evaluation on the first patient before continuing on to the next.[88]

4.7. Regulatory Bodies Interactions

4.7.1. Dialogue with regulatory bodies

A substantial body of literature has addressed the concept, structure and wisdom of dialogue between regulatory bodies and developers of innovative medical technologies.[20,60,62,108] Dialogue, or more precisely, *early* dialogue between institutions and producers can be defined as “exchanges between manufacturers and public institutions to obtain guidance on the evidence requirements for regulatory and reimbursement purposes”.[108,109] At least a decade ago, interviews conducted with agency representatives in seven major jurisdictions, including the US, recognized several potential benefits of early dialogue between manufacturers, regulators and HTA bodies, including greater opportunity to enhance the quality and type of clinical evidence to support approval and coverage decisions, increased efficiency for timelines to market, enhanced synergies between regulators and HTA bodies, all of which provide incentives to produce safe, effective, and ideally cost-effective innovative MDs.[60]

In the US, there are a number of processes for seeking advice from the FDA, from MD development phases and continuing throughout approval pathways. Current collaborations for advice between the FDA and sponsors of MDs are governed by the FDA Modernization Act from 1998, with final guidance dating from 2001, and through the Medical Device User Fee Amendments. [110,111] User fees are required when a company makes a pre-market submission or registers to market a device in the US, however, there are no fees for seeking advice.[111] The process of requesting formal feedback from the FDA dates from the pre-IDE program that was established in 1995, to help determine the need for an IDE.[112] Currently known as the Q-submission program, it is a voluntary program to guide

requests for formal feedback from the FDA on MD development, from early stages (i.e., planned non-clinical and clinical studies) to planned marketing approval submissions.[13] The feedback may be in the form of written communication or meetings and generally covers advice regarding the need for an IDE to initiate a clinical investigation to support a planned pre-market approval submission, including advice on various of the pre-market approval pathways, such as PMA, De Novo, 510(k), etc. The three types of Q- Submissions (Q-Subs) include Pre-Submissions (Pre-Subs), Submission Issue Requests (SIRS), Study Risk Determinations, and informational meetings, as well as a means to track instances of FDA advice in other documents, such as submissions associated with the Breakthrough Devices Program.[112] The Q-sub program provides a means to track (a unique identification number starting with Q) the various instances of interaction with the FDA, and sponsors are encouraged to provide an overview of expected interactions to avoid overlap and confusion. Timelines for written feedback and scheduling meetings are provided, ranging in general from 60 to 90 days, depending on the Q-Sub type.

In addition to details provided in guidance for the Q-Sub program, the CDRH has an Office of Product Evaluation and Quality (OPEQ) with the aim of implementing the evaluation and approval program areas. A series of eight OPEQs are dedicated to specific therapeutic areas; these eight are referred to as Review Groups in the FDA's EFS website (see **Error! Reference source not found.** above), and sponsors considering application to the EFS program are encouraged to contact the appropriate group (e-mails are provided).[73] There are also 18 panels (organized according to therapeutic area) which form the Medical Devices Advisory Committee, tasked with advising the FDA Commissioner on issues related to MD safety and efficacy. [113]

The need for establishing early dialogue during an application process is widely discussed by authors when debating the European landscape. Despite the fact that dialogue between stakeholders is often key in the development and non-clinical and clinical investigation processes in the US, including for an EFS, in contrast there are no harmonized pathways for dialogue during the pre-market phase at present in the EU.[6] While EU MDCG Guidance 2022-14 encourages NBs to organize structured dialogue with manufacturers "before and during the conformity assessment process aimed at regulatory procedures where this is useful to enhance the efficiency and predictability of the conformity assessment process", such dialogue is unlikely to support early MD development phases, including for EFS, and no formal process currently exists to govern such interaction.[114] The MDR and HTAR have both identified areas in the development and approval process where manufacturers may seek guidance from dedicated Expert Panels during pre-market approval processes or for Joint Scientific Consultations for HTA. Thus far, however, there are only two pilot programs in the EU in this area, one for obtaining Expert Panel advice for high-risk MD manufacturers and another for orphan medical device manufacturers. [115]

According to Siontis et al. (2024)[58] the lack of early consultation with regulatory bodies is partially responsible for high costs and long approval times, as manufacturers are not able to clarify the clinical evidence required for their device. Two studies confirm this challenge: according to a quantitative survey conducted with 68 experts working in MD manufacturing and regulation, as well as by qualitative interviews with eight clinical evaluation consultants from EU countries, the biggest challenge in the EU, with the new MDR with more stringent requirements, is understanding the amount of data required to collect enough clinical evidence to go ahead with the study.[38,39] According to study participants, the lack of guidance results in increasing queries during the review by the NB, thus, in delays and longer times for approval.[38,39] Not only could early dialogue prevent delays and high costs due to unnecessary testing,[4,27,38] but it could help improve CI design needed to support later reimbursement procedures.[34] Tarricone et al. (2023)[62] propose the establishment of an accelerated access pathway for innovative high-risk medical devices in the EU, and specifically refer to early dialogue with regulatory agencies as a key potential advantage for future applicants; as yet, however, such a pathway has not yet been established in the EU.

Many authors focus on the key role played by early dialogue in EFS. As described by Brooks (2017),[4] Ibrahim et al. (2020),[35] and Holmes et al. (2022)[29] a fundamental element of the FDA's EFS program is the provision for dialogue with regulatory authorities when determining whether to conduct an EFS, during preparation, design and conduction of the EFS, and when deciding to transition to post-EFS phases (e.g., traditional feasibility studies or pivotal studies). Herrmann et al. (2023)[27] define early communication as "critical for enabling the initiation of EFS studies in the US" and, along with Holmes et al. (2022),[29] stress the key role that close communication among sponsors, investigators and the FDA plays in addressing device performance issues and safety concerns. Callea et al. (2022),[6] following an FDA recommendation, include interactive dialogue among regulators, sponsors and innovators both before and during EFS IDE submission as a key principle underlying the program, along with predefined timelines for submission and review and risk-based management of modifications to clinical protocols and device designs during EFS. According to Herrmann et al. (2023),[27] having the FDA involved in the study could also shorten data collection periods for marketing applications and results in early access to new MDs for US patients. On the same line, Brooks et al. (2017)[4] highlight the importance of having an early interaction to avoid unnecessary testing, get clear timelines, and optimize budgeting. Indeed, in the US, consultation with the FDA is recommended prior to study initiation, especially if the study results are intended to support a US marketing application, even if the trials are conducted outside the US.[4] According to Brooks e al. (2017)[4] the FDA can "become an ally and collaborator in codevelopment", thanks to their knowledge and expertise. This collaboration between sponsors and the FDA is an integral part of the approval process and utilises a 'just-in-time testing principle' for data.[29] This dialogue often takes the form of pre-submission meetings, which play a pivotal role in the process by enabling early discussions on

proposed testing strategies.[27] The pre-submission pathway is a key opportunity to get guidance and feedback on technical and regulatory questions from the review team appointed.[4,27,57] For this phase, the FDA sets up a dedicated Q-submission process, to which the FDA commits to respond within 75-90 days, either in a written format or during a face-to-face meeting.[4,35]

4.8. Financial Barriers

4.8.1. Rising Costs for Innovation

According to a recent study analysing the costs associated with the development of therapeutic complex devices in the US between 2000 and 2018, the mean development cost for a complex device, without including the costs of post approval studies, was $54 million.[57] When considering the cost of failed studies and cost of capital, this rises to $552 million.

The costs of bringing a complex device to market in the US and the EU is discussed by a number of authors. According to Donnelley et al. (2021),[13] high regulatory testing costs are usually accepted with the expectation to recoup losses once the device is on the market; however, high risk devices take longer time to reach the market, and the costs are much higher due to the clinical testing that must be conducted. When discussing the new and more stringent technical and administrative requirements in the EU for high-risk devices compared to the US??, Fraser et al. (2022)[20] suggests that stricter requirements could lead to even longer time for bringing a device to market, whereas Sertkaya et al. (2022)[57] point out that, as a consequence of stricter rules since 2021, manufacturers have found themselves having to rethink their strategy in the EU.

High financial regulatory costs and the costs of generating clinical data in the EU have also been highlighted as main barriers by Guerlich et al. (2023)[24] and Kearney and McDermott (2023).24,38 According to the authors, as costs of the clinical investigation outweigh the potential return of investment, manufacturers may discontinue certain MDs and remove them from the EU market or postpone the launch of a novel device.[38]While the MDR was adopted to address the significant evidence gaps for high-risk devices under the previous system, a risk-based, balanced approach is needed to ensure that administrative burdens and requirements that do not improve patient safety do not impede patient access to potentially life-saving innovative devices.

In the US, the EFS program serves as a key facilitator to tackle these main barriers associated with time and costs. In the realm of economic sustainability, challenges related to the increasing difficulty in securing funding for traditional research and the strain on clinical revenue were recognized.[4] Burdensome interactions between industry sponsors and clinical sites, coupled with high local testing costs, have exacerbated the financial challenges associated with MD trials.31 Various sponsors and companies have focused on the problem of unforeseen costs, for instance, for extended patients or

contract agreement timeline, which are going to contribute to the financial barrier that sponsors face, but that could be consider to have a realistic overview of costs for an EFS.[116]

4.8.2. Coverage for investigational devices

To overcome some of these challenges, the FDA issued an EFS Guidance document.[31,74] This EFS program is recognized for its efficiency in reducing both time and costs (by requiring less clinical data and receiving faster approval), a benefit that is underscored in the CDRH 2018–2020 Strategic Priorities report.[6] In particular, coverage depends on the categorization of the device: routine care costs for A IDE studies, meaning for experimental devices where safety and efficacy are yet to be established, may be covered by Medicare, whereas costs for B IDE studies, aimed for non-experimental devices with established safety data, are covered.[117]

The EFS approach to MD development is praised for its capabilities in early trials, ensuring patient protection under IDE 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.[27]

4.9. Timelines for EFS vs other study types

Concerning the length of application review, Herrmann et al. (2023)[27] note that the FDA has tried to shorten review times for IDE submissions, with the median time for approval at 30 days since 2014. When discussing timelines and steps for conducting an EFS, Holmes et al. (2020)[103] focus on the time needed to enrol patients in the study. According to the authors “the patient population for whom the device is intended must be readily available and already screened for potential participation in the EFS study by the time IRB and contract negotiations are completed”. As far as patient enrolment is concerned, Brooks (2017)[4] notes that if after 30 days the FDA has not provided any response following the IDE application, patient enrolment can begin.

After an EFS, the progression typically includes more comprehensive trials and advanced regulatory processes. According to Holmes et al. (2020),[96] if the EFS has been successful, the sponsor and the FDA can decide to broaden the study’s scope by including more patients and sites, which is usually needed before submitting a PMA request to the FDA. In this case, a traditional feasibility study is conducted, which aims at evaluating the near-final device design, utilizing extensive non-clinical or existing clinical data.[27,103] However, as pointed out by Ibrahim et al. (2020),[35] the clinical data collected through an EFS could allow for moving directly into a traditional pivotal trial, without conducting a traditional feasibility study. This is also highlighted by the MDIC,[79] stating that the

completion of an EFS could shorten the time for the device entering the market, as a feasibility study may not be necessary.

Nevertheless, the transition from one study to another is not always smooth. Herrmann et al (2023),[27] Holmes et al (2020),[32] and Ibrahim et al (2020)[35] advocate for a systematic re-evaluation in a prospective and multicentre setting, emphasizing the necessity of a smooth transition between different phases.

When discussing the benefits of the EFS program, Ibrahim et al. (2020)[35] point out that the same data collected through an EFS can also be used to support future regulatory submissions. For instance, clinical data can be used to secure Breakthrough and Humanitarian Use Designation requests, such as in the paediatric field, aimed at devices that help patients with rare diseases or conditions.

Furthermore, the introduction of regulatory pathways characterized by short timelines and low assessment fees should also be considered. In the US, the FDA's EFS guidance document enhances the IDE review process by outlining the optional use of a device evaluation strategy.[27]

4.9.1. Regulatory system challenges

As described in Callea et al (2022),[6] in the EU there is a noted lack of standardized procedural frameworks for EFS, with existing procedures largely ill-suited for the frequent protocol or device modifications typical of such studies. Additionally, there are increased barriers for market access of high-risk MDs under the EU MDR, which disproportionately affect children and patients with rare diseases. Many of the key, even fundamental, features important to conducting EFS in the US mentioned by the many authors cited above are particularly challenging in the EU, not least among which, dialogue between regulators and MD developers and a lack of clear, focused guidance for these early-stage studies when MD design is not yet finalized. In addition, the decentralized nature of the EU system requires oversight from individual CAs in separate MSs, which introduces considerable variation in the process of seeking approval in the EU, as evidenced by the literature and the interviews conducted for this project as well as the documents collected for the PMAP database.

Adding to the difficulties are a number of challenges related to implementation of the MDR, primarily due to the disjointed process of seeking approval (and oversight) in different CAs in MSs of clinical studies, the limited capacity of the NBs charged with certifying new medical devices, not to mention the delays in implementing the information and tracking database designed to support the system, EUDAMED.[20,21,46] With more stringent requirements for clinical evidence and NBs, delays and difficulties were predicted by many,[21,45,46] and in fact, manufacturers have experienced increasing delays, which may have jeopardized timely access to new devices across the EU. The new and

significantly more demanding requisites for clinical data and documentation have also been problematic, especially for smaller companies. This has prompted calls from industry and other stakeholders for further reforms of the MDR (as well as the Regulation 2017/246 on in vitro diagnostic devices, IVDR)[118] [50]

There are also important challenges and barriers in the US system, despite the presence of a dedicated program for EFS. As Brooks et al. (2017)[4] report, the regulatory process for devices is often daunting, time-consuming, and expensive, aspects frequently unknown to diverse stakeholders. Holmes et al (2016, 2021) [30,32] and Leipheimer et al. (2019),[119] focus on some reasons for this, including lengthy reviews by Institutional Review Boards (IRB), inadequate infrastructure, limited access to suitable patient populations, complex contract negotiations, reimbursement issues, and unpredictability in study launch justification. According to Weiss and Farb (2023),[65] the stringent requirements for IDE protocol approval also represent an important barrier to early clinical research. While these findings highlight some of the main barriers associated with implementing and conducting EFS studies in different geographical areas, they also provide some ideas to improve the US EFS program, focusing on the ongoing effort to facilitate early interaction with regulatory authorities, streamline contracting processes, and leverage resources such as the MDIC.[65] Brooks et al. (2017),[4] on the other hand, mention the ongoing initiative to use mathematical modelling in preclinical phases to limit animal and human testing.

To overcome regulatory barriers, Holmes et al. (2016)[28] emphasize the importance of understanding U.S. regulatory requirements, providing regulatory toolkits, addressing IRB considerations, and clarifying responsibilities and liabilities. They also recommended the following measures:

- Forming working groups,
- Applying ‘just-in-time testing’ to facilitate device modifications,
- Standardising consent forms and IRB processes,
- Managing liability risk through contractual agreements.
- Collaborating with regulatory agencies and payers for reimbursement.

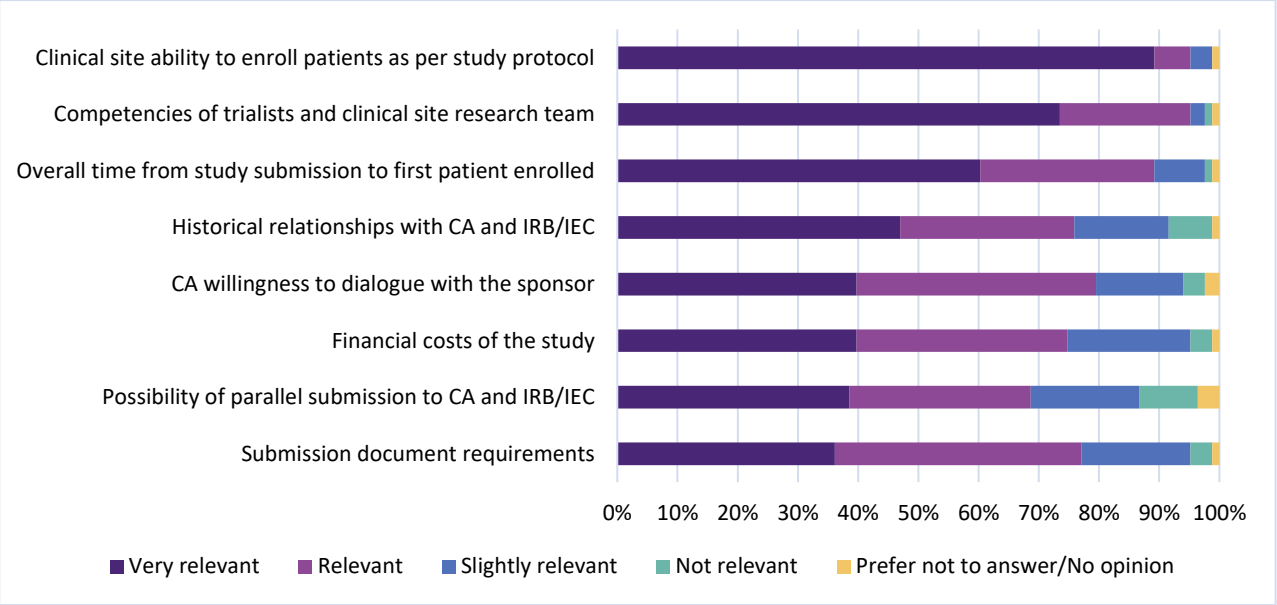
4.10. Stakeholders' perspectives regarding challenges of pre-market approval pathways

4.10.1. Survey with sponsors of clinical investigations

Sponsors of CI who responded to the survey expressed a strong preference for conducting pre-market studies in Europe (48% out of 83 responses) over the US (26%), followed by 18% of people indifferent to the two jurisdictions and 8% without a clear idea. This preference appears to be equally

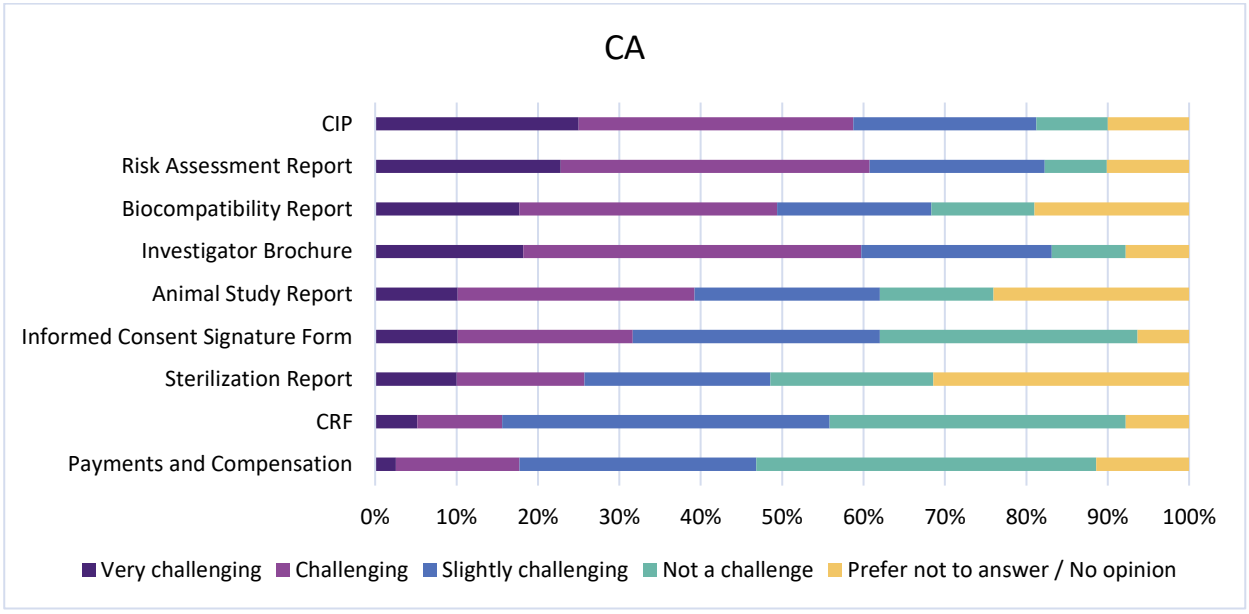
distributed among companies regardless of their size. The most important factors for stated preferences were related to the competencies of trialists and clinical site research teams, as well as the clinical site's ability to enrol patients as per study protocol; this was considered very relevant or relevant by 95% of respondents, followed by overall time from study submission to first patient enrolled (89%) (**Figure 10**). The identification of investigational sites willing to participate in pilot pre-market CIs was considered difficult or very difficult by 53% of EU and US respondents. The challenge was perceived more by micro, small and medium companies (62% consider it difficult or very difficult) and less by large companies (46%).

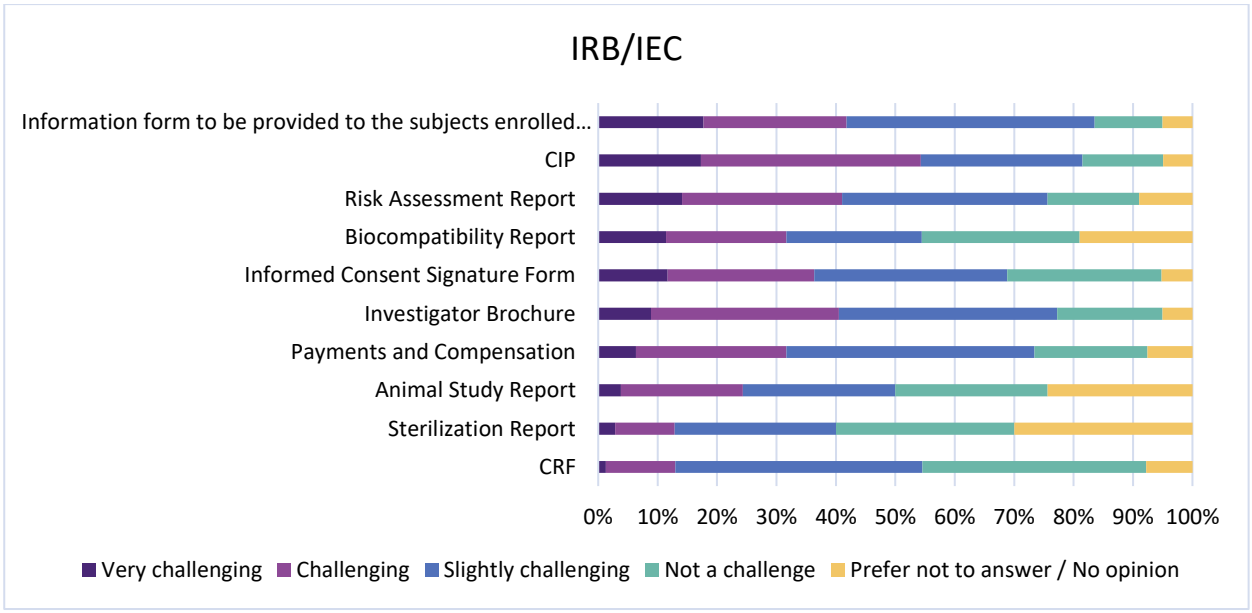
Figure 10: Key criteria that most influence the selection of a country for initiating a pilot clinical investigation



The risk assessment report and clinical investigation protocol (CIP) were deemed the most complex documents, since approval by CAs (IRB/IEC) was considered very challenging or challenging by 57-58% (39-53%) of the respondents, followed by the investigator's brochure (55% and 39%, respectively); approval of the information form to be provided to subjects enrolled in the CI and patient informed consent was considered more challenging by IRB/IECs than CCAs (**Figure 11**).

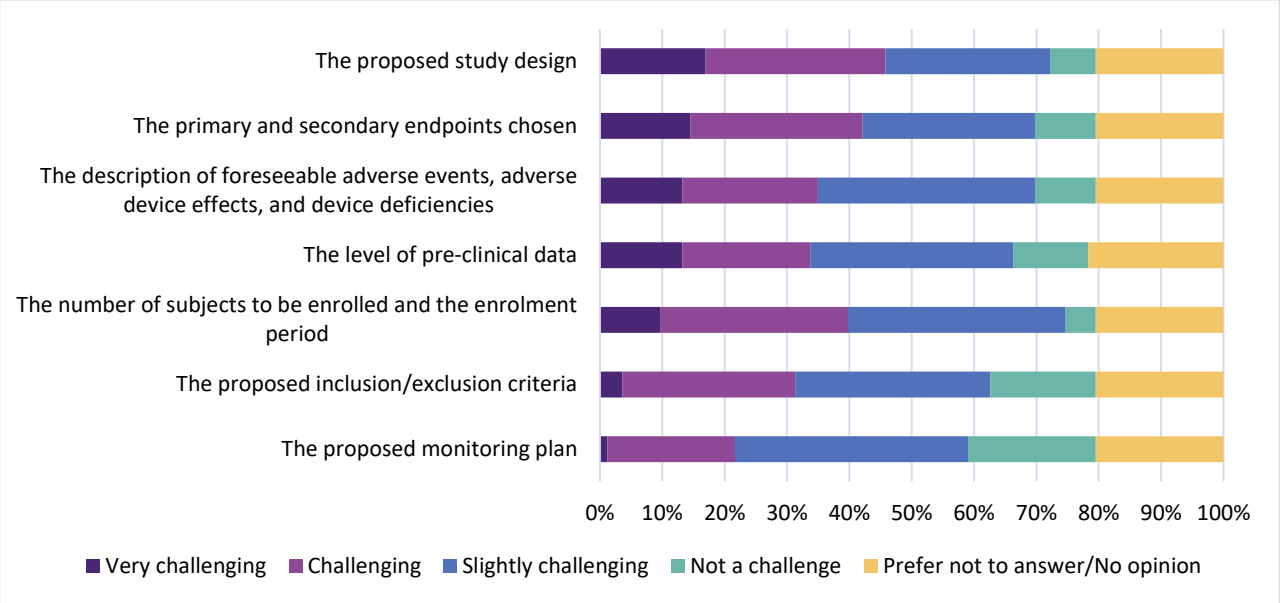
Figure 11: Most challenging document to get approved by CA (panel a) and IRB/IEC (panel b)





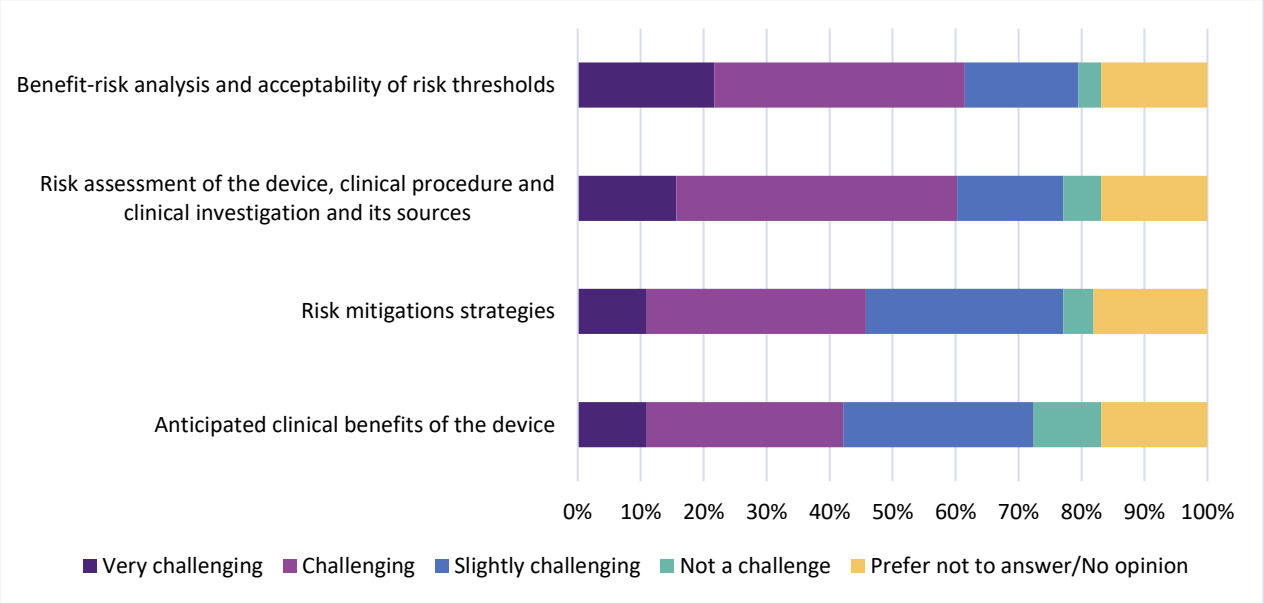
The proposed study design, primary and secondary endpoint chosen, and number of subjects to be enrolled and enrolment period were identified as the most difficult aspects to receive approval from CAs or IRB/IECs (they were considered challenging or very challenging by 46%, 42%, and 40% of the sample) (**Figure 12**).

Figure 12: Most challenging aspects of the CIP to receive approval from CAs or IRB/IECs



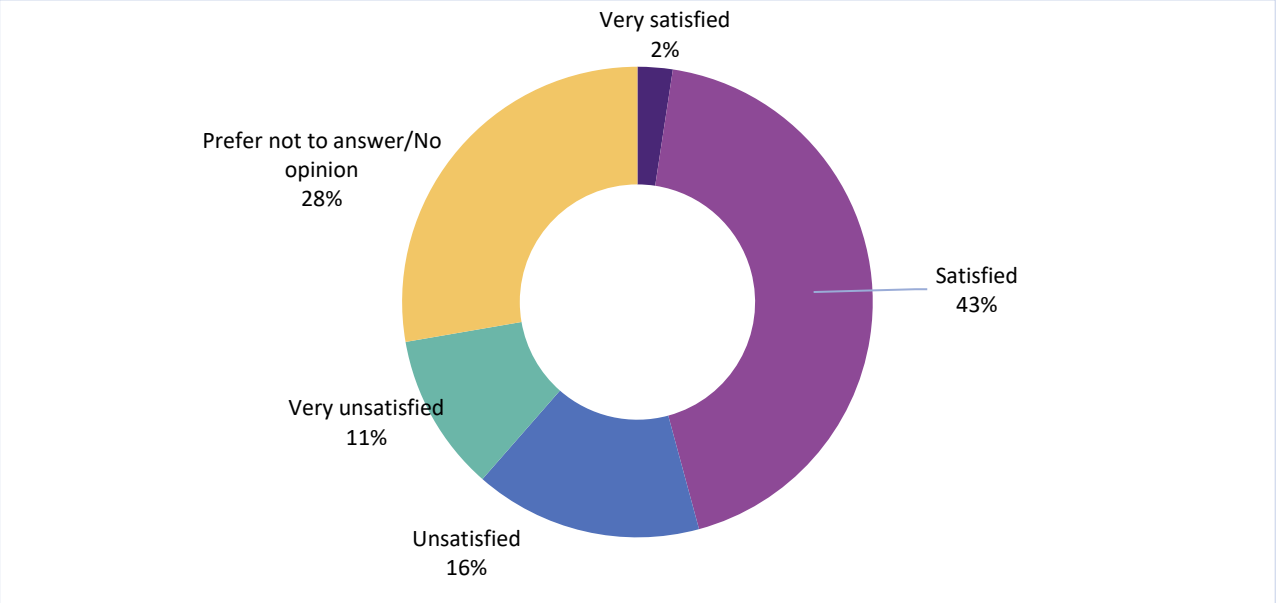
Over 60% of the respondents considered the benefit-risk analysis and acceptability of risk thresholds and the risk assessment of the device/clinical procedure/clinical investigation and its sources (**Figure 13**) the most difficult aspects to get approved by CAs or IRB/IECs.

Figure 13: Most challenging aspects of the benefits-risks assessment to receive approval from CAs or IRB/IECs



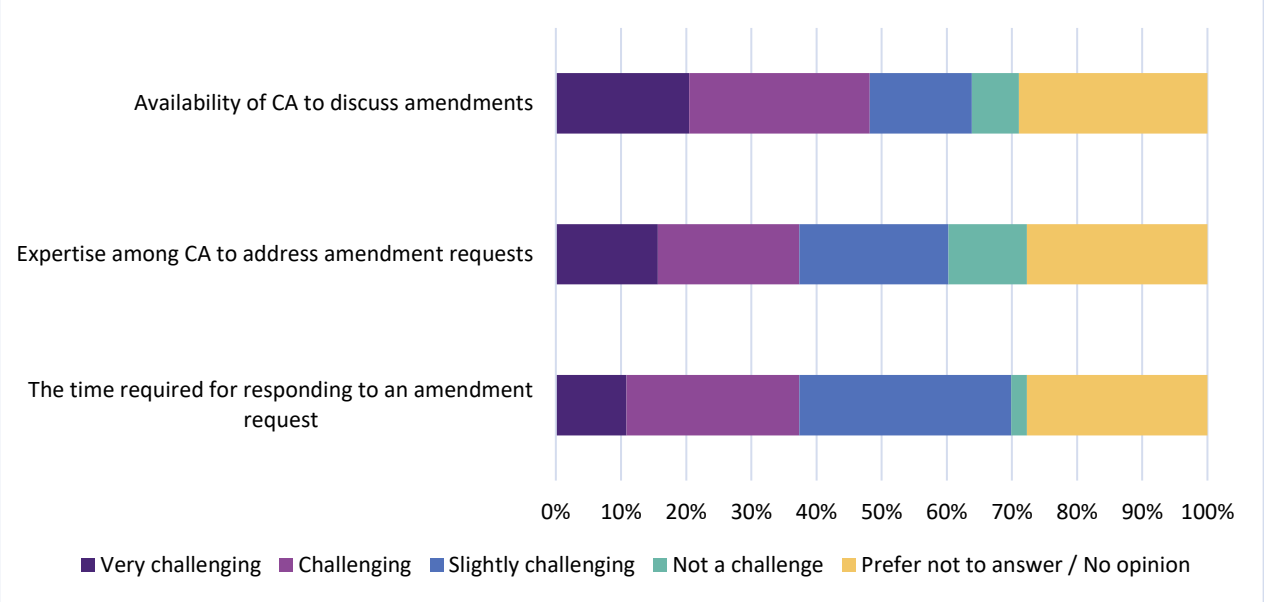
Respondents do not seem to be dissatisfied with the CA and IRB/IEC response times during the conduct of the study, given that only 16% declare they are unsatisfied and 11% very much unsatisfied (**Figure 14**).

Figure 14: Level of satisfaction with CA and IRB/IEC response times during the conduct of the study



Almost half of the respondents considered CAs openness to dialogue the most challenging aspect when managing amendments to the CIs (**Figure 15**).

Figure 15: Challenging aspects of the dialogue with CA when managing amendments to the CI



4.10.2. Survey with PAG members

A first challenge raised by patients is the lack of information regarding clinical trials. Survey results show that patient awareness is fragmented and limited, with respondents finding information about upcoming or ongoing clinical trials difficult to identify. Respondents mentioned sources of information varied widely, including healthcare professionals, national databases, patient support groups, NGOs, local/national government organisations, manufacturers/sponsors and private organisations, EU-funded projects, and social media. Accessibility of information was also considered a priority to ensure the inclusion of disadvantaged or minority communities in clinical trials. Patients also raised concerns about the complexity and lack of comprehensiveness of the information provided concerning clinical investigations. Many felt that informed consent forms were not tailored to patients' level of understanding. It is, therefore, essential that information about the clinical trial, risks and benefits related to the medical device and participation, trial sites, clinical investigation teams, and possible conflicts of interest be easy-to-understand, transparent, and comprehensive. In this context, clarifying whether a clinical trial is an EFS is crucial for patient understanding and engagement. This distinction is vital as it informs patients about the experimental nature of the trial and the level of risk involved.

According to respondents, current key challenges for patient participation in clinical investigations are also related to informed consent processes, travel, compensation, and support. Survey results highlight insufficient time and information to carefully assess the risks and benefits of participating as part of the informed consent process. Some participants found travel to the site burdensome, specifically time spent organising a trip, traveling (sometimes with a carer), and associated costs. Other participants shared additional perspectives, explaining that they are willing to travel far if the treatment or medical device in the trial provides real added value to the patient; they also highlighted specific conditions, such as mobility issues, where travel is impossible even if there is willingness to travel. Adequate compensation for participation and full reimbursement of costs was regarded as essential, also considering that some patients need to take time off work. Sufficient support from the investigation team and peers before, during, and after the trial were also identified as important.

Many respondents found accessing clinical investigations in other countries to be highly complex due to regulatory differences and logistical barriers. However, there is a willingness among patients to participate in trials abroad if the necessary support systems are in place. A concern raised is patients' efforts invested to participate in trials abroad, given the uncertainty about whether a trial is placebo-controlled and whether they will benefit from the innovative device tested.

Another point raised by participants refers to post-trial considerations. In particular, access to results post-trial was highlighted as a critical concern. Patients expressed a strong desire for transparency

regarding outcomes and continued access to treatments or devices after trials conclude, particularly when they are successful and lead to regulatory approval.

Finally, respondents shared a keen interest in co-designing clinical trials. Responses, however, indicated limited involvement of patients and patient organisations in the development of clinical investigation protocols. Key challenges include lacking awareness of involvement opportunities and perceived barriers related to required expertise among patients, as well as insufficient understanding of the value of patient involvement among stakeholders. While there was some awareness of initiatives engaging patients/patient organisations in protocol development, few of them are coordinated among each other or result in tangible changes, according to results.

4.10.3. Interviews with stakeholders involved in pre-market clinical investigations

To better understand the challenges faced in pre-market clinical research in the EU by stakeholders directly involved in the process, interviews and/or focus groups were conducted with representatives of Team-NB, national EU ethics committees, trialists, clinical sites, HTA agencies and small and medium enterprises (SMEs). A meeting with a representative of the FDA was also organized to gather their perspective on the FDA EFS program and the related challenges. Through this round of interviews, stakeholders shared their experiences and perspectives. For every group of stakeholders, below are highlighted the main points raised during the discussion.

The interview with Team-NB highlighted the vital role NBs play in approving MDs. Although unable to directly advise on product development or clinical investigations, they provide guidance documents in the form of checklists, Best Practices Guidances (BPG) and similar, to help meet the requirements of established regulations. During the interview, structured dialogue between NBs and stakeholders was indicated as a way to minimize delays and improve information gathering. When identifying key challenges, Team-NB mentioned ensuring manufacturers collect accurate clinical data in order to avoid disputes. The potential for greater advisory roles was also discussed, although the current focus is on clarifying data requirements. Finally, Team-NB expressed commitment to foster collaboration with other stakeholders in order to streamline regulation and facilitate market access for MDs.

The interview with the ethics committee highlighted several challenges related to the complex normative framework based on the MDR and ISO 14155, not freely accessible. An additional layer of complexity, especially for smaller countries, is represented by a two-step evaluation system, involving both ethics committees and the Ministry of Health (MoH), which leads to overlapping assessments of certain aspects. Sometimes, the lack of necessary expertise among researchers,

CROs, and ethics committee members due to the lack of specific trainings on this matter is a key issue, hampering the preparation, submission, and evaluation of clinical investigation applications. To tackle these challenges, it was suggested to develop clear and accessible instructions for researchers, particularly regarding ISO 14155, and to organize training sessions for both researchers and ethics committee members. The interview also pointed out the difficulty of meeting challenging deadlines because of the low quality of certain submitted applications, complicating timely evaluations. Finally, the heavy workload was also identified as a problem, as it often falls on the sole medical device expert within the ethics committee.

According to the trialists interviewed (including members from ESC and EACTS, also member of MDCG and Expert Panel), the shift from the Medical Device Directive (MDD) to the Regulation (MDR) in Europe has added regulatory complexity in the EU landscape, with inconsistent NCA decisions which led sponsors to favour the US landscape for approvals. Trialists highlighted the week research support and resource-poor hospitals as two major factors of Europe's fragmented system, hindering EFS. Trialists also noted how dialogue among regulators, sponsors, and clinicians remains underdeveloped in the EU, while Expert Panels often lack methodological or clinical expertise due to strict conflict-of-interest policies.

The interviews with clinical sites revealed critical challenges in conducting CIs for MDs in the EU. One major issue is the difficulty of finding qualified investigators and teams with the necessary clinical expertise and experience in early phase trials, which can delay or complication the study initiation. Partially, this is due to the lack of specific trainings that professional can take to develop necessary skills and knowledge. Significant hurdles are also posed by regulatory compliance, as obtaining ethical and regulatory approvals is often time-consuming, while understanding or mastering standards like ISO 14155 as well as navigating variations in national requirements can be complex. Additionally, many hospitals, particularly smaller or non-teaching ones, lack the specialized equipment or facilities required for investigational devices, which is the reason why they often need further investments or adjustments to meet operational standards and safety. Such lack of experience could hinder hospitals' ability to demonstrate reliability and capability, affecting their selection for future studies. Stakeholders involved in the interview also mentioned patient recruitment as another significant challenge, with hospitals frequently struggling to enrol the required number of eligible subjects within the expected timeline, which could jeopardize study outcomes.

According to HTA agencies, improving collaboration among HTA agencies, regulatory bodies, and NBs is crucial. Early HTA involvement can align trials with regulatory and HTA needs, generating key evidence and avoiding pitfalls. Early trial data is also key for carefully assessing patient populations and their safety, especially with the new and stricter MDR requirements, for which comparative trials for effectiveness analysis are needed.

The discussion with SMEs focused on the complexities in the field of MD development faced by start-ups and SMEs, in light of stringent regulatory landscapes. When dealing with the fragmented EU system, a big problem relates to the lack of useful contacts of SMEs compared to larger networks and corporations, which can get in touch more easily with stakeholders involved in the process to solve any doubts and get clarifications where needed. Moreover, in the EU, SMEs may have different experiences depending on the countries involved in the study. For instance, France and Belgium are known for their efficient regulatory processes and support from medical professionals. On the other hand, Italy faces challenges due to lack of resources and internal expertise. According to SMEs, the process in the US, although less fragmented, is still lengthy, costly, and inefficient, partially due to the FDA limited resources invested in the program. Howevr, fees in the US for SMEs are proportional to their size, missing aspect in the EU landscape. Both in the EU and the US, SMEs have found lower tolerance for risk and uncertainty, which may hamper innovation and the approval of new MDs in the long term. They also found collaboration between industry, regulatory bodies, and scientific society key to facilitate innovation. SMEs advocated for a clearer and more accessible regulatory pathways, which include open and standardized platforms aimed to clarify requirements and answer basic questions, so as not to burden SMEs with tasks which are typically outsourced to external consultants. Although the EU landscape is complicated, SMEs expressed their commitment to support innovation and collaboration in the EU.

Before focusing on the main challenges, the meeting with the FDA opened up by clarifying the reasons why the FDA launched an EFS study program in 2013. As previously stated in this document, historically, early testing of novel devices often happened overseas, delaying patient access to innovative technologies in the US. The EFS program was designed with the aim to ease clinical studies in the US and accelerating approvals for novel devices when non-clinical testing is available or informative to refine the device. Two main priorities of the program are balancing risk-benefit considerations with patient safety through strategies including “just-in-case” risk mitigation, which ensures monitoring and defines responses to potential risks, and "just-in-time" testing, reducing unnecessary testing upfront. The success of this program is shown by numbers: since 2013, over 430 EFS IDEs applications have been approved. Several challenges where presented during this meeting, including delays because of biocompatibility and animal testing requirements, difficulties in involving patients and gathering inputs in design and risk assessment, collaborating with other stakeholders to streamline processes when conducting EFS, and ethical considerations. To respond to these challenges, the FDA proposed the initiative EFS 2.0, which aims to address these ongoing challenges to further promote patient safety while fostering innovation.

4.11. Performance and impact of pre-market approval

pathways

In the US, the Medical Device Innovation Consortium (MDIC) plays a key role in tracking and setting performance measures for EFS. The MDIC is a US based, public-private partnership, with the mission to "break down barriers in the medical technology life cycle to accelerate innovation and adoption of safe, effective and high-quality medical technologies".[120] One of the key initiatives of MDIC is building a successful US EFS ecosystem by bringing together key stakeholders, including the government, industry, healthcare providers, non-profit organizations (e.g. patients, providers, academics). A main performance target of the MDIC is the **60/60/60 goal**, aimed at streamlining the process of EFS studies in the US by completing all necessary steps (FDA IDE and IRB approval, contract and budgeting completion, enrolling the first patient) within 60 days each.[78] In 2017, the MDIC elaborated performance metrics for 22% of EFS studies conducted between 2015 and 2017 by 13 sponsors in 50 different clinical sites. In this regard, it is important to note that the MDIC does not have a mandatory study performance monitoring system, but rather relies on voluntary data sharing by sponsors. While most studies included in the analysis got IDE approval in less than 60 days and most sites got IRB approval in less than 60, the time needed for contracting and for patient enrolments, in most cases, was more than 180 days.[121] MDIC noted improvements when performing the same analysis in 2019 across 60 clinical sites, with time for getting IDE approval down to 53 days, IRB approval to 51, time for enrolling patients to 88 days.[113] Today, after 10 years since the inception of the FDA EFS Program, the program and its timeline have improved substantially. Overall, around 60 EFS studies are reviewed each year and over 70% of them are approved by the FDA within 30 days.[122]

Besides tracking and reporting EFS metrics to check progress and identifying areas of improvements, the MDIC has implemented several activities to improve the FDA EFS program, including developing toolkits and templates, offering trainings to sponsors and clinical sites, and developing best practices, showcasing key factors for success in EFS applications (Box 5)

An organisation with similar characteristics in the European landscape is not present, as no standardised framework for EFS currently exist across MS.[6] While metrics such as time to IDE approval and first patient enrolment are closely monitored in the US, in the EU these are less standardised. Approval times for clinical investigations, for instance, depend on the national CA and a unified timeline has not been discussed.

As far as impact of pre-market approval pathways is concerned, the findings from the scoping literature review did not highlight any specific results, including, for instance, the ability to attract R&D investments.

Box 5: Finding the right timing to ensure a successful EFS application: experience from Industry and clinical centres

Timing is a critical factor for success in an EFS. Although timing for EFS applications have shortened, completing an EFS study within the expected timeline is not automatic. Northwestern Medicine Bluhm Cardiovascular Institute in Chicago, Illinois, had a positive experience with timing. The median time for conducting 10 EFS (3 heart failure studies and 7 transcatheter valve studies) was 60.5 days to IRB, 64.5 days to clinical trial agreement (CTA), 97 days for patient enrolment Among factors impacting on timing, the Cardiovascular Institute highlighted the advantage of relying on a good partnership with the industry sponsor, the flexibility of different actors involved, and institutional buy-in industry partnership.[116] Similarly, Arrhythmia Research Group had a positive experience with 10 EFS. When launching the Conformal CLAAS Device EFS, it took the group 95 days to get IRB approval, 149 days to get the first patient in the study, 130 days from first patient enrolment to study completion. According to Arrhythmia Research Group, the experience of the clinical site chosen for the study and its unified leadership allowed such right timing.[116]

When considering timing of an EFS application, AQUA heart, a medtech startup, distinguishes between time factors controlled by the company, including R&D development, data collection, tests and data analysis, as well as time factors out of company control, including IRB approval, site selection and contracting, government approval, patient selection and enrolment. As far as this second category is concerned, several companies highlighted the advantages of relying on an existing model clinical trial agreement (MCTA) template provided by MDIC, which allowed companies to cut the amount of time needed to finalize an EFS contract from 45 days to about 30.[123] The goal of MCTA is to facilitate the EFS contracting process by providing a starting point for contract negotiation. Many companies benefitted from the application of this template. For instance, Columbia University Irving Medical Center was able to cut the amount of time needed to finalize an EFS contract from 45 to 30 days, whereas Conformal Medical, after experiencing a delay due to last-minute changes to clinical trial reimbursement, was able to launch the study at a clinical site in 26 days.[124] According to various Institutes, using the MDIC guidance and Network has also been useful when enrolling patients. Baylor Scott & White Research Institute, for instance, attribute the success of quick patient enrolment in 13 EFS in the area of cardiology and vascular devices to the collaboration with MDIC.[124]

5. Implications for designing an EU EFS Program

The regulatory landscape described above highlights the multifaceted hurdles in bringing medical innovations to market, which ranges from ideation and design, nonclinical and clinical investigation, product approval to reimbursement, and underscores the need for collaborative efforts to effectively navigate these challenges. Our goals in this deliverable were to investigate the distinguishing features of pre-market approval pathways in the EU and elsewhere through a scoping review of the scientific literature, supplemented by grey literature review and surveys and interviews with key stakeholders and industry partners, of particular relevance to designing and establishing an EU EFS program. We have highlighted not only the characteristics, best practices and performance measures according to a wide range of themes, but also the gaps, challenges, and barriers encountered in the development and commercialization of medical devices, covering diverse geographical areas, that are likely to influence its design, implementation and monitoring over time. All activities and information gathered here contribute directly to the ongoing WPs charged with designing, implementing, pilot testing and monitoring a proposed EU EFS program.

The key features necessary for the design of an EU EFS Program have been highlighted in this deliverable to guide efforts to pre-emptively address gaps, challenges and barriers that are likely to influence its implementation and build in knowledge gained from best practices in the US EFS program. Our purpose here has been to provide information and examples necessary for the work already begun in the core design WPs of this project, to be applied and tested in the pilot phase, and to provide a framework for the safe involvement of patients in the conduction of EFS.

The recommendations for an EU EFS program (which will be summarized more in detail in Deliverable 1.4) emphasize streamlining processes and prioritizing patient-centric approaches. Clear guidance on trial design, testing, risk analysis, and performance metrics is essential, alongside a dedicated coordination group to oversee efforts. Regular benchmarking of key indicators and a unified risk assessment framework may work towards this effort, as they would enhance efficiency and safety.

The findings collected highlighted the importance of improving dialogue with regulatory bodies, with pre-submission meetings and expert panels specializing in early-stage medical devices. As far as devices are concerned, it is essential to establish clear eligibility criteria based on technology types, medical conditions, and clinical centre capabilities, which will support efficient evaluations.

A key recommendation involves patient involvement, which should rely on transparent communication with simple language, visual aids, and comprehensive trial information. Patients must have time to review details like trial objectives, risks, and post-trial results. Information should be accessible to underserved populations, with the Clinical Trials Information System (CTIS) as a model for a public database on medical device investigations. Support systems such as reimbursement policies, logistical aid, and cross-border participation mechanisms would reduce barriers, ensuring equitable access across the EU, especially for rare diseases.

Patients should also co-create trial designs, contribute to protocols, and review results through advisory boards representing diverse experiences. Follow-up should ensure access to results and beneficial devices post-trial.

Finally, collaboration and knowledge sharing are vital. A centralized website with tools, templates, checklists, and mapped MDR standards would support stakeholders. And enhance monitoring. These measures may support the creation of an efficient, patient-centered EFS program in the EU.

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