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Pre-market clinical investigation approval pathways and the role of Early Feasibility Studies for medical devices: a scoping review to guide EU policy

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ABSTRACT

Introduction: Early Feasibility Studies (EFS) enable limited early-stage clinical evaluation of novel medical devices when non-clinical testing is insufficient to inform design, safety, or performance. While the US Food and Drug Administration has an established EFS program, the EU lacks a dedicated framework, creating uncertainty for innovators and regulators.

Areas covered: This scoping review examines pre-market regulatory pathways for elements critical for EFS implementation. A literature search was conducted in PubMed, Scopus, and Web of Science without time or geographic restrictions. Eight key dimensions were identified, primarily across EU and US systems: regulatory frameworks; eligibility criteria and preclinical evidence; iterative innovation mechanisms; early dialogue; structural and medico-legal challenges; clinical site capacity; risk management; and patient communication, involvement, and safety. The FDA model supports EFS through clear guidance, flexible testing, early dialogue, and support for protocol and device iteration. In contrast, EU regulation acknowledges early investigations but lacks a dedicated framework, resulting in fragmented implementation.

Expert opinion: A coherent EU EFS framework could strengthen patient protection by improving regulatory clarity, oversight, and the quality and timeliness of early-stage evidence, accelerating innovation and strengthening European competitiveness. Priority actions include formal guidance, structured early dialogue, capacity building, harmonized liability, and enhanced patient involvement.

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KEYWORDS
Early Feasibility Studies; medical devices; pre-market clinical investigation; medical device regulation; scoping literature review; patient safety; clinical innovation

1. Introduction

Medical device (MD) regulation worldwide is driven by the need to achieve two central aims: protecting patients through rigorous requirements for safety, effectiveness, and quality, and ensuring timely access to innovations that can improve health outcomes and strengthen health system performance [1–4]. Although these objectives are broadly shared, the means by which they are pursued differ considerably between regulatory systems. Decisions about how clinical evidence is generated, assessed, and applied influence not only the trajectory of innovation but also competitiveness, investment flows, and ultimately the opportunities available to patients [1,5,6].

Among the various approaches for generating evidence to support regulatory approval of MDs, clinical investigations (CIs) are a cornerstone in demonstrating safety and performance. As framed in ISO 14155:2020 – Clinical investigation of medical devices for human subjects — Good clinical practice, these investigations encompass different study designs and stages, among which Early Feasibility Studies (EFS) have gained increasing relevance over the past decade [7]. Their value lies in enabling the collection of preliminary clinical data in a safeguarded environment, supporting iterative innovation in device development [5,8,9]. Defined in International Organization for Standardizations (ISO) 14155:2020 as limited CIs conducted early in device development, often before design finalization, EFS provide an opportunity to collect preliminary safety and performance data when additional non-clinical testing is uninformative or unavailable to support further design development [5,7]. Unlike pivotal trials, EFS are specifically designed to inform design refinement, validate safety assumptions, and minimize downstream risks [5,8]. By structuring iterative learning at the front end of development, EFS bridge the gap between preclinical work and later-stage studies, thereby creating opportunities to accelerate both device optimization and patient access [8,10,11].

The United States (US) has been the most proactive in formalizing this approach. Since 2013, the Food and Drug Administration (FDA) has operated a dedicated EFS program for novel, often high-risk MDs, supported by detailed guidance and early dialogue mechanisms, including the Q-Submission process [8,10–12]. The framework permits small, staged studies and accommodates iterative device modification,

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Article highlights

- Early Feasibility Studies (EFS) enable limited clinical evaluation of medical devices when non-clinical testing is insufficient.
- The US Food and Drug Administration (FDA) EFS program offers a structured, innovation-enabling model with formal guidance and early regulatory dialogue.
- The European Union (EU) lacks a harmonized EFS framework, leading to fragmented implementation and regulatory uncertainty.
- Procedural rigidity, limited site readiness, and inconsistent medico-legal requirements hinder EFS in the EU.
- A coherent EU EFS framework could accelerate innovation, enhance patient protection, and strengthen Europe's competitiveness.

facilitated by continuous dialogue with regulators, while linking early testing to broader innovation pathways [8,10–13]. These features have made the US the most predictable jurisdiction for early-stage device testing, streamlined progression to later development phase, and encouraged steady growth in EFS uptake [5].

The European Union (EU), by contrast, has no dedicated framework for EFS [5]. The Medical Device Regulation 2017/745 (MDR) [14] requires that exploratory and confirmatory investigations be distinguished within clinical development plans, and subsequent Medical Device Coordination Group (MDCG) guidance acknowledges EFS as a type of pilot study [15]. Yet neither the MDR nor the MDCG guidance defines EFS as a category or sets out harmonized procedures to undertake EFS in the EU. Unfamiliarity among Member States with the unique aspects of EFS compared to other pre-market CIs can lead to uneven implementation, fragmented oversight, and uncertainty for sponsors [5].

The contrast with the US is striking and raises an important question for the EU: can EFS be given a coherent framework that preserves patient safety while enabling the kind of iterative, innovation-friendly development already established in other jurisdictions? Without such a pathway, Europe risks slower patient access to innovative technologies, diversion of early clinical research to more predictable jurisdictions, and erosion of competitiveness in its Medtech sector [5,16]. Small and medium-sized enterprises (SMEs), which dominate the European market, are particularly affected as they often lack the resources to navigate national variation or conduct studies abroad [17]. The advantages of structured EFS programs, particularly the FDA's model, are well described [1,5,9–11,18,19], p.20]. A European EFS program would improve the quality and timeliness of evidence, provide regulatory clarity and flexibility, strengthen competitiveness and research and development (R&D) attractiveness, support SMEs developing MDs, and enhance clinical expertise as well as patient access to innovation.

In recognition of these challenges and the growing strategic value of an EU EFS program, the EU and the Innovative Health Initiative (IHI) launched a public call aimed to develop a harmonized methodology to promote uptake of EFS for clinical and innovation excellence in the EU in 2022. The Harmonized approach to Early Feasibility Studies for Medical Devices in the European Union (HEU-EFS) project was awarded in 2023 [20]. Against this backdrop, a global scoping review of pre-market CI approval pathways (PMAPs) was conducted to identify how EFS are framed, facilitated, or constrained within different regulatory and health system contexts.

This paper does not attempt to reproduce the findings regarding the advantages of structured EFS programs. Instead, it draws on published evidence to examine enabling conditions, barriers, and recurring themes—including eligibility criteria, preclinical requirements, iterative design, site capacity, risk management, dialogue with regulators, and patient involvement—that are most relevant for European discussions. In doing so, the review provides a critical basis for considering whether and how a harmonized EU pathway for EFS could be developed, particularly in the context of an MDR currently under revision [21].

2. Methods

2.1. Study design

This scoping review was conducted as part of the HEU-EFS project to map and characterize the literature on PMAPS for MDs. The review followed the updated methodological guidance from the JBI Scoping Review Methodology Group, outlined in Peters et al. [22] and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines.

Consistent with JBI guidance [22], the aim of this review was to systematically identify and map key concepts, characteristics, and gaps in the literature and summarize the evidence rather than assess effectiveness. Methodological quality and risk of bias assessment were therefore not undertaken.

2.2. Search strategy

Search terms were structured around four key concepts, joined using Boolean operators (Box 1), and searches by title and abstract in PubMed; title, abstract and keywords in Scopus; and in all fields in Web of Science, were conducted from 12/2023 to 2/2024, updated in April 2025. Digital health technologies (DHT) were included in the search terms; however, papers specifically related to DHT were extracted to inform a series of stakeholder interviews, reported elsewhere [23]. No restrictions were applied regarding publication year or country.

The searches covered PMAPs globally; though emphasis was given to EU systems compared to the US (the only

Box1. Search terms used in the scoping literature review for peer-reviewed literature searches in PubMed, Scopus and Web of Science.

(('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*'))

country with a dedicated EFS program), data was collected from all jurisdictions (e.g. Japan and Canada) where specific features were judged informative.

In addition to database searches, key gray literature sources were purposively consulted, including regulatory guidance from the US FDA EFS program, the EU MDR [14], relevant EU MDCG guidance, and resources from the US Medical Device Innovation Consortium (MDIC, a public–private partnership supporting the FDA EFS program). These sources were consulted due to their central relevance to the regulatory context, but were not searched with defined terms and were not included in the PRISMA flow diagram. However, a brief list of key resources consulted is provided in Supplementary Materials.

Details on the full search strategy are provided in Supplementary Materials.

2.3. Eligibility criteria

Eligibility criteria (see also Supplementary Materials) were defined in accordance with the objectives of the review and guided by the framework recommended by JBI [22]:

- Concept: Features, characteristics, performance, and challenges of PMAPs for MDs, including aspects relevant to the design and implementation of EFS.
- Context: Regulatory systems for MDs across jurisdictions, with particular emphasis on the EU and US.
- Sources of evidence: Peer-reviewed articles.

2.4. Study selection process

Search results were exported and managed using Zotero and Stata v. 19 to remove duplicates. Results (730 records) were uploaded to the web-based platform, RAYYAN.ai, to facilitate blind screening. At least two independent reviewers manually screened each record by title and abstract. Potentially relevant studies ($n = 172$) were retrieved for full text screening, assessed independently by two reviewers. Discrepancies at both stages were resolved through full group discussions (details are provided in Supplementary Materials).

The study selection process is reported using a PRISMA-SCR flow diagram (Figure 1).

2.5. Data extraction and analysis and synthesis of results

A standardized data extraction template was developed collaboratively by the research team, aligned with inclusion criteria and review objectives. Data extraction was conducted for all full-paper screens, and covered study characteristics, regulatory context, and information relevant to PMAP and EFS features, implementation, and challenges (Supplementary Table S1 summarizes the data extraction conceptual categories).

Consistent with JBI guidance for scoping reviews, decisions on inclusion and data analysis focused on descriptive mapping

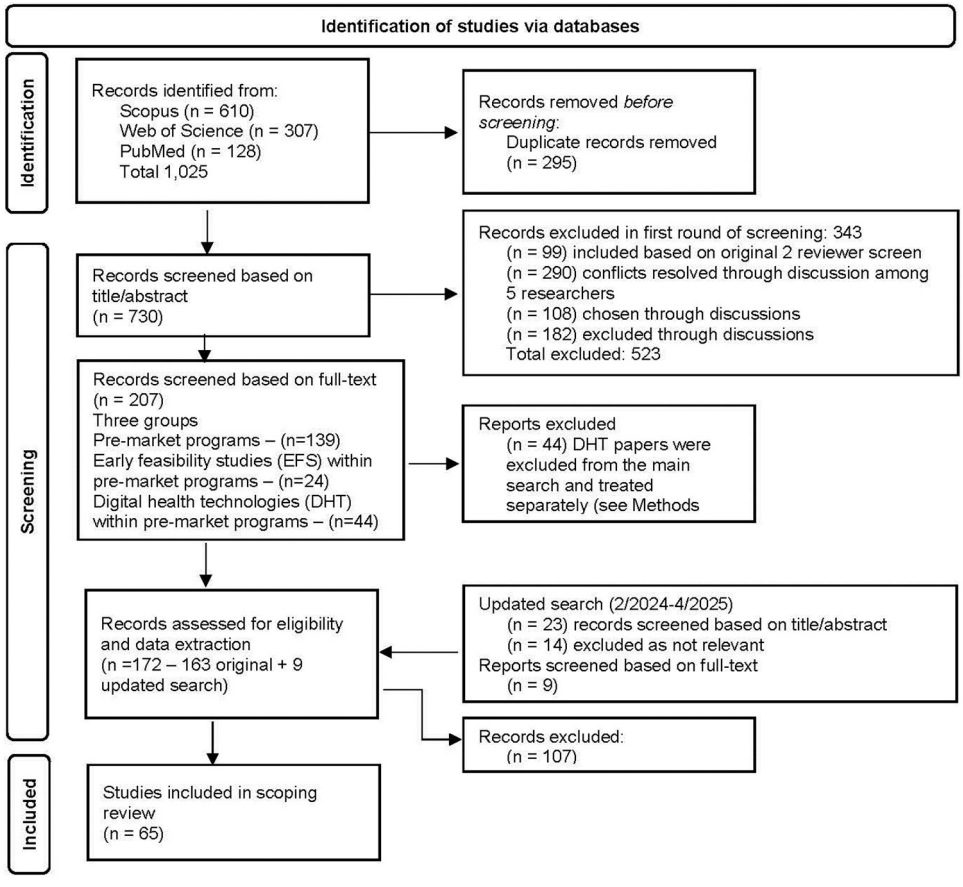

Figure 1. PRISMA 2020 flow diagram of scoping literature review for pre-market clinical investigation approval pathways (PMAPs), including EFS.

of the evidence rather than formal synthesis of study findings. Analysis was conducted by all researchers divided into two groups (3 for EFS-specific and 3 for general regulatory papers); all were experienced in MD regulation, health policy, and/or evidence synthesis to organize extracted data into key conceptual categories. The final list of included studies ($n = 65$) was identified by two researchers based on the mapping and data analysis, and discussed with all researchers for final consensus. Documents from the purposeful consultation of gray literature, including presentations and summaries of the EFS program and the MDR regulator review were shared for final analysis of findings.

Finally, all researchers identified and discussed together the conceptual organization of findings incorporating the included papers and gray literature into eight dimensions relevant for building a framework for an EU EFS program.

3. Results

To inform the potential design of a European EFS framework, the scoping review examined the current regulatory context for PMAPs, the characteristics of existing programs, and the advantages some programs provide that might be adapted to the EU context to address challenges and barriers to EFS.

The detailed list of the 65 articles [1,3–6,8–11,17,18,24–77] included in the review is provided in Supplementary Materials Table S1 (gray literature in Table S2). Table 1 summarizes the number and percentage of articles divided according to each of the conceptual categories used for data extraction.

Regarding jurisdictions other than the US and EU, the search criteria had no geographic restrictions, but only 12 of the 172 papers earmarked for full paper screening and data extraction after title and abstract screening considered other countries. These included China, Taiwan, Canada, Japan, India, Latin America, Australia, and the United Kingdom (UK). The rest were not relevant for our study objectives. Of the 65 included studies, seven discussed settings other than the US and EU. Five considered other countries and the US and/or EU [42,44,45,55,64,76], one described the use of overseas clinical data in China [40], and one described UK rules for claims of benefit [29]. Where relevant, these studies informed the results described here, but they did not provide enough information to widen the main analysis beyond the US and EU. However, a separate project database which gathered details on procedures and documents required for PMAPs in over 50 jurisdictions worldwide is the subject of a paper in development (details are available on the HEU-EFS website).

Table 1. Conceptual categories identified in the included papers to inform data extraction.

Conceptual category	N	%
Barriers, challenges, and solutions to EFS	61	94%
Risk assessment and mitigation	28	43%
Characteristics, features, regulatory processes of PMAPs	25	38%
Impact on R&D investments	19	29%
Requirements for EFS (eligibility, site readiness, risk assessment)	19	29%
Implementation of EFS (operational, procedural, regulatory)	15	23%
Ethical and legal aspects	14	22%
Patient consent and involvement	13	20%

Abbreviations: EFS – Early Feasibility Studies, PMAP – Pre-market clinical investigation approval pathways, R&D – Research and development.

Study results here are organized according to eight interrelated dimensions identified in the literature that are critical for EFS. Taken together, these dimensions highlight both the structural requirements and the practical lessons that should be considered in developing a coherent and effective European EFS program and also provide insights on its potential impact on building R&D capacity and investment in the EU.

3.1. Regulatory frameworks: divergence and fragmentation

Gathering information on current regulatory frameworks [1,6,12,25,72,78], including how they differ across jurisdictions and what this implies for EFS, provided the basis for the investigation. The search also served as a check for the existence of worldwide dedicated EFS programs, confirming the US EFS program as the only example. In response to increased migration of MD CI to other jurisdictions, with negative effects on US patient access to innovative technologies, the FDA established the EFS Program in 2013 to support early-stage clinical testing of novel, often high-risk MDs, particularly when nonclinical data alone are insufficient to assess safety, performance, or design [13,68]. The program is supported by formal guidance—Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Clinical Studies, including First in Human (FIH) Studies [13]—which clarifies requirements for early clinical trials and enables iterative development through small-scale studies, typically involving fewer than 15 participants [8,9,11,13,79]. A defining strength of the US framework lies in its integration within a broader innovation ecosystem, linked to FDA pathways such as Premarket Approval, Breakthrough Devices and De Novo Programs [13,80]. Among the elements most frequently credited for the program's effectiveness is the facilitation of structured engagement with regulators through mechanisms like the Q-Submission process [81], which enables early and timely dialogue between sponsors and the FDA [10,18]. This process ensures that applications are aligned with FDA requirements and expectations, which may help minimize clock stops (temporary pauses in FDA review times) and post-submission delays. As protocol modifications are anticipated within the EFS framework, a dedicated amendment process is built into the timeline, informed by prior discussions between the sponsor and the FDA [13]. This structured flexibility facilitates real-time design iteration and timely progression to subsequent phases (Figures 2 and 3) [10–13].

By contrast, the EU currently lacks a dedicated, harmonized pathway for EFS. The MDR, in force since 2021, provides the overall framework for CIs, while each NCA has specific approaches and processes (e.g. in practical terms on timing, ethics review); although Annex XIV acknowledges early-stage CIs—including FIH, feasibility, and pilot studies—it does not define EFS or provide a tailored framework [14]. Instead, ISO 14155:2020 and subsequent MDCG guidance (over 100 documents issued since the MDR entered into force) offer the most detailed, albeit indirect, references [5,15,82]. In the case of EFS,

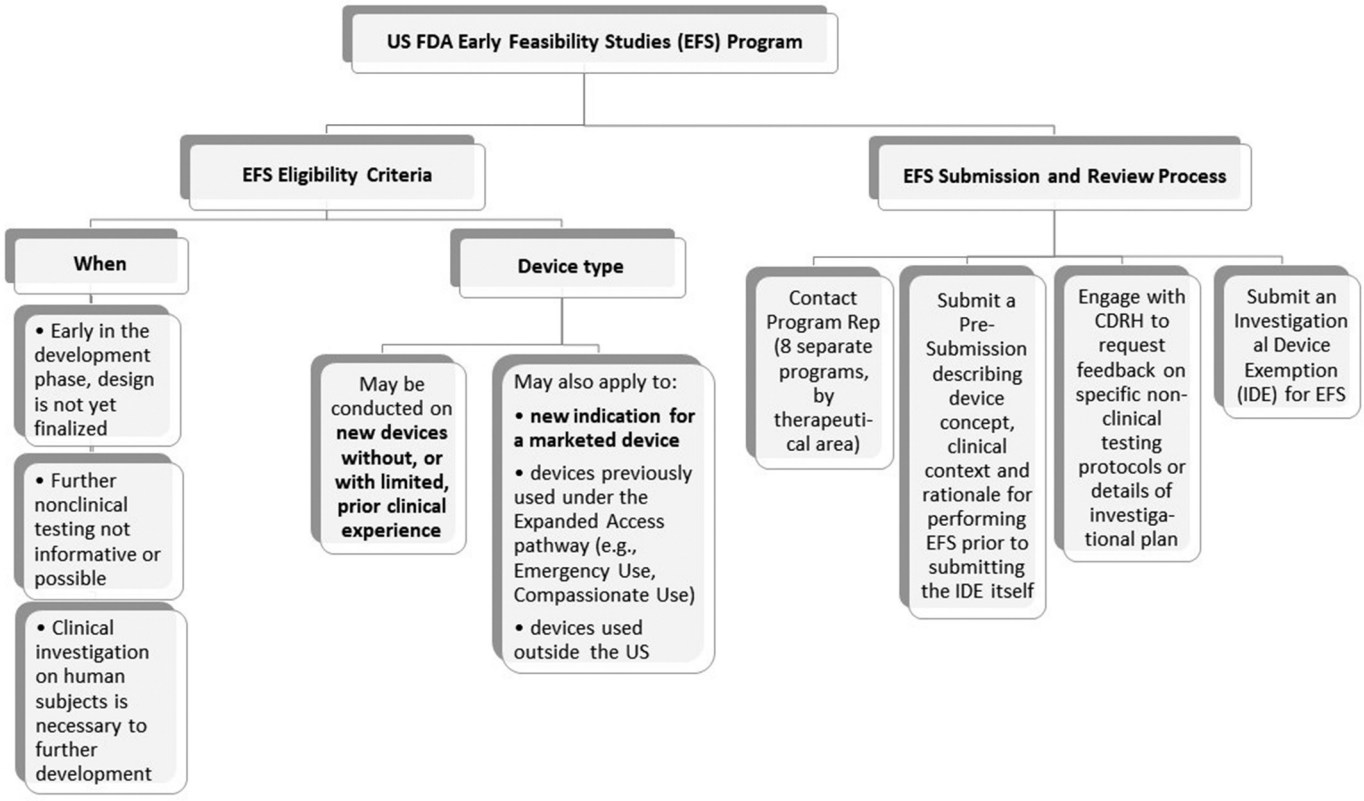

Figure 2. Schematic representation of the United States (US) Food and Drug Administration (FDA) Early Feasibility Studies (EFS) Program.
Source: Author elaboration based on FDA EFS Guidance [13], FDA EFS Program description website [80], US Medical Device Innovation Consortium (MDIC) EFS Blueprint [79].

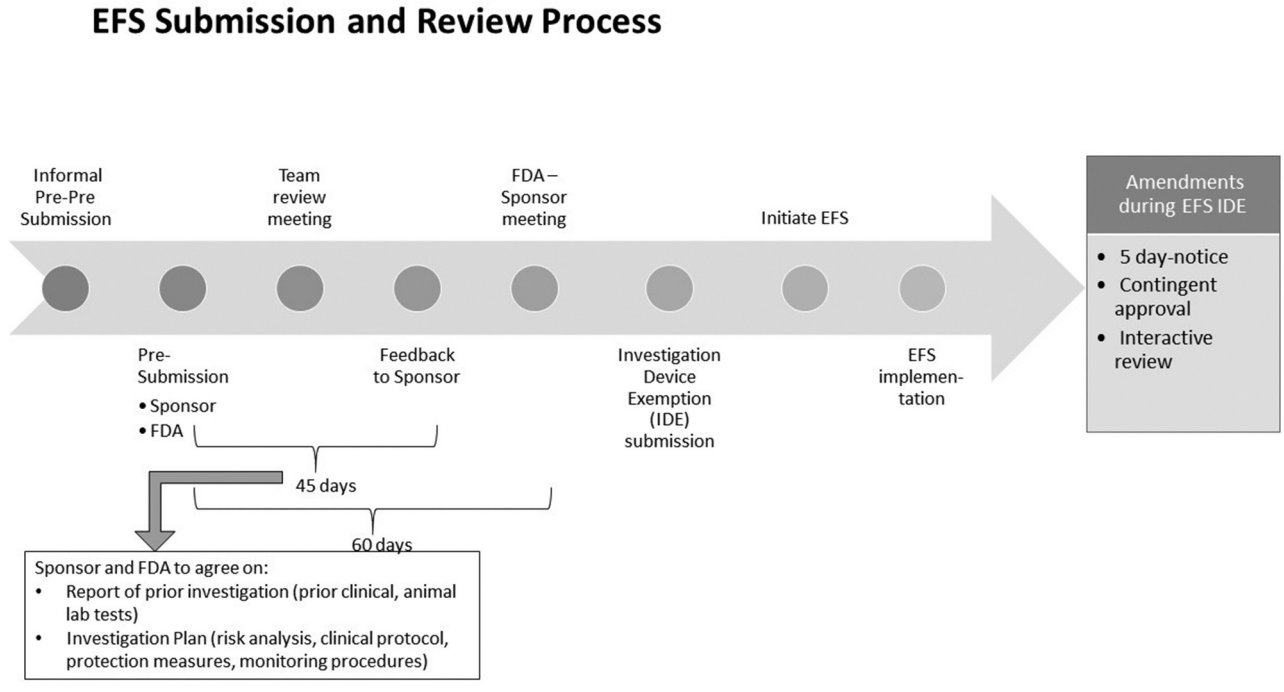

Figure 3. The United States (US) Food and Drug Administration (FDA) Early Feasibility Studies (EFS) Program submission and review process timelines.
Source: Author elaboration based on the US Medical Device Innovation Consortium (MDIC) EFS Blueprint [79].

MDCG guidance 2021–6 rev.1 (revised in 2023) [15] on CIs for preliminary safety and performance, explicitly mentions EFS as a type of pilot or early-stage investigations (sometimes also referred to as proof-of-concept studies). Article 70 of the MDR [14] specifies timelines and conditions under which CIs of devices are authorized by NCAs and ethics committees.

While the approval timeline for CIs in the EU can be as short as 55 days when no questions are raised (Figure 4), this does not reflect a predictable process. In the absence of structured pre-submission dialogue, sponsors often encounter clock stops and iterative requests once the review has begun. Although the MDR does not expressly reference design modifications, study changes – especially those considered substantial – generally require resubmission under Article 75, since the regulation provides no mechanism for amending an ongoing study [14]. As a result, despite shorter nominal timelines, the EU process is often less predictable and less flexible in practice, especially for early-stage investigations.

3.2. Eligibility and preclinical evidence

The literature identifies a consistent set of characteristics that define eligibility for EFS and specifies the role of preclinical data in supporting them. EFS are typically reserved for early-stage, often novel or substantially modified devices where existing bench or animal models cannot adequately predict use in humans [10,11,18]. Although the FDA's EFS guidance does not formally specify risk classes, it is principally intended for significant-risk devices where non-clinical evidence is limited, yet early human evaluation is essential to assess viability, optimize design, or refine functionality (Figure 2) [13,80]. Common eligibility criteria include the lack of appropriate predicate devices, the absence of satisfactory alternatives, and the potential need to refine procedural technique or target population [10,11,18]. Devices studied using EFS in the US may also be targeted for inclusion in programs such as the US Breakthrough Medical Devices program, specifically aimed at devices that address unmet medical needs, with no existing treatments, or for which treatments are inadequate, have severe side effects or are not accessible [3–5,11]. In particular, Holmes et al. [18], consider the assessment of unmet patient needs as the first building block, echoing other authors and guidance that stress analyzing the clinical needs a new device would address and its potential to lessen significant gaps in healthcare [10,13,79].

Noting that devices aimed to treat severe conditions or unmet needs are likely candidates for EFS, Callea et al. [5], identified two core eligibility criteria across sources: (i) that early clinical data are required to support continued development, and (ii) that an acceptable risk–benefit profile can be demonstrated based on existing evidence. These principles align with the IDEAL and IDEAL-D frameworks, which advocate a staged approach to innovation and emphasize that early human studies should proceed only when potential patient benefit justifies residual uncertainty [45,83]. Collectively, these academic and regulatory approaches reflect a shared emphasis on early but controlled clinical exploration, justified by preclinical data and guided by ongoing risk–benefit evaluation.

FDA guidance [13] builds on these eligibility principles by detailing preparatory elements required to support initiation of an EFS, including prior testing reports, risk analyses and

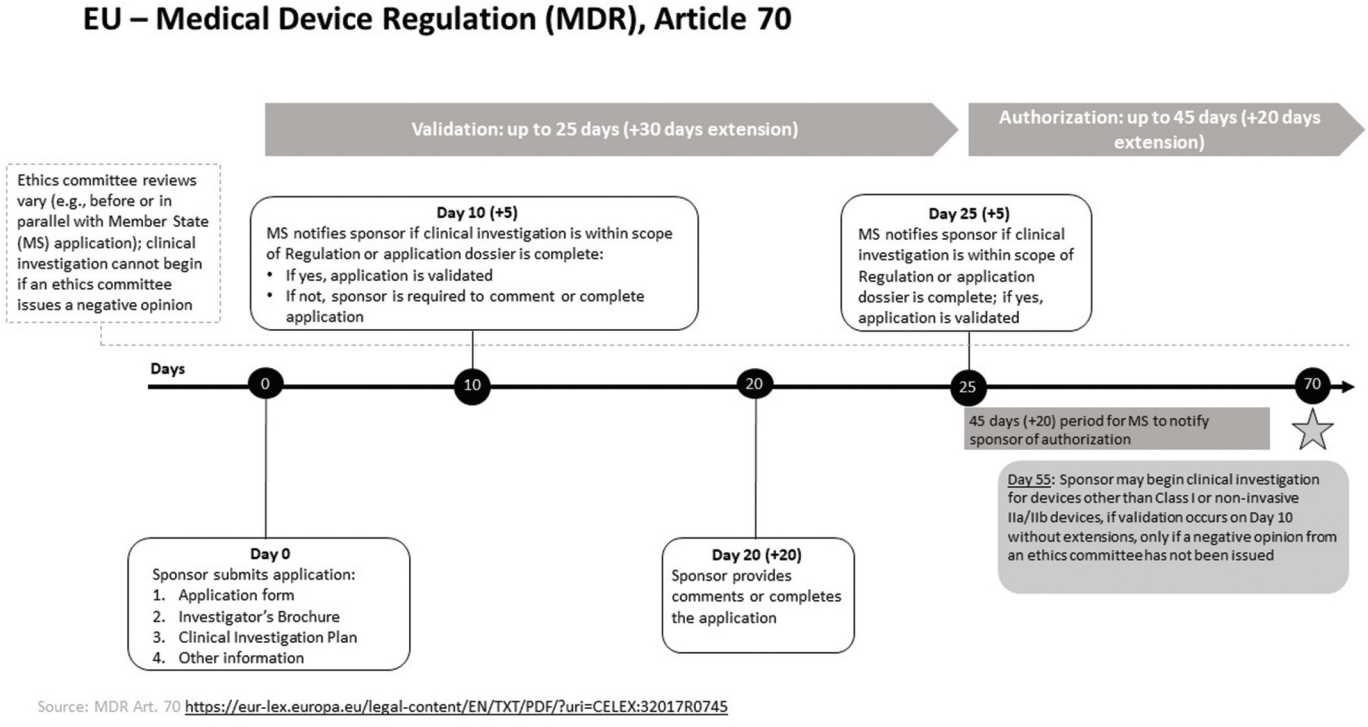

Figure 4. Timeline for clinical investigations of medical devices (MD) according to MDR Art.70 [14].

Source: Author elaboration based on a figure developed within the HEU-EFS project based on Article 70 of the European Union Medical Device Regulation (2017/745) 70 (allowing for national interpretations) [14].

mitigation plans, patient protection measures, and independent monitoring [11]. Work by Overgaard et al. [52] complements this discussion by distinguishing incremental modifications from genuinely novel innovations, proposing a five-level framework for classifying implantable orthopedic devices.

Preclinical data remain central to establishing the risk-benefit profile for EFS. While bench and animal studies may not fully capture design performance or procedural complexity, they provide a basis for safe first-in-human use [71,84]. Holmes et al. and Weiss and Farb highlight that EFS can help refine device design, procedural technique, and patient selection – elements difficult to assess ex vivo [18,71]. The expectation is that the same scope of preclinical testing (such as bench and animal tests) will eventually be covered, but the FDA permits a staged or 'just-in-time' approach in which only the most critical tests addressing immediate safety concerns are required up front, while other preclinical studies can be deferred until the device design is more finalized [10,13]. This flexibility enables sponsors to begin human testing sooner while maintaining safety.

A key distinction therefore lies in timing rather than scope. In the US, partial preclinical packages may be accepted at the EFS stage, allowing sponsors to begin carefully controlled human testing while remaining nonclinical evaluations continue in parallel [10,11,13]. In the European Union, the MDR, notably Article 62, Annex I, and Annex XV together with MDCG 2024–3 and MDCG 2024–5, outlines expectations for preclinical evaluations [14,82,85]. These provisions emphasize that investigational devices must demonstrate safety and performance through appropriate bench, animal, and other nonclinical testing before first-in-human use, as reflected in the requirements for the Investigator's Brochure under Annex XV, Section 2.7 [14,82,85]. While the MDR and its supporting guidance establish broad requirements for preclinical evidence, they do not operationalize a staged or adaptive pathway comparable to the FDA model. Consequently, although flexibility is not formally precluded, the absence of procedural mechanisms to accommodate evolving preclinical data limits opportunities for early, iterative investigation within the EU. Addressing this structural gap will be critical to the development of a coherent European framework for EFS.

3.3. Iterative innovation and study timeline

A key advantage of EFS is the ability to support real-time refinement of device design and clinical use under controlled clinical conditions [10,11,72]. The US framework, supported by the previously described 'just-in-time' testing strategy, prioritizes addressing the highest-risk failure modes before clinical use while deferring less critical nonclinical tests until after the device design is more finalized [10]. Iterative design changes during EFS may also effectively represent an improvement over the FDA Supplements program (where manufacturers may submit a supplement to make modifications to previously approved devices that are aimed to incrementally improve safety and efficacy), which has been associated with a 30% increased risk of recall [30,33–35,61]. As mentioned above, the EU MDR lacks a specific mechanism for design changes, generally requiring resubmission (Article 75) for study changes [14].

FDA guidance also facilitates study progression through faster timelines, with median IDE review periods reduced to around 30 days since 2014 [11]. Following a successful EFS, studies may transition into broader feasibility or pivotal trials [18], and in some cases may skip traditional feasibility altogether [10,11]. Though little data is available on EFS transitions to later studies, a study examining EFS approvals from 2014 to 2017 found that about 10% had transitioned to later-stage trials [9]. Efficiency is further reinforced by initiatives such as the MDIC's 60/60 benchmark, which sets targets for completing regulatory approval, contracting, and first patient enrollment within 60 days each [79]. The US EFS program is likely driving the increase in the number of EFS per year observed since 2013 (from about 9 in 2013 to a peak of 30 in 2021), more than 73% of which have been conducted in the US [5]. Recent data published on the MDIC website noted as many as 60 IDE EFS submissions to the FDA per year in recent years, most of which were approved within 30 days [86]. Together, these features support faster early-stage development while preserving safety, an approach not yet fully realized in the EU.

3.4. Dialogue

Early and structured dialogue between sponsors and regulators is a critical enabler of EFS, supporting timely, high-quality evidence generation and smoother progression through the clinical development pathway [4,36,55,87]. In the US, engagement with the FDA starts before submission: applicants are encouraged to contact the appropriate representative by therapeutic area (Figure 2), in keeping with the Q-Submission program previously mentioned, providing structured opportunities for study risk determinations, informational meetings, and regulatory pathway guidance, typically within 60 to 90 days and without associated fees [88]. This framework supports interaction from study planning through later trial phases, helping to reduce redundant testing, clarify expectations, and accelerate development [10,67,87,89].

In contrast, the EU lacks a formal, harmonized mechanism for early regulatory consultation during the pre-market phase [5]. While MDCG guidance encourages structured dialogue during Notified Body conformity assessments [90], authors consistently highlight the absence of early-phase dialogue as a missed opportunity to support safe and adaptive innovation [5,91,92]. According to Siontis et al. [74], the lack of early consultation with regulatory bodies is partially responsible for high costs and long approval times, due to sponsor uncertainty regarding clinical evidence requirements. Early dialogue could prevent delays, high costs, and potential harm to patients due to unnecessary testing [11,41,67], and help improve clinical investigation design needed to support later reimbursement procedures [38].

Recently, however, progress has been made: in 2024, the EU launched a pilot project enabling expert panels to provide scientific advice to manufacturers on their clinical development strategies and/or clinical investigation proposals for certain high-risk devices [93]. Preliminary results show that most

requests concerned pre-market studies, giving manufacturers the chance to engage with EU experts to receive methodological guidance and clarify evidence requirements for conformity assessment under the MDR [93]. However, a recent analysis of expert panels noted limited technical and biological expertise among experts (though strong expertise in clinical research), which may limit their use for early advice for EFS [73]. There is hope that ongoing efforts to revise the MDR will address establishing a formal dialogue process for MD development at all stages, engaging experts with the most relevant experience [21].

3.5. Structural challenges

Despite the importance of enabling factors and conditions for success, the literature also points to structural challenges that must be addressed for an EU EFS program to function effectively. A recurring theme is the limited training and expertise in early-stage CIs among key actors—particularly ethics committees and SMEs – which complicates compliance with MDR and ISO 14155:2020 requirements and can introduce delays [18,41,42,47,48]. From an economic perspective, rising regulatory and trial costs create disproportionate burdens for smaller enterprises, who are already disadvantaged by the fragmented nature of the EU system [32,41,54]. Finally, medico-legal uncertainty, disjointed insurance frameworks, and inconsistent indemnification requirements across EU Member States continue to discourage participation in early-stage studies [5,68]. Many of these challenges were observed early on with the US EFS program, including identifying suitable sites for EFS, lengthy ethics approval processes, inadequate access to target patient populations, contracting and device reimbursement difficulties [8,12,70]. To address such challenges, the literature recommends training, standardized templates and operational tools for patient engagement, informed consent, study initiation, contracting, and ethics review [8,11,12,18,70,79], many available on the MDIC website.

The experimental nature and heightened risk of EFS amplify challenges surrounding medical liability. In the US, early contractual agreements typically clarify indemnification responsibilities, with sponsors assuming primary liability for device-related harm [8,9]. In contrast, within Europe, the absence of harmonized medico-legal guidance and inconsistent national insurance requirements continue to generate operational delays and limit site participation [5]. Under the EU MDR, *Annex XV* mandates sponsors to provide evidence of insurance coverage for investigation-related injuries, yet implementation remains fragmented across Member States, creating persistent uncertainty [14].

3.6. Clinical site capacity and concentration of expertise

Clinical site readiness and investigator expertise are critical to EFS implementation. Studies show that successful EFS hinge on sites with robust infrastructure, experienced investigators, and efficient internal processes [8,18,71], able to identify and recruit appropriate patient populations, train qualified personnel, and navigate the operational and regulatory complexities unique to early-stage studies [79,94]. Site readiness, both technical and organizational, often determines whether an EFS can be launched, particularly in contexts where regulatory timelines are tight, or device designs are still evolving.

In the US, resources provided by the MDIC outline critical features of high-performing sites such as prior experience with FIH studies, robust ethical review protocols, capacity for timely contracting and budgeting, and the ability to engage patients meaningfully in study procedures [69,94]. Tools such as a weighted scoring method further enhance site selection by providing a structured approach to compare key parameters such as investigator experience, contracting efficiency, and patient access [79]. In practice, most US EFS are concentrated in three to five centers working closely with sponsors on protocol design and early data collection [18].

By contrast, in the EU, such expertise and infrastructure are unevenly distributed, which may undermine Europe's ability to compete effectively in early-stage device development. Even in Member States with prior EFS experience, the literature highlights procedural inefficiencies, limited staff expertise, and restricted access to suitable patient populations as central bottlenecks to expanding early-stage studies [25,78]. Developing experience in EFS would benefit the sites themselves (e.g. increased trial process efficiency, enhanced reputation and recognition) and also increases access to new technologies for patients by widening the geographic pool of clinical sites [19].

3.7. Risk management and safety oversight

EFS require intensified risk management and regulatory oversight due to higher uncertainty regarding safety and performance in early-stage investigations, making participant protection a central regulatory and ethical mandate [3,8,10,13,18,95]. Consistent with the principles of ISO 14971:2019 (Medical devices – Application of risk management to medical devices), sponsors are required to conduct a comprehensive risk assessment that identifies known and foreseeable hazards, evaluates their probability and severity, specifies risk-control measures, and provides a clear justification that anticipated benefits outweigh potential harms [96].

In the US, devices investigated under EFS protocols are frequently classified as Category A (experimental) by the Centers for Medicare & Medicaid Services (CMS), signifying unresolved questions of safety and effectiveness and reinforcing the need for strong preclinical rationale and rigorous oversight [71]. Selection of candidate devices must therefore be supported by robust preclinical evidence, independent expert safety evaluation, and multidisciplinary input to ensure scientific and ethical integrity [11].

Recommended safeguards include staged enrollment, predefined study pause criteria, and independent safety oversight [11]. In the EU, risk management is primarily addressed through MDR requirements and supplemented by MDCG 2024–3 guidance, which similarly promotes patient safety by advising that early-stage trials – particularly those involving high-risk devices – limit patient numbers and evaluate outcomes from initial cases before proceeding with additional patients [82].

Table 2. Summary of dimensions relevant to Early Feasibility Study (EFS) implementation identified from the literature.

Dimension	Elements described in the literature	Relevance for EFS implementation
Regulatory framework	Dedicated pathways, with requirements proportionate to EFS	Enables predictability
Eligibility and preclinical evidence	Early-stage devices, unmet need, staged evidence	Supports appropriate study entry
Iterative mechanisms	Protocol/device modification pathways	Enables real-time learning
Dialogue	Early regulator–sponsor interaction	Reduces delays and uncertainty
Clinical site capacity	Trained investigators, specialized centres	Improves feasibility
Structural challenges	Stakeholder training in early-stage investigations, ethics approval, contracting, insurance	Reduces delays and uncertainty, provides common knowledge base
Risk management	Staged enrollment, oversight, risk mitigation plans	Protects participants
Patient involvement	Tailored consent, participatory design	Enhances ethics and trust

3.8. Patient communication, involvement and safety

Effective patient communication and comprehensive safety frameworks are increasingly recognized as pivotal determinants of success in EFS. Transparency is essential in early-stage investigations [12,28,68].

Informed consent processes must accurately reflect the elevated risk profile and limited evidence base that characterize EFS [5,11]. Consent materials should clearly delineate investigational status, foreseeable risks and benefits, and the scope of data collection, ensuring comprehension without overstating therapeutic intent [5,11,13,79]. Moreover, both site and participant selection should consider factors such as sociocultural context, clinical complexity, and individual vulnerability, to safeguard ethical integrity and feasibility and promote equitable access [12,28,68].

To enhance comprehension, trust and study quality, recent literature advocates for co-development of study materials with patient representatives, enabling clearer articulation of study aims, risk–benefit balance, and follow-up expectations. This participatory approach–endorsed by the FDA, the MDIC, and various European regulatory bodies–emphasizes direct engagement of patient priorities and perspectives, ensuring that their insights and experiences shape the research, and supports a broader transition toward patient-centered governance and involvement in all research phases (e.g. protocol design development, recruitment, patient reported outcome measurements) [3,26,28,31,43,51,97–100]. Patient involvement has been shown to be beneficial at all stages of MD development, especially if implemented during the early stages (e.g. design concept and development, prototype testing, and clinical trials) [43]. The IDEAL-D Framework also recommends patient preference testing before proceeding to first-in-human clinical investigations [45].

The eight dimensions identified above can be synthesized into a set of key elements consistently described in the literature as relevant to EFS implementation (Table 2). This synthesis reflects patterns identified across sources with associated implications for EFS. Detailed operational recommendations, however, will be addressed separately in ongoing work within the HEU-EFS project and will be the subject of a future publication.

4. Conclusion

The results from this review show that while the US FDA EFS program provides a structured, innovation-friendly model that balances safety and flexibility, Europe remains constrained by fragmented regulation, uneven site capacity, and procedural rigidity.

From these findings, several priorities emerge for policy development in the EU. First, a dedicated regulatory framework for EFS is needed, building on MDR provisions but clarifying definitions, scope, and requirements to reflect the iterative nature of innovative MD development. Second, early and ongoing mechanisms for dialogue between sponsors and regulators could improve predictability and reduce unnecessary delays. Third, investment in site capability as well as training – for investigators, ethics committees, SMEs, and regulators unfamiliar with EFS – would expand Europe's capacity to host EFS. Fourth, harmonized approaches to address liability, insurance, and indemnification are necessary to build trust and facilitate cross-border studies. Finally, patient involvement––from protocol design to consent processes––should be strengthened to ensure transparency and alignment with patient priorities.

Taken together, these measures would support a coherent European Union EFS framework, enhancing patient safety, reducing unnecessary costs, and positioning the EU as an attractive environment for MD development and innovation.

5. Expert opinion

The EU regulatory framework for medical devices is extensive, but not ideal for early innovation. Although the MDR, now under review [21], strengthens requirements for clinical investigations, safety and performance, it does not include a specific, dedicated regulatory pathway for EFS. This limits EU capacity for supporting iterative, early-stage innovation where flexibility is key. The EU is recognized as an established leader in innovation in the Medtech industry, yet the absence of a coherent EFS framework contributes to the migration of early development of innovation elsewhere, creating a contradiction for a region renowned for its research excellence and creativity. In practical terms, this regulatory gap may delay patient access to innovative devices, increase development costs, and reduce the attractiveness of the EU for early-stage clinical research.

Findings from our scoping review explain this paradox. Core elements that determine the success of EFS – structured regulatory pathways able to adapt to the iterative nature of medical device development, clear eligibility criteria, dialogue mechanisms, flexibility in the application process, trained staff and well-equipped clinical sites – remain absent or under-

developed in the EU. Instead, the US FDA EFS program builds precisely on these characteristics. The US model combines formalized guidance, flexible preclinical requirements (including just-in-time testing), structured early dialogue, and mechanisms for iterative device and protocol modifications. These features enable predictable timelines, better alignment between regulators and innovators, and timely decisions on study progression or interruption, ultimately improving development efficiency and reducing late-stage failure risks.

In Europe, the lack of such mechanisms, coupled with procedural and regulatory inefficiencies, inconsistent access to appropriate patient populations, and limited training and expertise in early-stage clinical investigations, compromises the ability to conduct EFS. The result is a system that is rigid where it should be agile, causing delays, inefficiencies, innovator uncertainty, and unnecessary costs. This rigidity obstructs real time learning and increases the complexity of early-stage development and may also increase the risk that European developers – especially SMEs – interrupt development of promising devices, unable to sustain the costs of conducting EFS in other jurisdictions. These barriers highlight regulatory, operational and methodological limitations that currently prevent wider adoption in clinical research practice.

The strategic value of EFS is clear. These studies serve as an early assessment and refinement stage before larger trials, allowing health technology developers to assess feasibility, functionality, and safety in a controlled setting. The HEU-EFS project represents a critical step toward reverting current trends. Rather than creating parallel systems, it builds on existing EU structures, enhancing the MDR's comprehensiveness through harmonizing templates and checklists for patient informed consent, clinical investigation plan, master clinical site contracts, and insurance agreements; control mechanisms for iterative development; structured early dialogue opportunities between sponsors and regulators. Crucially, it integrates patients as partners in decisions on governance, consent design, and adverse-event oversight––enhancing ethical accountability, trust, and study efficiency. Together, these elements can create a more transparent, cost-effective and collaborative environment for early-stage clinical research, not as an effort to compete with the US program for a finite number of devices in development, but to augment innovation and timely patient access overall, providing increased opportunities for testing innovative devices in qualified, safe settings. If successfully implemented, such a framework could influence clinical practice by accelerating innovation cycles, improving trial design, and supporting more efficient evidence generation for regulatory and reimbursement decision-making.

Additionally, given the international nature of device development and clinical investigation, established EFS programs on both sides of the Atlantic with similar frameworks would facilitate site selection and multi-center studies, and may also further efforts to streamline regulatory pathways across jurisdictions, a first step in moving toward mutual recognition of regulatory approval for MDs across selected countries. In fact, calls for global harmonization of medical device regulation cite analogous goals, predicting that advances in technology will aid in harmonization efforts [1,72].

Nevertheless, implementation will require investments in trained clinical and regulatory personnel, clinical site infrastructure, and alignment of ethical review standards across Member States. Broader adoption will also depend on demonstrating that EFS outputs can meaningfully inform further clinical investigation and, eventually, market approval, pricing and reimbursement decisions, linking early data to long-term safety and cost-effectiveness evidence. Addressing these challenges will require coordinated policy action, targeted funding, and methodological work to better integrate EFS data into the overall evidence-generation continuum.

With the ongoing revision of the MDR, the EU now faces a unique opportunity to build a stronger and more coherent foundation for early innovation. MDCG guidance on Breakthrough Devices was released in late 2025, and Breakthrough designation has been included in the first draft of MDR revisions. Importantly, dialogue between notified bodies and developers has been inserted into the draft revision, but early dialogue between regulators and developers has not, despite evidence that a lack of formal dialogue processes leads to fragmented application among NCAs in this area [91,92]. What remains absent is an operational pathway that translates regulatory ambition into practical support for early-stage development.

The HEU-EFS project offers such a mechanism: it safeguards patients, promotes engagement, and repositions the European Union as a global leader in medical technology innovation. Looking five years ahead, the field will likely converge toward frameworks where preclinical testing, EFS, subsequent clinical investigations, and real-world registries interact smoothly, greatly facilitated upon full implementation of European EUDAMED database. Further research will be essential to evaluate the predictive value and long-term impact of EFS, with the goal of establishing a continuous and adaptive evidence-generation model across the device lifecycle. An EU EFS program could shorten innovation cycles, improve efficiency across evidence generation stages, and contribute to restoring Europe's global competitiveness. If implemented, procedures for medical device evaluation in the future may be more patient-centered, faster, less costly, transforming current procedural complexity and limited flexibility into an innovation-enabling ecosystem. More broadly: the future of the field is likely to depend on the integration of EFS with the new Breakthrough designation as well as other emerging areas such as real-world evidence generation and digital health technologies, which may further enhance adaptive and data-driven regulatory approaches – and increasingly push toward global harmonization of regulatory approvals for innovative devices.

Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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