



Original Research

Early Feasibility Studies for Medical Devices: Insights From an Empirical Global Mapping

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ABSTRACT

Purpose: Early feasibility studies (EFS) are a critical but poorly documented phase of clinical evidence generation for novel medical devices. Despite their growing relevance, no dedicated databases currently exist, limiting transparency and policy learning. This study aims to provide the first comprehensive empirical mapping of EFS studies globally, describing their volume, characteristics, geographical distribution, and key trends, and to derive insights relevant for the development of a dedicated European EFS framework.

Methods: A systematic search of major public clinical trial databases (ClinicalTrials.gov, International Clinical Trials Registry Platform, ANZCTR, ISRCTN) was conducted to identify EFS-like studies initiated from 2013 to May 2025. Due to the absence of an explicit EFS classification, an operational definition was applied based on study design features (interventional, sample size ≤ 30 , single-arm, nonrandomized) and EFS-related terminology in studies' title or summary. Additional sources included scientific literature, regulatory documents, and specialized medical news outlets. Extracted variables covered study design, endpoints, clinical area, geography, duration, and status. Records were manually validated by two researchers, resulting in the construction of a dedicated EFS database.

Findings: A total of 621 EFS-like studies were identified, with a steady increase over time, peaking in 2024. Forty percent of studies were conducted entirely or partially in the United States (US), 30% in Europe, and 36% involved at least a center from other regions. EFS-like activity was highly concentrated, with 10 centers accounting for nearly one-fifth of all studies, most of them US-based. Cardiovascular devices dominated the landscape, representing 45% of all studies and 68% of multi-country trials. Safety was the most common primary endpoint, reported in 68% of studies. While 42% of studies were completed, early termination occurred in 10% of cases, most often due to recruitment challenges, funding limitations, or business decisions. European studies were more frequently single-center and, on average, involved fewer sites than US studies.

Implications: Findings demonstrate that EFS are increasingly used worldwide but remain unevenly implemented, particularly in Europe. The concentration of studies in a small number of experienced centers highlights the importance of site capability and raises concerns about capacity constraints and equitable access to early-stage innovation. The absence of standardized EFS identification in registries hampers transparency, evaluation, and learning. Establishing a harmonized European EFS framework, supported by clearer regulatory guidance, improved data integration, and defined requirements for EFS-capable centers, could enhance innovation efficiency, reduce development risks, and strengthen Europe's competitiveness in medical device research.

Introduction

Early feasibility studies (EFS) represent an increasingly critical step in the lifecycle of clinical evidence generation for novel medical devices. Defined by ISO 14155:2026 *Clinical investigation of medical devices for hu-*

man subjects—Good clinical practice,¹ EFS are limited clinical investigations performed early in device development, typically before the technical design of the device has been finalized. Their primary purpose is to guide iterative device development by generating early clinical data from a small number of subjects on safety, performance, or effective-

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ness (if appropriate) when such evidence cannot be obtained through additional nonclinical tests or when appropriate nonclinical tests are unavailable.^{2–7} The United States (US) Food and Drug Administration (FDA), and specifically the Center for Devices and Radiological Health (CDRH), launched the EFS program in 2013 to support early-stage testing of novel and significant risk medical devices.^{2–7} Requirements for these limited clinical studies, ideally with 15 or fewer participants, along with provisions for iterative development and dialogue with regulators, are outlined in formal program guidance (Investigational Device Exemptions [IDE] for Early Feasibility Medical Device Clinical Studies, Including First in Human [FIH] Studies).^{8–10} These studies aim to collect preliminary safety and performance data and help refine device design, procedural approaches, and intended user populations.⁹ The EFS program was established in response to a decline in the proportion of medical device clinical studies conducted in the US. ClinicalTrials.gov data indicate that, although 87% of registered medical device studies were conducted in the US in 2004, this proportion had fallen to 45% by 2009.^{6,10} The strategic goals of the program aligned with the *21st Century Cures Act* (2016), which sought to accelerate research and innovation in the development of drugs and medical devices. The US framework, rather than create a separate pathway to approval, integrates EFS into existing pathways (eg, Premarket Approval, Breakthrough Devices, De Novo) and employs existing dialogue mechanisms (eg, Q-Submission).⁵

In contrast, the European Union (EU) does not currently offer a dedicated regulatory pathway for EFS. Since 2017, the Medical Device Regulation (MDR) 745/2017 has governed device approval across Member States, introducing stricter requirements for clinical evidence and surveillance while retaining a decentralized implementation model involving Notified Bodies and National Competent Authorities.^{4,11,12} Although Annex XIV of the MDR acknowledges early-stage trials—including FIH, feasibility, and pilot studies—it does not define EFS or provide a tailored framework.¹¹ As mentioned, the most detailed definition to date, although vague, appears in ISO 14155:2026 (ie, limited clinical investigations conducted early in development).¹

Public access to information on EFS remains highly limited, representing one of the major challenges to understanding their role in device development. No comprehensive databases or repositories currently classify studies as EFS, either in the US or globally. Even well-established international registries, such as ClinicalTrials.gov or the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), do not require studies to indicate their classification as EFS, not even as an optional field. As a result, the scope, characteristics, and distribution of EFS worldwide remain largely unknown.

The present paper addresses this gap by presenting the findings from a comprehensive empirical investigation aimed at identifying and characterizing EFS studies globally. Through the construction and analysis of an EFS database, this study explores where, how, and for which types of medical technologies EFS are being carried out. The analysis highlights key features, emerging trends, and barriers that may inform the design of a dedicated European EFS framework.

This work was developed within the Harmonized Approach to Early Feasibility Studies for Medical Devices in the EU (HEU-EFS, grant agreement No. 101112185, <https://heuefs.eu/>) project, which aims to establish a harmonized methodology for conducting EFS and foster clinical and innovation excellence across the EU.

Methods

Between March and April 2024, public clinical trial databases were systematically searched using a predefined query designed to maximize sensitivity in identifying EFS studies. The following databases were included: ClinicalTrials.gov, ICTRP, Australian New Zealand Clinical Trials Registry (ANZCTR), and International Standard Randomised Controlled Trial Number Database (ISRCTN). Search terms encompassed a wide range of expressions synonymous with early feasibility, such as: “early feasibility,” “preclinical feasibility study,” “first-in-human,”

Table 1
Early feasibility studies database extracted fields and definition.

Data field	Definition
Study ID	Study registration number
Study title	Study title
Summary	Brief summary of the study, as provided by the sponsor at study registration
Intervention type	Name and type of the investigational device
Phase	Phase of the study
Target patient enrolment	Initial target sample size at study registration
Study type	The general design of the clinical study (eg, interventional, observational)
Allocation	The method used to assign participants to different groups or interventions (if any)
Intervention model	The general strategy for assigning therapies or interventions to participants (eg, Single Group Assignment, Parallel assignment, etc.)
Masking	The process of concealing the assignment of interventions to reduce bias (eg, open-label, single or double blind)
Sponsor	The organization or individual responsible for initiating, managing, and financing a clinical study
Collaborators	Organizations or individuals that work with the sponsor to conduct a clinical study
Trial start date	Start date of the study
Trial end date	End date of the study
Study status	The current stage of a clinical study (eg, not yet recruiting, recruiting, active, not recruiting, or terminated)
Primary end points	Primary endpoints used in the study
Funder type	The source of funding for a clinical trial (eg, NIH or Industry)
Patient condition/disease	Condition being investigated in the study
Locations	Locations of the study
Investigators	Principal Investigators of the study
Withdrawn reason	Reason for withdrawing of the study

“proof of concept,” “prototype study,” and “limited clinical investigation.” In June 2025, the search was updated to include studies up to May 31, 2025. Full details of the search are reported in Supplemental (Online Only) Materials.

Due to lack of a specific flag for EFS in the databases, an ad hoc operational definition was developed to guide study extraction. Eligible studies were those initiated from 2013 onward involving medical devices or device-drug combinations explicitly labelled as EFS or early feasibility in the title or summary. In the absence of such labelling, we further identified studies as likely EFS that met a set of specific inclusion criteria: interventional design, sample size ≤ 30 , single-arm, open-label, and nonrandomized configuration.

Additional data sources included: literature searches performed in PubMed and Scopus using EFS-related terms and synonyms (to identify published EFS that could be compared with those captured by the database search), Centers for Medicare & Medicaid Services (CMS.gov) approved IDE studies, specialized medical news websites (eg, Cardiovascular News, Endovascular Today), and previous EFS identified by Callea et al.¹³ For each study, a structured set of variables was extracted, encompassing identification details, study objectives and design, planned patient enrolment, trial timelines (start and completion dates), recruitment status, primary endpoints, targeted condition or disease, and geographical information. Extracted fields are detailed and defined in Table 1.

Though clinical trial registration in publicly available trial databases is widely recommended and encouraged, it is not mandatory in all jurisdictions. As a means to informally assess the accuracy and completeness of study identification, findings from the database searches were discussed with medical device sponsors and National Competent Authorities participating in the HEU-EFS project. Information obtained through these stakeholder interactions was used to assess whether the search strategy adequately captured publicly identifiable EFS and to check for

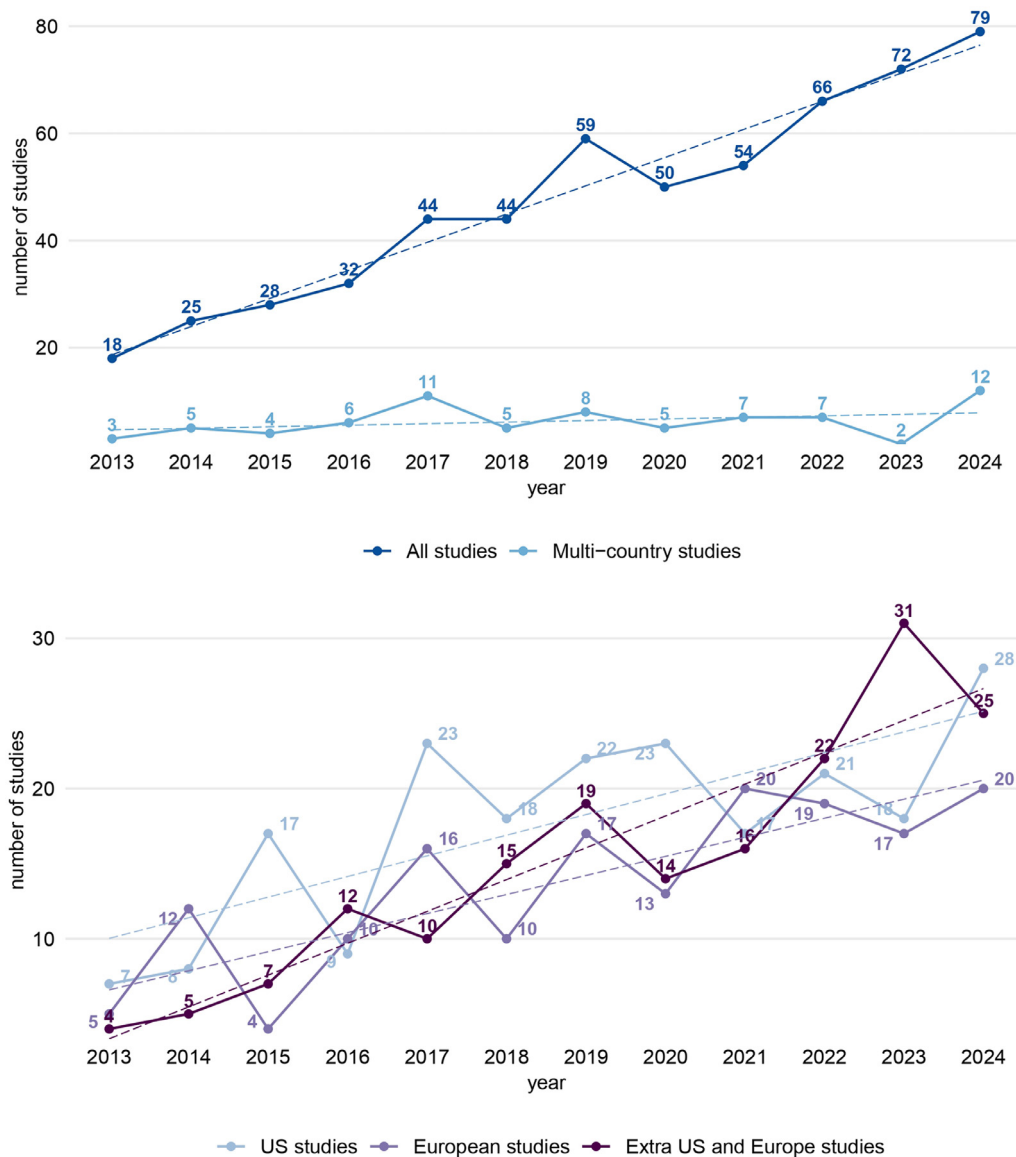


Figure 1. Number of EFS-like studies by start date year (2013–2024). (1) Studies started in 2025 are not shown in the graph, due to the incompleteness of the data (up to June 2025) and consequent influence on the trendlines. Respective partial quantities of studies in 2025 are: 38 overall, 2 European, 7 US, and 20 outside US and Europe, and 1 multi-country (9 had no available geographic information). (2) Multi-country studies are defined as studies that have been conducted in multiple sites, located in more than one country. (3) Studies are geographically categorized based on the location of the centers where they were conducted. Multi-country studies involving multiple centers across regions are counted in each applicable region. (4) European countries are not limited to EU member states, but also include Albania, Andorra, Belarus, Bosnia and Herzegovina, Iceland, Kosovo, Liechtenstein, Moldova, Monaco, Montenegro, North Macedonia, Norway, San Marino, Serbia, Switzerland, Ukraine, United Kingdom, Vatican City. (5) Dashed lines represent trendlines. (6) Start year data was unavailable for nine studies (1.4% of the sample).

any studies that were erroneously identified as EFS. These discussions informed iterative refinement of the database throughout its development.

Data were cleaned for duplicates and manually validated by two researchers to ensure inclusion accuracy. Records were divided between the two researchers for independent review, and any uncertain cases were jointly discussed to reach a final consensus on inclusion. In the context of this study, the final corpus of studies included are referred to as EFS-like studies and the resulting database as EFS-DB.

Endpoint categories were classified according to ISO 14155:2026¹ and FDA guidance,⁹ including safety, efficacy, technical success, technical performance, and procedural feasibility. Information on patient conditions was grouped according to the International Classification of Diseases, Tenth Revision.¹⁴

Results

A total of 621 EFS-like studies were identified. Not all variables were available for all studies; therefore, missing values are indicated where appropriate. The majority were sourced from ClinicalTrials.gov (473, 76%), with the remainder retrieved from other national and international registries and supplementary sources (additional details are available in Supplemental Materials [Online Only], Table S.I). Annual study counts have shown a steady increase since 2013, peaking at 79 new studies in 2024 (Figure 1). This upward trend is evident across the full sample and consistent in both the US and Europe, with an even steeper increase also observed in countries outside these two regions.

Of the 553 studies with available country-level geographic data (Figure 2), 40% (221) were conducted either entirely or partially in the

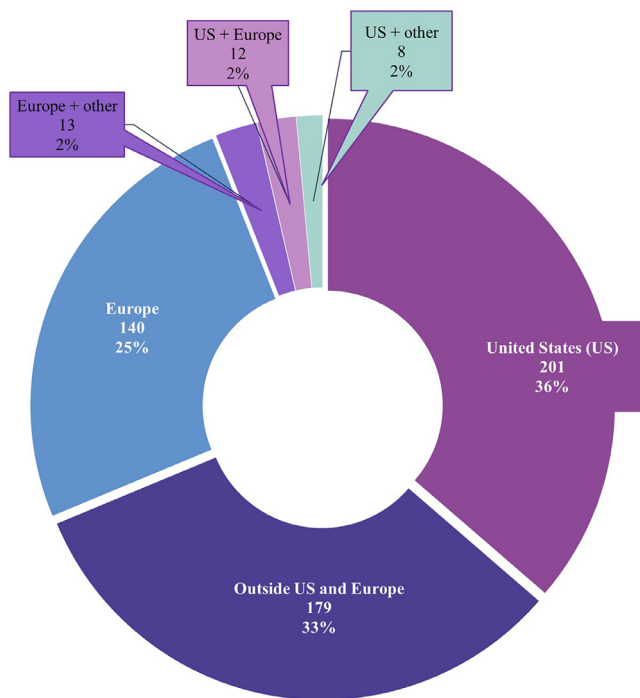


Figure 2. EFS-like studies by geographic area ($n = 553$). Country-level geographic data were not available for 68 studies (11% of the sample).

US, while 30% (165) involved sites in Europe. Among European countries, the top contributors were the United Kingdom (30; of which 16, 53%, conducted before Brexit and 14, 47%, after), Belgium (23), Germany and France (each 22), and Switzerland (20). Countries outside US and Europe accounted for a total of 200 studies (36%), distributed over 17 countries. The most represented ones were Australia (58), New Zealand (27), Canada (22), Israel (21), and China (20). Geographical country-level data was not available for studies sourced from the ICTRP database or, less frequently, incomplete records in other registries.

Global EFS activity was highly concentrated among a few institutions: 10 centers were involved in over 19% (101) of all identified studies (Figure 3). These centers were all US-based, except for Auckland City Hospital, New Zealand, with 14 studies. Columbia University Medical Center, New York led with 34 studies, followed by Emory University, Atlanta (23) and the Mayo Clinic, Rochester (22). Among European centers, the most active were Inselspital (Bern University Hospital), Switzerland, and ZNA Middelheim, Belgium (7 studies each), followed by University Hospital Zurich, Switzerland (6). Finally, the most recurring non-US or European centers were the already cited Auckland City Hospital, New Zealand (14), Tbilisi Heart and Vascular Clinic (11), and Victorian Heart Hospital, Australia (8).

Multicountry studies represented 14% (76) of the total and were primarily concentrated within Europe (28) or involved both Europe and the US or other regions (25). Among European countries participating in multinational studies, Belgium (14), Germany (12), the United Kingdom (11), and France (10) were the most frequently involved.

Approximately 53% (277) of studies were conducted at a single site (Table 2). Overall, 82% (426) took place in four or fewer locations, while the remaining 18% (96) involved five or more sites. Single-centre studies were more frequent in Europe and in other countries outside US and Europe, accounting for 56% (87) of European studies and again 56% (101) of the extra US and Europe studies, compared to 40% (89) of those conducted in the US. Conversely, US-based studies more often involved a higher number of centers: nearly 25% (52) included six or more sites, compared to just 5% (18) in Europe. This difference is likely due to regulatory factors—specifically, the unified FDA approval process in the

US, while European studies require separate approvals when sites span multiple countries, as was the case for 32% (53) of the European sample. Finally, the maximum number of centers involved in a single EFS-like study was 36.

Overall, 45% (282) of all studies focused on devices targeting circulatory system diseases. Other common condition areas included endocrine, nutritional, and metabolic diseases (50, 8%), neoplasms (44, 7%), and diseases of the nervous system (37, 6%). The prevalence of circulatory system-targeted devices was particularly high in multicountry studies, accounting for 68% (52) of them, compared to 50% (111) in US-based studies and 40% (42) in European studies.

Regarding endpoints, safety was the most common primary outcome, reported in 68% (425) of studies, followed by efficacy (287, 48%) and technical success (132, 21%). This appears to be consistent in all geographic locations, and even more so in multicountry studies.

As of June 2025, 42% (230) of the studies had been reported as completed. Completed studies had an average duration of 22.6 months, whereas ongoing studies had a projected average duration of 52.0 months. Study status was unavailable or unknown for 78 studies. Notably, multicountry studies tend to take longer to conclude, with an average duration of 33.6 months, approximately 9 months longer than studies conducted in Europe or the US, representing a 36% increase.

Early termination was reported in 10% (65) of studies. The most frequent reasons cited included patient enrolment challenges (15, 23%), funding limitations (9, 14%), business decisions (7, 11%), and device-related issues (7, 9%). In 15% of cases (10), no clear reason for termination was provided.

Sponsor information was collected for the EFS-like studies, with the exception of 10 studies identified in the literature searches. Although sponsor information is available in the ClinicalTrials.gov database, it does not appear to be updated consistently (a limitation common to other databases as well) and generally does not account for mergers and acquisitions that may occur during device development. Because the data may not reflect an accurate representation of EFS sponsors, we have not included formal analysis in the tables. However, some indications of types of sponsors emerge from text analysis of the sponsor names for the 611 EFS-like studies, though they should be interpreted with caution.

There were 455 unique sponsor names (after standardizing for names that appeared slightly differently in the data); nearly 60% of sponsors registered only one EFS-like in the databases consulted. Those with four or more studies accounted for 14.2% of the identified EFS-like, generally large companies and two university or research organizations, as follows: Edwards Lifesciences (15), W.L.Gore & Associates (7), Boston Scientific Corporation (6), Medtronic (6), Polares Medical SA (6), Eli Lilly and Company (5), Shape Memory Medical, Inc (5), Xeltis (5), Abbott Medical Devices (4), Abiomed Inc. (4), Anteris Technologies Ltd. (4), Hangzhou Endonom Medtech Co., Ltd. (4), InnoCon Medical (4), National Heart, Lung, and Blood Institute (4), John Hopkins University (4), and Tau Pnu Medical Co., Ltd. (4). A total of 69 (11.3%) had “University” in the sponsor name, and a further 65 (10.6%) had “Hospital” (or similar), “Center,” “College,” “Clinic,” or “Institute” in the name. Altogether, 115 (18.9%) of the sponsors were either universities, hospitals, or both, leaving roughly 80% sponsored by industry representatives of various nature.

Discussion and Recommendations

By integrating data from diverse sources, this research generated the first comprehensive database of EFS-like studies, providing some preliminary insights into various aspects of early-stage medical device research. Findings confirm that EFS are increasingly used in early-stage medical device development, particularly for high-risk technologies in cardiology and neurology.

The US, due to its favorable environment and its dedicated regulatory framework, remains the jurisdiction with the highest number of EFS-like conducted (201 over the whole period), although Europe and

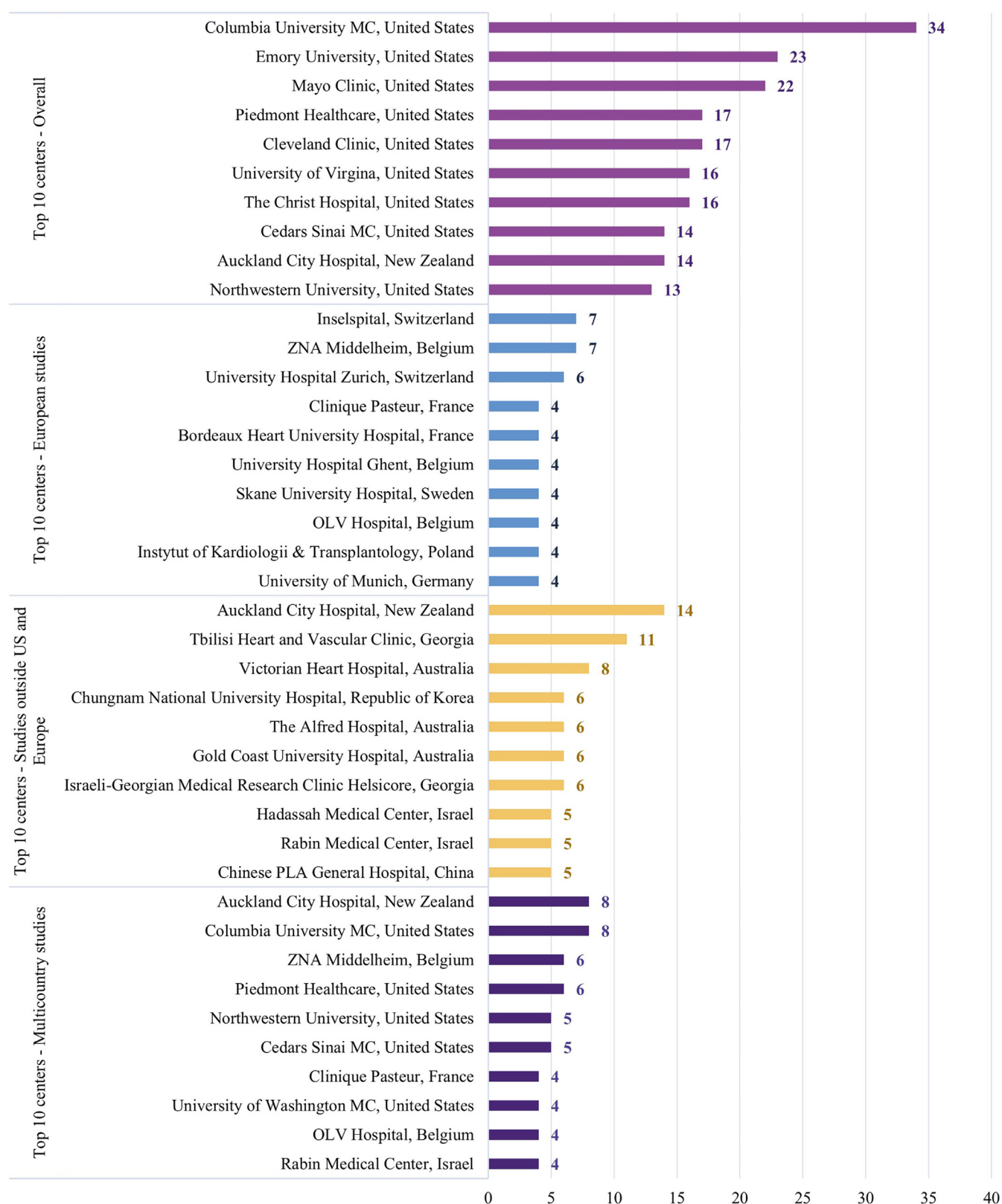


Figure 3. EFS-like study location: clinical sites participating in the highest number of studies.

Table 2

Characteristics of EFS-like studies, overall and geographically divided into US, European outside US, and Europe.

Variable (shown data)	United States studies		European studies		Extra US and Europe studies		All studies		Multi-country studies	
N. observations (n)	n = 221		n = 165		n = 200		n = 621		n = 76	
Number of countries involved in a study (n, column %)										
1	201	91%	112	68%	164	82%	477	86%	0	0%
2	12	5%	24	15%	22	11%	41	7%	41	54%
3	3	1%	18	11%	11	6%	23	4%	23	30%
4	2	1%	6	4%	2	1%	7	1%	7	9%
5	2	1%	3	2%	1	1%	3	1%	3	4%
6–10	1	0%	2	1%	0	0%	2	0%	2	3%
Total	221	100%	165	100%	200	100%	553	100%	76	100%
Missing	0		0		0		68		0	
Number of centers involved in a study (n, column %)										
1	89	40%	87	56%	101	56%	277	53%		
2	28	13%	19	12%	33	18%	75	14%	16	22%
3	19	9%	15	10%	18	10%	48	9%	12	16%
4	16	7%	8	5%	5	3%	26	5%	9	12%
5	16	7%	9	6%	8	4%	28	5%	12	16%
6–10	30	14%	11	3%	12	7%	44	4%	16	9%
11–15	12	5%	4	1%	1	1%	14	1%	5	4%
Over 15	10	5%	3	1%	1	1%	10	1%	4	1%
Total	220	100%	156	100%	179	100%	522	100%	74	100%
Missing	1		9		21		99		2	
Condition category (n, column %)										
Diseases of the circulatory system	111	50%	66	40%	99	50%	282	45%	52	68%
Endocrine, nutritional and metabolic diseases	19	9%	11	7%	15	8%	50	8%	2	3%
Neoplasms	14	6%	14	8%	13	7%	44	7%	2	3%
Diseases of the nervous system	14	6%	8	5%	12	6%	37	6%	1	1%
Diseases of the genitourinary system	6	3%	14	8%	14	7%	36	6%	8	11%
Diseases of the eye and adnexa	9	4%	6	4%	8	4%	23	4%	1	1%
Injury, poisoning and certain other consequences of external causes	14	6%	6	4%	3	2%	23	4%	1	1%
Diseases of the musculoskeletal system and connective tissue	3	1%	9	5%	5	3%	22	4%	3	4%
Diseases of the digestive system	3	1%	5	3%	8	4%	20	3%	1	1%
Diseases of the respiratory system	5	2%	3	2%	6	3%	15	2%	2	3%
Diseases of the skin and subcutaneous tissue	5	2%	2	1%	3	2%	10	2%	0	0%
Diseases of the ear and mastoid process	3	1%	3	2%	1	1%	8	1%	1	1%
Pregnancy, childbirth and the puerperium	0	0%	2	1%	3	2%	5	1%	1	1%
Certain infectious and parasitic diseases	3	1%	0	0%	0	0%	4	1%	0	0%
Certain conditions originating in the perinatal period	2	1%	1	1%	0	0%	3	0%	0	0%
Congenital malformations, deformations and chromosomal abnormalities	1	0%	1	1%	0	0%	2	0%	0	0%
Factors influencing health status and contact with health services	0	0%	2	1%	0	0%	2	0%	0	0%
Mental and behavioral disorders	0	0%	0	0%	2	1%	2	0%	0	0%
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	0	0%	1	1%	0	0%	1	0%	0	0%
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	0	0%	1	1%	0	0%	1	0%	0	0%
Nonspecific	9	4%	10	6%	8	4%	31	5%	1	1%
Total	221	100%	165	100%	200	100%	621	100%	76	100%
Missing	0		0		0		0		0	
Primary endpoints category (n, column %)										
Safety	164	74%	114	69%	138	69%	425	68%	67	88%
Efficacy	105	48%	80	48%	84	42%	287	46%	36	47%
Technical success	40	18%	31	19%	57	29%	132	21%	18	24%
Technical performance	14	6%	20	12%	10	5%	47	8%	3	4%
Ergonomics	3	1%	4	2%	0	0%	7	1%	0	0%
Procedural feasibility	0	0%	4	2%	2	1%	6	1%	1	1%
Other endpoints	3	1%	4	2%	0	0%	8	1%	0	0%

(continued on next page)

Table 2 (continued)

Study status (n, column %)										
Completed	73	35%	85	57%	76	42%	230	42%	29	42%
Recruiting	55	26%	28	19%	49	27%	124	23%	18	26%
Active, not recruiting	42	20%	12	8%	27	15%	73	13%	16	23%
Suspended/terminated/withdrawn	29	14%	18	12%	11	6%	65	12%	5	7%
Not yet recruiting	9	4%	5	3%	19	10%	51	9%	1	1%
Total	208	100%	148	100%	182	100%	543	100%	69	100%
Missing	13		17		18		78		7	
Average study duration in months (mean, std)										
Completed	24.6	26.6	24.5	22.8	20.1	20.1	22.6	23.2	33.6	28.1
Recruiting	66.4	42.7	48.5	33.7	38.1	31.9	51.0	39.0	69.1	38.2
Active, not recruiting	91.8	47.8	82.1	44.2	53.3	47.1	73.6	47.0	87.6	55.4
Suspended/terminated/withdrawn	30.6	28.7	28.5	22.9	25.9	21.8	30.1	27.0	27.4	20.0
Not yet recruiting	24.5	26.9	11.6	8.2	15.0	17.6	22.4	23.6	4.1	nd
Total	50.1	45.3	33.7	31.9	29.7	31.3	36.7	36.6	54.3	44.6
Missing	13		17		18		78		7	
Reasons for suspension, termination, withdrawal (n, column %)										
Enrollment issues	6	21%	5	28%	3	27%	15	23%	2	40%
Funds issues	4	14%	0	0%	1	9%	9	14%	0	0%
Business decision	3	10%	2	11%	1	9%	7	11%	0	0%
Device issues	4	14%	2	11%	0	0%	6	9%	1	20%
COVID impact	3	10%	1	6%	1	9%	5	8%	0	0%
Study design issue	0	0%	2	11%	0	0%	2	3%	0	0%
Other reasons	5	17%	4	22%	2	18%	11	17%	0	0%
Unspecified reason	4	14%	2	11%	3	27%	10	15%	2	40%
Total	29	100%	18	100%	11	100%	65	100%	5	100%

The last column shows multi-country studies for comparison. Studies are geographically categorized based on the location of the centers where they were conducted. Studies involving multiple centers across regions are counted in each applicable region.

other regions also show a steady increase. Notably, the application of the EU MDR in May 2021 appears not to be associated with a decline in EFS activity; on the contrary, 2021 to 2024 represents the period with the highest number of such studies initiated in Europe (76, compared to 56 in the previous 4-year period), suggesting no immediate adverse effect on medical device innovation. Indeed, despite the absence of a dedicated regulatory pathway for EFS under the MDR, these studies continue to be actively conducted across Europe. This highlights both their importance for medical device development and the need for greater regulatory clarity. A harmonized European framework, promoted by the HEU-EFS project, could foster more consistent uptake and reduce disparities across Member States, as currently the EFS implementation remains uneven, with most studies concentrated in a few experienced centers and countries.

Indeed, findings from our analysis on the EFS-DB and from HEU-EFS project underline the importance of site capability: EFS are best conducted in clinical centers with advanced infrastructure, experienced investigators, streamlined contracts and review processes, and access to high-risk patient populations.^{10,15–17} To this end, EFS-DB findings consistently show that nearly one in five studies involved at least one of the top 10 centers. However, the dominance of a few centers, nearly all of them US-based, reflects a significant capacity constraint. Even in EU countries with EFS experience, innovation is hindered by procedural and regulatory inefficiencies, inconsistent access to appropriate patient populations, and lack of specialized staff, factors that also compromise effective risk evaluation.^{13,18–20}

Data from the EFS-DB highlights as well how the centralized approval process in the US facilitates broader study implementation. In the US, one quarter of all studies (52) involved six or more participating sites, whereas only 5% (18) of European studies reached this level of multicentric participation. The streamlined US process allows sponsors to engage with a higher number of centers, thereby expanding access to potential study candidates. In contrast, similar efforts in Europe often require multiple national approvals when sites are distributed across different countries, leading to longer timelines and increased administrative burden. However, the European Commission appears to have

acknowledged this limitation and is currently piloting a coordinated assessment procedure among Member States to streamline approvals and improve cross-border study implementation.

EFS-DB data also supports the strategic value of EFS in mitigating risks. EFS may act as a filtering mechanism before larger trials, allowing developers to assess feasibility and safety in a controlled setting.²¹ It is therefore unsurprising that the by far most commonly measured primary endpoints refer to safety, present in almost 70% (425) of EFS-like, avoiding unnecessary resource use and limiting patient exposure to underperforming technologies. Moreover, the proportion of studies that were terminated early and did not reach completion was relatively low in the sample (65, 10%). This might suggest a generally good capacity for managing EFS by the proposing centers and clinicians. However, this observation could be confounded by the lack of updates regarding study status in the databases, which is difficult to verify. This limited evidence supports the potential role of early-stage, small-scale clinical investigations, such as EFS, in informing go/no-go decisions by product developers and in guiding efforts to optimize product portfolios before committing to broader, more costly, clinical investigations. In the long term, this might result in lower overall research and development costs and better, more cost-effective technologies being developed.

Based on the findings from our empirical database, we devised several recommendations to support the development and implementation of an EFS framework in the EU.

Improve quality and availability of data on EFS: This study has revealed significant challenges in accessing and retrieving reliable information on EFS conducted both in Europe and globally. To address these gaps, there is a need to promote more transparent, standardized, and systematic data collection on EFS. Such data should be integrated into broader clinical development pathways and embedded into existing data infrastructures, following the FAIR principles (Findable, Accessible, Interoperable, and Reusable).²² Within the HEU-EFS project, further work will focus on how best to embed EFS data into EU regulatory frameworks and structures, such as exploring integration with the EUDAMED clinical investigation module under development. Additionally, given the recognition of EFS in ISO 14155:2026, incorporating EFS-specific op-

tions in European Commission templates and forms would be a logical next step.

Implement monitoring and evaluation systems for EFS: To fully understand the value of EFS in enhancing evidence quality, accelerating time-to-market, and safeguarding patients, robust and transparent monitoring and evaluation systems must be established. These systems should provide National Competent Authorities with the necessary tools to assess the contribution of EFS to medical device development. Moreover, such tools should include performance indicators to evaluate whether a dedicated EU-EFS program can foster innovation and enhance Europe's global competitiveness.

Investigate the necessary requirements and competency set for centers to successfully manage EFS: Findings from this study show that early-stage clinical investigations are currently concentrated within a small group of investigational centers worldwide. For a European EFS program to thrive, it is crucial to define the core competencies, infrastructure, and organizational frameworks that centers must have in place to effectively conduct EFS. Identifying and promoting these standards will support the development of a high-quality and geographically diverse network of EFS-capable centers across Europe.

Finally, some limitations should be acknowledged, especially in the construction of the EFS-DB. First, in the absence of a standardized classification, study selection relied on assumptions that may not apply universally to EFS. In fact, some studies that authors identified as EFS in the title or summary of the database record included more than 30 subjects, which we used as a cutoff for the studies we identified using inclusion criteria. We deemed it important to include all studies that were explicitly labelled as EFS. Inconsistent data quality, limited detail, and sponsor-initiated (not always traceable) updates to trial records further complicated study identification and data extraction. Additionally, differences across databases resulted in missing or incomplete information, limiting the ability to consistently reconstruct evidence generation processes.

Finally, because no mandatory global registry specifically identifies EFS, some studies may not have been captured. This limitation is particularly relevant for sponsor-initiated studies that were neither registered nor publicly disclosed. This necessarily required that the objective of the EFS-DB be to identify publicly identifiable EFS through systematic searches of registries and complementary public sources rather than to estimate the absolute number of EFS conducted worldwide. The EFS-DB might therefore be skewed toward countries with stricter reporting requirements or toward clinical investigations intended for publication. Nevertheless, several factors likely mitigate this risk. First, many commercial sponsors routinely register studies to support future publication, regulatory interactions, or reimbursement processes.²³ Second, our informal completeness checks against sponsor portfolios within the HEU-EFS project revealed high consistency with sponsor interviewee knowledge of registered studies. However, most of the sponsors interviewed were larger companies and may have been more likely to register their studies in registries for governance or transparency reasons. Nevertheless, caution in interpreting our database results is warranted. Conversations with National Competent Authorities, rather than serving as a check of all EFS conducted in the respective countries, elicited considerable discussion regarding how to define and recognize EFS as a regulator. Considering the evidence from this study, inclusion of a clear definition of EFS in the MDR (currently under revision), and requirements to register EFS in publicly available clinical trial registries and report EFS results should be explored to improve consistency across European countries.

Conclusion

This study presents the first large-scale, empirical mapping of EFS for medical devices, enriched by stakeholder validation. The data reveal that while EFS are gaining traction globally, their implementation remains uneven, with the majority concentrated in a few experienced

centers and hindered in Europe by regulatory, infrastructural, and procedural fragmentation.

To harness the full potential of EFS in the EU, there is a clear need for coordinated policy action. Establishing a formal EFS pathway aligned with ISO 14155, improving transparency through better registry integration, supporting centre readiness through capacity-building, and addressing medicolegal and ethical challenges are all critical. Taken together, these reforms could enable the EU to better support responsible innovation, reduce delays in patient access to high-risk technologies, support the work of National Competent Authorities, foster cooperation and harmonization, and bolster the EU position in the global MedTech research landscape.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2026.07.015.

References

1. International Organization for Standardization. ISO 14155:2026 Clinical investigation of medical devices for human subjects – good clinical practice. <https://www.iso.org/standard/83968.html> (accessed July 10, 2024).
2. Van Norman GA. Drugs and devices: comparison of European and U.S. approval processes. *JACC Basic Transl Sci.* 2016;1:399–412.
3. Van Norman GA. Drugs, devices, and the FDA: Part 2: an overview of approval processes: FDA approval of medical devices. *JACC Basic Transl Sci.* 2016;1:277–287.
4. Amon A, Marjenin T, Duarte RV, et al. Regulatory framework for implantable neurostimulation devices: comparison of systems in the US and European Union. *Neuro-modulation: Technol Neural Interface.* 2024;27:447–454.
5. FDA Center for Devices and Radiological. Regulatory controls. FDA. 2023. <https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls> (accessed July 4, 2025).
6. Holmes DR, Shuren J, Califf R, et al. Clinical perspective – early feasibility device medical studies in the United States: time for more than regulatory reform. *JACC: Cardiovasc Interv.* 2016;9:626–628.
7. Consortium MDI. Early feasibility studies program. MDIC Medical Device Innovation Consortium. 2024. <https://mdic.org/program/early-feasibility-studies-efs/> (accessed June 18, 2024).

8. FDA Center for Devices and Radiological. Early feasibility studies (EFS) program. FDA. 2023; <https://www.fda.gov/medical-devices/investigational-device-exemption-ide/early-feasibility-studies-efs-program> (accessed July 4, 2025).
9. FDA. Investigational device exemptions (IDEs) for early feasibility medical device clinical studies, including certain first in human (FIH) studies. 2013. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-device-exemptions-ides-early-feasibility-medical-device-clinical-studies-including> (accessed June 19, 2024).
10. Holmes DRJ, Califf R, Farb A, et al. Overcoming the challenges of conducting early feasibility studies of medical devices in the United States. *J Am Coll Cardiol*. 2016;68:1908–1915.
11. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA relevance). 2017 <http://data.europa.eu/eli/reg/2017/745/oj/eng> (accessed Oct 29, 2024).
12. Peñarrubia-Ortiz S, Calvo E. European medical devices regulation: a plea for ensuring safety without slowing access to innovation. *J Shoulder Elbow Surg*. 2025;34:332–336.
13. Callea G, Federici C, Freddi R, Tarricone R. Recommendations for the design and implementation of an early feasibility studies program for medical devices in the European Union. *Expert Rev Med Devices*. 2022;19:315–325.
14. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), 2019 version. Geneva: World Health Organization; 2019. <https://icd.who.int/browse10/2019/en>.
15. Holmes DR, Geffrion R, Hunt J, et al. Regulatory strategies for early device development and approval. *Catheter Cardiovasc Interv*. 2022;99:1784–1788.
16. Valledor A, Tangila Kayembe O, et al. Early feasibility studies in Europe: a multisite qualitative study of operational challenges and site selection determinants at 6 university hospital. *Clin Ther*. 2026 S0149-2918(26)00191-8. doi:10.1016/j.clinthera.2026.06.003.
17. Banks H, Buzelli ML, Tangila Kayembe O, et al. Pre-market clinical investigation approval pathways and the role of early feasibility studies for medical devices: a scoping review to guide EU policy. *Expert Rev Med Devices*. 2026;25:1–14. doi:10.1080/17434440.2026.2693727.
18. Tarricone R, Banks H, Ciani O, et al. An accelerated access pathway for innovative high-risk medical devices under the new European Union Medical Devices and health technology assessment regulations? Analysis and recommendations. *Expert Rev Med Devices*. 2023;20:259–271.
19. Windecker S, Fraser AG, Szymanski P, et al. Priorities for medical device regulatory approval: a report from the European Society of Cardiology Cardiovascular Round Table. *Eur Heart J*. 2025;46:1469–1479.
20. Watson C, Richmond FJ. EU's medical device expert panels: analysis of membership and published clinical evaluation consultation procedure (CECP) results. *Ther Innov Regul Sci*. 2024;58:910–916.
21. Weiss JP, Farb A. Early feasibility studies in the United States: focus on electrophysiology. *J Cardiovasc Electrophysiol*. 2023;34:2158–2162.
22. Wilkinson MD, Dumontier M, Aalbersberg IJJ, et al. The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data*. 2016;3:160018.
23. De Angelis C, Drazen JM, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *Lancet*. 2004;364:911–912. doi:10.1016/S0140-6736(04)17034-7.