

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

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

DELIVERABLE 1.3

Characteristics and state of play of EFS

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ABBREVIATIONS

ANZCTR	Australian New Zealand Clinical Trials Registry
CE	Conformité Européenne
CMS	Centers for Medicare & Medicaid Services
CT.gov	ClinicalTrials.gov
EFS	Early Feasibility Studies
EFS-DB	Early Feasibility Studies Database
EU	European Union
FDA	US Food and Drug Administration
HEU-EFS	Harmonized Approach to Early Feasibility Studies for Medical Devices in the European Union
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10 th Revision
ICTRP	International Clinical Trials Registry Platform
IDEs	Investigational Device Exemptions
ISO	International Organization for Standardization
ISRCTN	International Standard Randomized Controlled Trial Number Registry
MD	Medical Device
PMA	Pre-market approval
UB	Bocconi University
US	United States
WP	Work Package

EXECUTIVE SUMMARY

Introduction. Early Feasibility Studies (EFS) are defined by ISO 14155:2020 as limited clinical investigations of a device early in its development, typically before the device design is finalized. These studies are relevant for evaluating initial clinical safety and performance, particularly for innovative, high-risk technologies. EFS are proposed to streamline clinical evidence generation for medical devices (MDs), fostering innovation and reducing time to market while maintaining ethical standards and patient safety. However, little is known about the extent of EFS implementation, their integration into manufacturers' evidence generation plans, or their impact on evidence quality and time-to-market. The objective of this report was to build a database of EFS (EFS-DB) conducted worldwide and analyse their main characteristics, with the aim of informing the future development of a harmonized EFS framework in the EU.

Methods. In the absence of an approach to objectively identify EFS in clinical trial databases, broad inclusion criteria were used to build the EFS-DB. EFS-like studies were defined as studies explicitly identified as EFS in their titles or summaries, or any other open-label, non-comparative interventional study with an estimated sample size of 30 or fewer patients. EFS were extracted from multiple public clinical trial databases and manually screened to verify they met the eligibility criteria. Data was supplemented with information from literature reviews and specialized news sites. The search included all studies initiated worldwide with no time constraints. Focused interviews to MD manufacturers within the HEU-EFS project were also conducted to validate the search strategy and collect additional information on the evidence generation pathways for a subset of medical devices identified in the search.

Results: A total of 559 EFS-like studies were identified in the database, showing a steady increase over time since 2013, both globally and within the EU. Of the identified studies, 37% (n = 205) were conducted either solely in the US or in collaboration with US sites, while European clinical investigation sites participated in 28% of them. The overview showed that 10 centres conducted over 25% of global EFS-like studies, mostly in the US. This concentration may reflect the stringent requirements for planning and conducting EFS, which may exceed those for later-stage device investigations. Nearly half of studies (46%, n = 257) focused on devices targeting circulatory system diseases. Most studies initiated after 2019 (81.4%, n = 162) were still active (i.e., either not yet recruiting, enrolling, or active but not enrolling) as of March 2024, suggesting long enrolment and follow-up periods for these studies. About 10% (n = 53) of studies were not completed due to suspension, termination, or withdrawal, with enrollment challenges being the most common issue (20%, n = 14). Device or study design issues led to discontinuation in 14% (n = 10), and 13% (n = 9)

were discontinued due to funding issues. However, information on the reasons for study termination was insufficient for 25% of the sample (n = 17). Further insights were gained through surveys and interviews conducted with consortium partners aimed at partially validating the database and investigating the EFS they conducted, relating to 33 devices. The analysis showed a sensitivity of the search strategy of 94%, with over 9 out of 10 EFS conducted by the industry partners being identified in the EFS-DB, and highlighted that 19 devices underwent formal FDA-EFS processes. The 33 devices investigated have been further explored with respect to clinical evidence generation pathways defined by the manufacturers, including pre-market, market access, and post-market phases.

Discussion: Despite the absence of a formal program, National Competent Authorities (NCA) approve EFS-like studies that are hosted by European clinical sites, suggesting the need for formalizing a transparent, unified framework for EFS in Europe, akin to the dedicated EFS program in the US.

- **Promote Multistakeholder Dialogue on EFS:** Given the increasing trend of early-stage clinical investigations in Europe, it is crucial to foster structured dialogue among all stakeholders involved in MD development and regulation, beyond the HEU-EFS project.
- **Improve Data Quality and Availability:** Efforts should focus on promoting systematic collection and integration of EFS data into existing data flows at the EU level. Data should be managed according to FAIR principles to ensure accessibility and reuse for research and innovation.
- **Implement Monitoring and Evaluation Systems:** Establish transparent monitoring systems to assess whether EFS can enhance evidence quality, accelerate time-to-market, and improve patient outcomes. Monitoring tools should help NCAs evaluate EFS as a key component in MD evidence generation and assess its impact on innovation and competitiveness in Europe.
- **Investigate Requirements for EFS Management:** It is essential to define the competencies and organizational characteristics required for clinical sites to successfully manage EFS. HEU-EFS will develop eligibility criteria for clinical sites as part of its efforts to establish an EU EFS program.

This report presents unique data on EFS-like studies, which could improve decision-making and policy formulation in MD research in Europe. It also outlines a roadmap for enhancing the monitoring and evaluation of EFS to ensure a transparent, effective, and accountable European EFS program.

1. Introduction

This document is part of the activities under the *Harmonised Approach to Early Feasibility Studies for Medical Devices in the European Union* (HEU-EFS) project. The initiative aims to develop a harmonized framework for EFS in the EU as one integrated step of the evidence generation cycle. Specifically, the work presented here contributes to Work Package 1 (WP1) *Research and Analysis on the State of Pre-Market Programs and Barriers to EFS Implementation* that aims to gain a robust understanding of the characteristics, strengths, weaknesses, and opportunities of current pre-market clinical evidence generation programs.

This deliverable addresses Task 1.3 *Empirical Investigation of the Impact of Individual EFS on Lifecycle Evidence Generation and MDs Safety*. In this task we sought to obtain a granular representation of the characteristics of EFS conducted so far and understand whether, and to what extent, EFS represented the first step in the lifecycle clinical evidence generation pathway for medical devices (MDs).

EFS are defined by the International Standard ISO 14155:2020 Clinical investigation of MDs for human subjects – Good clinical practice as “*a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication [...]. It can be used to evaluate the device design concept with respect to initial clinical safety and device clinical performance or effectiveness (if appropriate) as per intended use in a small number of subjects when this information cannot practically be provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable. Information obtained from an early feasibility clinical investigation can guide device modifications.*” (International Organization for Standardization, 2020).

EFS can be particularly impactful when applied to innovative, high-risk technologies, with lifesaving potential for patients with no alternative treatment options. Although EFS are formally recognized under ISO standards, the United States (US) is the only jurisdiction to have established a dedicated program to support their adoption. In 2013, the Food and Drug Administration (FDA) issued guidance on Investigational Device Exemptions (IDEs) for EFS as part of a broader effort to revitalize pre-market clinical research (Food and Drug Administration, 2013). This initiative aimed to reverse a decline in MD clinical studies conducted in the US, which dropped from 87% to 45% between 2004 and 2009 (Holmes et al., 2016). 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 MDs.

Despite these initiatives, public access to information on EFS remains limited. No comprehensive databases or repositories currently classify studies as EFS, either in the US or globally. Even well-

established international clinical trials databases, such as ClinicalTrials.gov or the International Clinical Trials Registry Platform (ICTRP), do not require studies to indicate their classification as EFS, not even as an optional field.

This report addresses the lack of comprehensive information on EFS by collecting publicly available data to identify EFS and comparable studies and provides an in-depth analysis of their characteristics to support the development of the EU EFS program.

The report is organized as follows. Section 2 outlines the methodology used to identify relevant studies and gather additional case-specific data from device manufacturers. Section 3 presents the main findings from the analysis. Last, section 4 draws some conclusions to support the development of the EU EFS Program.

2. Methodology

The methodology employed in the study combines both quantitative and qualitative approaches. The quantitative component involved searching clinical trial databases and analysing the extracted studies. The qualitative component consisted of surveys and interviews to validate and complement the findings. A concise overview of the methodological approach is provided here and illustrated in Figure 1. Each step is detailed in the subsequent sections. First, we identified potentially relevant studies from international clinical trial databases and other sources using a comprehensive set of search terms. Second, information available from the databases was extracted and consolidated into an Early Feasibility Studies Database (EFS-DB). Since no objective criteria exist for identifying EFS within these databases, EFS-like studies were included based on a predefined set of inclusion and exclusion criteria using the information available from the databases. Third, descriptive analyses were performed on the identified subset of EFS-like studies. Finally, interviews with consortium members were conducted to validate the data and gain additional insights into a subset of medical devices from studies they sponsored, with a particular focus on the clinical evidence pathways of these devices.

Figure 1 Schematic representation of research methodology



2.1. Building of an EFS database

A comprehensive database called EFS-DB¹ was constructed searching public databases of clinical investigations and other sources, adapting the methods described by Callea et al. (2022). Specifically, their approach to identify EFS was extended by including a more extensive set of registries as data sources, adopting a broader range of keywords to identify relevant studies.

Between February and March 2024, we searched several publicly available clinical trial databases, including ClinicalTrials.gov ([CT.gov](https://clinicaltrials.gov)), the World Health Organization International Clinical Trials Registry Platform ([ICTRP](https://www.who.int/clinical-trials-registry-platform)), the Australian New Zealand Clinical Trials Registry ([ANZCTR](https://www.anzctr.org.au)), and the International Standard Randomized Controlled Trial Number Registry ([ISRCTN](https://www.isrctn.com)). A broad array of keywords was employed to maximize inclusivity and ensure the retrieval of all potentially relevant

¹ The database can be accessed on HEU-EFS website.

studies. The search query, allowing for a few minor differences to accommodate the different syntaxes of the registries, is presented in Box 1. The scope was restricted to studies involving MDs or combinations of MDs and drugs. Duplicate entries were removed.

Box 1 Search query employed for database extractions

"early feasibility" OR "preclinical feasibility study" OR "early clinical feasibility" OR "early clinical study" OR "early clinical studies" OR "proof of principle" OR "proof of concept" OR "iterative development" OR "translational research" OR "early stage clinical" OR "early clinical evaluation" OR "early clinical evaluations" OR "initial clinical safety" OR "prototype study" OR "prototype studies" OR "first in human" OR "premarket study" OR "limited clinical investigation" OR "pre-clinical feasibility study" OR "first in man" OR "FIM" OR "FIH" OR "pre-market study" OR "EFS"

Subsequently, data for each study was downloaded from the included databases. Information extracted included: source (i.e., the name of the database), study ID, study title, summary, intervention type (e.g., device, drug, radiation, biological, behavioural, procedure, other), study phase (Early Phase 1, Phase 1, Phase 2, Phase 3 or Phase 4), estimated enrolment (i.e., target number of participants that the researchers need for the study), study type (interventional or observational), allocation (randomized or non-randomized), interventional model (e.g., single group, sequential, parallel, crossover assignment), masking (e.g., open, double, triple), primary purpose (i.e., treatment, prevention, diagnostic, supportive care, screening, health services research, basic science, other), sponsor name, collaborators, trial start and end dates, recruitment status (i.e., not yet recruiting, recruiting, enrolling by invitation, active not recruiting, suspended, terminated, completed, withdrawn, unknown), primary endpoints, funder type (i.e., U.S. National Institutes of Health, Other U.S. Federal agencies, Industry, All others), patient condition/disease, location (i.e., Country, State, City), investigator, withdrawal reasons, and related publications.² The database was completed with additional searches and elaborations. An automated web scraping algorithm using Python was designed to extract relevant information when not directly available in the downloaded data from the databases. Information on patient conditions were grouped according to the International Classification of Diseases, Tenth Revision (ICD-10)³. The primary endpoints cited by the studies were also classified into specific categories, depending on what the outcome measures referred to: ergonomics, procedural feasibility, technical performance, technical success, safety, efficacy, and other. Categories were defined based on existing definitions by the FDA (2013) and ISO (2020) and methodological guidelines on EFS and discussion among the HEU-EFS consortium.

² See [ClinicalTrials.gov Glossary Terms](#) for details regarding the variables' occurrences.

³ [ICD-10-CM | Classification of Diseases, Functioning, and Disability | CDC](#)

From the list of identified studies, pre-specified inclusion and exclusion criteria were applied to identify EFS. Due to the lack of a clear way for identifying EFS in the databases, we defined “EFS-like” studies as detailed in Box 2. Studies missing any of these details were nevertheless included in the initial list of studies and then screened manually at a later stage.

Box 2 Definition of EFS-like study

- Study name or study description including "early feasibility" OR "EFS".
- No requirements with respect to other variables.

OR

- Intervention or treatment: Device or combination of MD and drug AND
- Estimated (or target) sample size: 30 or less patients AND
- Study type: Interventional AND
- Interventional Study Model: “Single arm” or “Single group” AND
- Masking designation: “Open label” or none AND
- Allocation: Non-randomized.

The criteria considered reflected the ISO14155:2021 definition of EFS and the exploratory nature of these type of studies, which are mostly limited interventional, open-label, non-comparative studies. The maximum sample size was set at 30, corresponding to three times the number of subjects indicated by the FDA Guidance for EFS (Food and Drug Administration, 2013) and two times that indicated by the Medical Device Innovation Consortium (MDIC)⁴ Blueprint for EFS (2016). This higher threshold was set to increase the sensitivity of the search strategy, as experts within the consortium reported EFS being conducted with a bigger sample size than the target one proposed by FDA and MDIC.

To further supplement the database, we incorporated studies identified from additional sources: literature reviews conducted on PubMed and Scopus as part of WP1, task 1.1 *Scientific review of characteristics and impact of pre-market programs for MDs in the EU and other relevant jurisdictions*, data from CMS.gov⁵ (pertaining to MDs approved for reimbursement), and studies reported by specialized news sites such as CardiovascularNews,⁶ Cardiovascular Business,⁷ Cardiac

⁴ MDIC is a public-private partnership between the FDA and industry founded in 2012 (see <https://mdic.org/>).

⁵ <https://www.cms.gov/medicare/coverage/investigational-device-exemption-ide-studies/approved>

⁶ <https://cardiovascularnews.com/>

⁷ <https://cardiovascularbusiness.com/>

Interventions Today,⁸ Endovascular Today,⁹ PR Newswire,¹⁰ and NeuroNews.¹¹ We also reviewed the database of EFS identified by Callea et al. (2022) until April 2022 to include any additional studies not captured in the current search. Whenever possible, these additional studies were linked back to their corresponding clinical trial database, and the same information described above was collected and included in the EFS-DB.

Finally, in June 2024 two researchers conducted a manual review of the identified studies to ensure that inclusion criteria were actually met, and uncertain cases were discussed with another researcher.

2.2. Survey to medical device manufacturers

The second part of the research methodology involved a survey with MD manufacturers among the consortium members with experience in the conduction of EFS, to validate and integrate the information retrieved from the databases. The survey aimed to: (1) assess whether the EFS-like studies identified in the EFS-DB and sponsored by consortium members were conducted under the US FDA EFS program; (2) verify the accuracy of the EFS-DB by identifying any missing EFS; and (3) gather additional information on the medical devices studied and their clinical evidence generation pathways.

During this phase, all the HEU-EFS technology developers received the list of MDs sponsored by their company that appeared in the EFS-DB. Partners were asked to provide additional information on each device. Specifically, the survey focused on the following items: (1) further device and study identification details, (2) whether the MD was investigated under the US FDA EFS program, (3) clinical pre-market studies conducted prior to the identified EFS-like study, (4) clinical pre-market studies conducted after the identified EFS-like study, (5) regulatory approval status of the device in the US, EU, and other regions, (6) clinical post-market studies conducted following regulatory approval, and (7) safety issues observed post-approval. The survey is presented in Table 1.

⁸ <https://citoday.com/>

⁹ <https://evtoday.com/>

¹⁰ <https://www.prnewswire.com/>

¹¹ <https://neuronewsinternational.com/>

Table 1 Survey to HEU-EFS technology developers

Question #	Question
Section 1: Device study identification	
1	Device name
2	Clinical study database identification code (NCT code if available)
3	Study title
4	Study start date
5	Study end date (actual or estimated)
6	EMDN category (if available)
7	Device risk class (US), if available
8	Device risk class (EU), if available
Section 2: EFS conducted under FDA program	
9	Was the device investigated under the FDA EFS program?
Section 3: Clinical pre-market studies conducted prior to the identified EFS-like	
10	For each device, please indicate whether other clinical trials have been conducted prior to the identified EFS-like study <i>If yes, please provide the kind of study conducted and the NCT (or alternative database) reference for each of the studies</i>
Section 4: Clinical pre-market studies conducted after the identified EFS-like study	
11	For each device, please indicate whether other pre-market clinical trials have been conducted after the identified EFS-like study <i>If yes, please provide the kind of study conducted and the NCT (or alternative database) reference for each of the studies</i>
12	In case no other pre-market study have been conducted for the device, please select a reason for their lack <i>If you selected "Other (please specify)", please indicate the reason</i>
Section 5: Regulatory approval	
13	Was the device approved in the US?
14	Type of FDA approval
15	Date of FDA approval (year-month)
16	Has the device obtained the CE mark for EU?
17	Date of EU approval (year-month)
18	Name of the Notified Body that granted the CE mark?
19	Has the device obtained the regulatory clearance in other countries?
Section 6: Clinical post-market studies conducted after regulatory approval	
20	For each device, please indicate whether other clinical trials have been conducted after the regulatory approval <i>If yes, please provide the kind of study conducted and the NCT (or alternative database) reference for each of the studies</i>

Section 7: Device safety issues after approval	
21	Has the device received any recall in any jurisdiction after the market approval?
22	Has the device received any field safety notice (other than recalls) in any jurisdiction?

To partially validate the list of studies identified in the database search, industry partners from the consortium were also invited to review the list of their devices included in the EFS-DB and supplement it with any unreported devices that had undergone an EFS under the FDA program. For each additional device reported, they were also asked to provide the same set of information described in Table 1. The survey, finalized in consultation with industry members, was open from June to August 2024. Finally, one-on-one interviews were conducted with respondents in September 2024, to discuss and validate the findings from both the database and the survey.

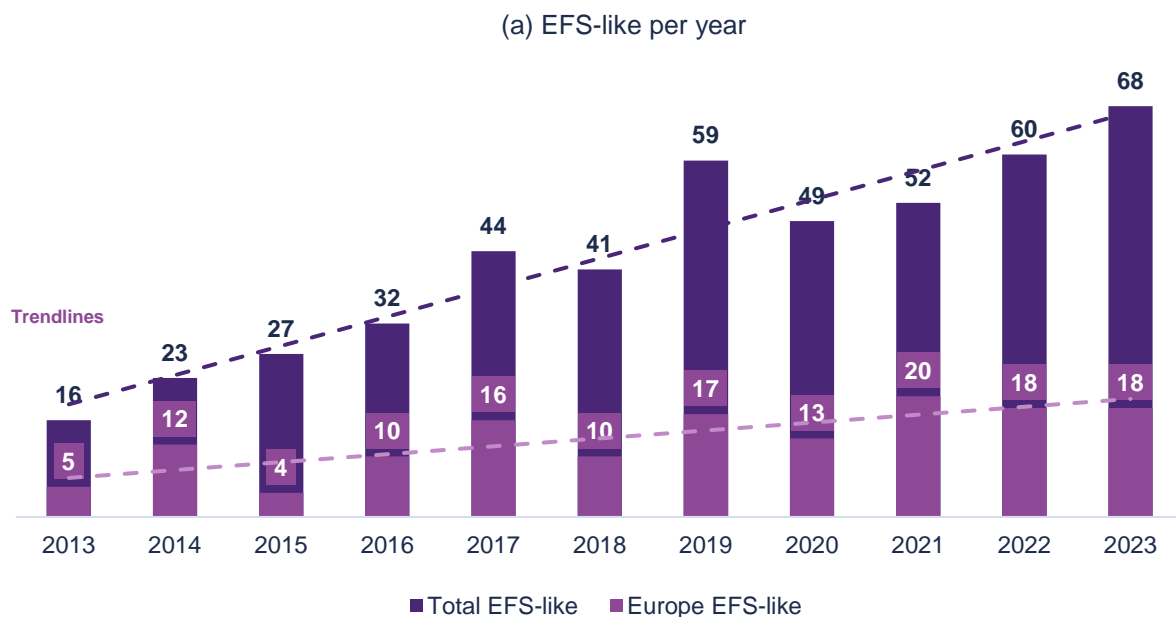
3. Results

3.1. EFS database

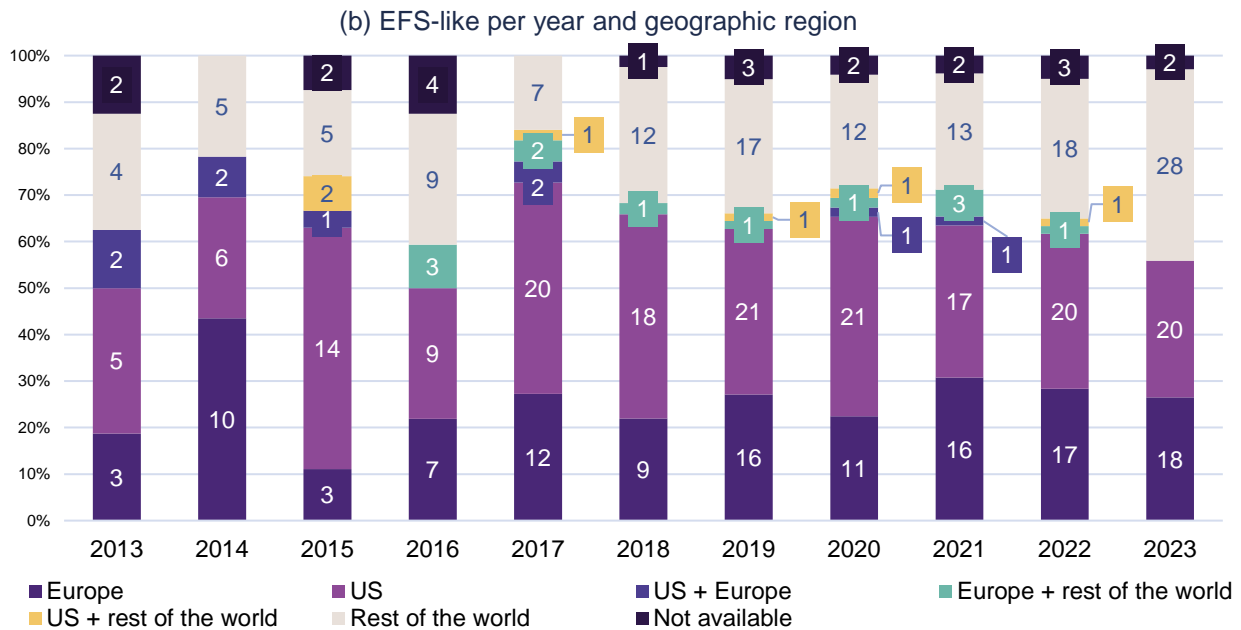
A total of 559 studies were identified and included in the EFS-DB. Most of these studies originated from ClinicalTrials.gov (435 studies), while 76 were obtained from other databases, and the remaining 48 from additional sources.

Figure 2, panel a) shows a generally steady upward trend in EFS-like studies from 2013 to 2023, both globally and at the European level,¹² though the observed increase was somewhat less pronounced in Europe. The phenomenon shows a similar progression also in the rest of the world studies (Figure 2, panel b).

Figure 2 Number of EFS-like studies per year and time trend (2013-2023)



¹² European countries here are intended geographically and not limited to EU member states, and include also Albania, Andorra, Belarus, Bosnia and Herzegovina, Iceland, Kosovo, Liechtenstein, Moldova, Monaco, Montenegro, North Macedonia, Norway, San Marino, Serbia, Switzerland, Ukraine, United Kingdom, Vatican City. Moreover, we consider as European EFS-like all those studies that have at least one location in a European country.



Regarding study locations, 37% (n = 205) were conducted either solely in the US or in collaboration with US sites (Figure 3, panel a). Overall, European countries were involved in 28% of studies (n = 158). Among European participants, Germany ranked first with 23 studies, followed by Belgium (21), the UK and France, each with 20 studies (Figure 3, panel b). The most experienced clinical sites in the conduction of EFS are shown in Figure 3, both for the whole database (panel c) and for European countries only (panel d). Columbia University Medical Center leads this list, participating in 29 studies, over 30% more than any other centre. All the top ten centres for number of studies conducted are US-based. At the European level, ZNA Middelheim (Belgium) and Clinique Pasteur (France) are the centres that participated in the highest number of studies, both with 5.

Finally, Figure 3 panel e) illustrates the number of locations involved in EFS-like studies. This data is available for 471 observations, representing 84% of the total sample. Of these, 45% (n = 250) were conducted at a single location, while 39% (n = 221) involved multiple locations. Specifically, 69 studies (12%) were conducted at two locations, another 69 (12%) at three or four locations, and 83 studies (14%) at five or more locations.

Figure 3 EFS-like study location (2013-2023)

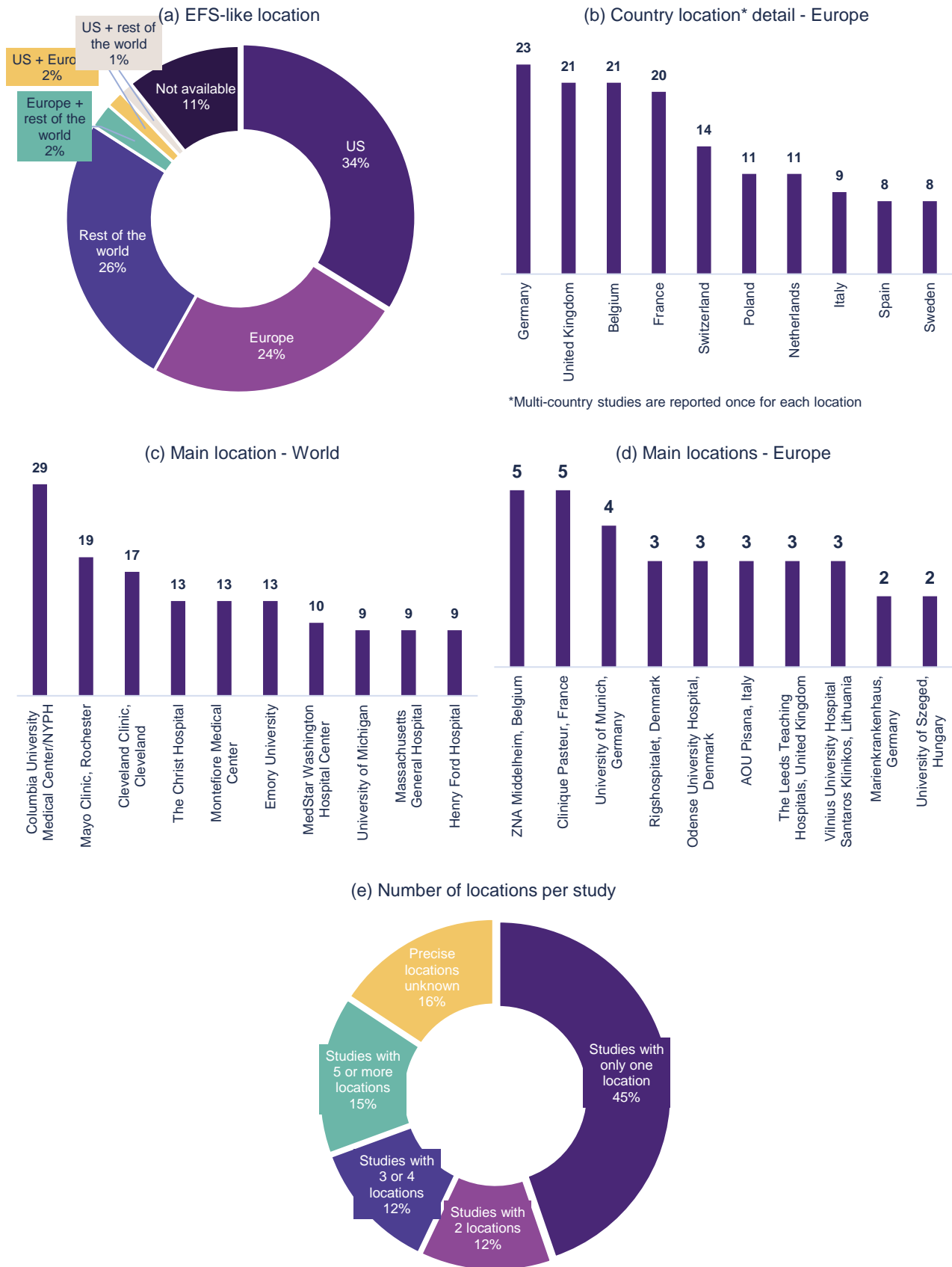
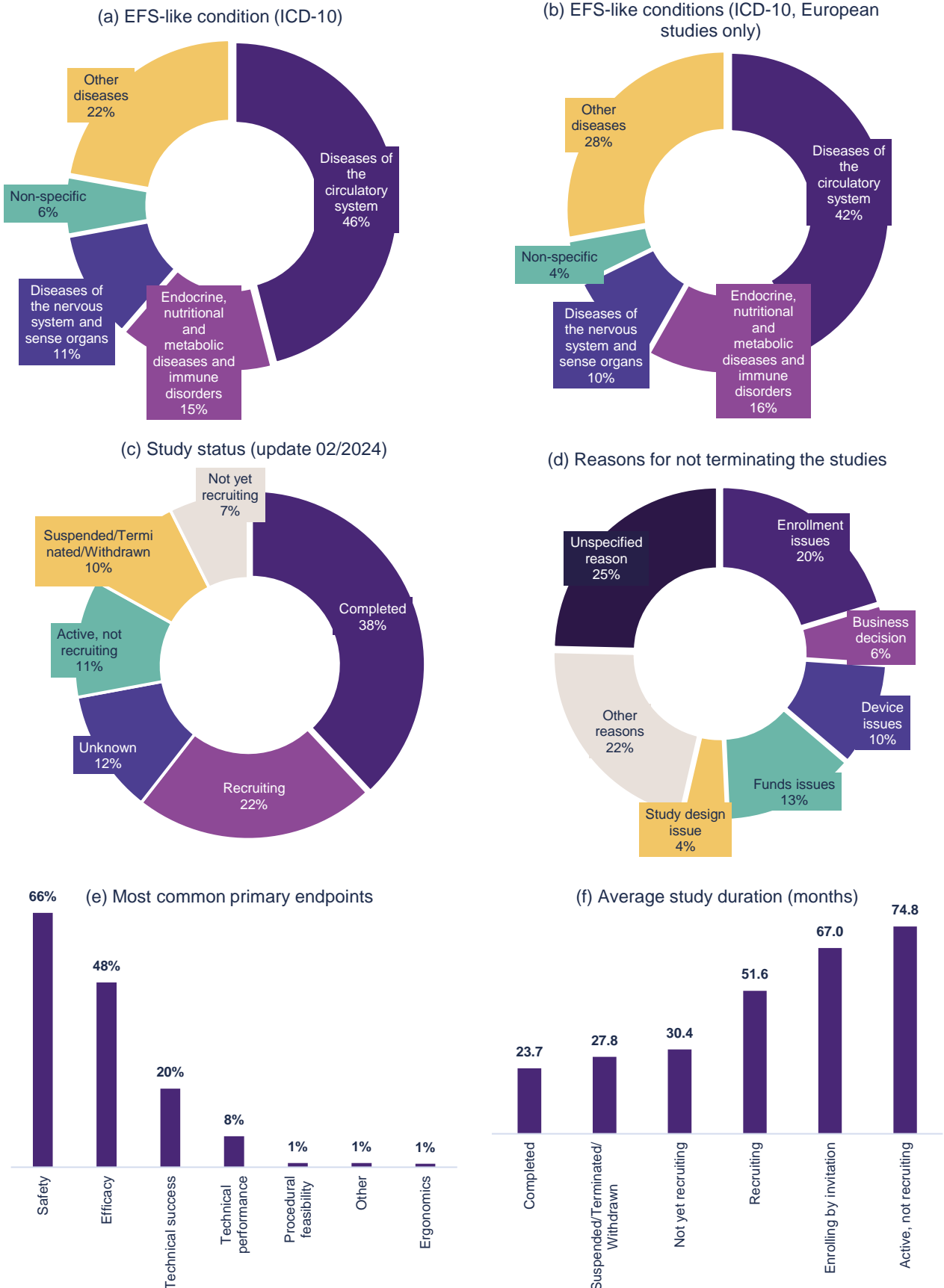


Figure 4 provides an overview of several key characteristics of the EFS-like studies included in the EFS-DB. Across the entire sample, almost half (46%, $n = 257$) of studies focused on devices targeting circulatory system diseases (Figure 4 panel a). These were followed by devices associated with endocrine, nutritional, metabolic diseases, and immune disorders - including diabetes and cancer - which collectively accounted for 15% of the sample ($n = 86$). Studies related to the nervous system and sensory organ diseases represented another 11% ($n = 60$). When focusing solely on studies conducted in Europe, a similar distribution emerged, with these categories representing 42% ($n = 66$), 16% ($n = 26$), and 10% ($n = 15$), respectively (Figure 4, panel b).

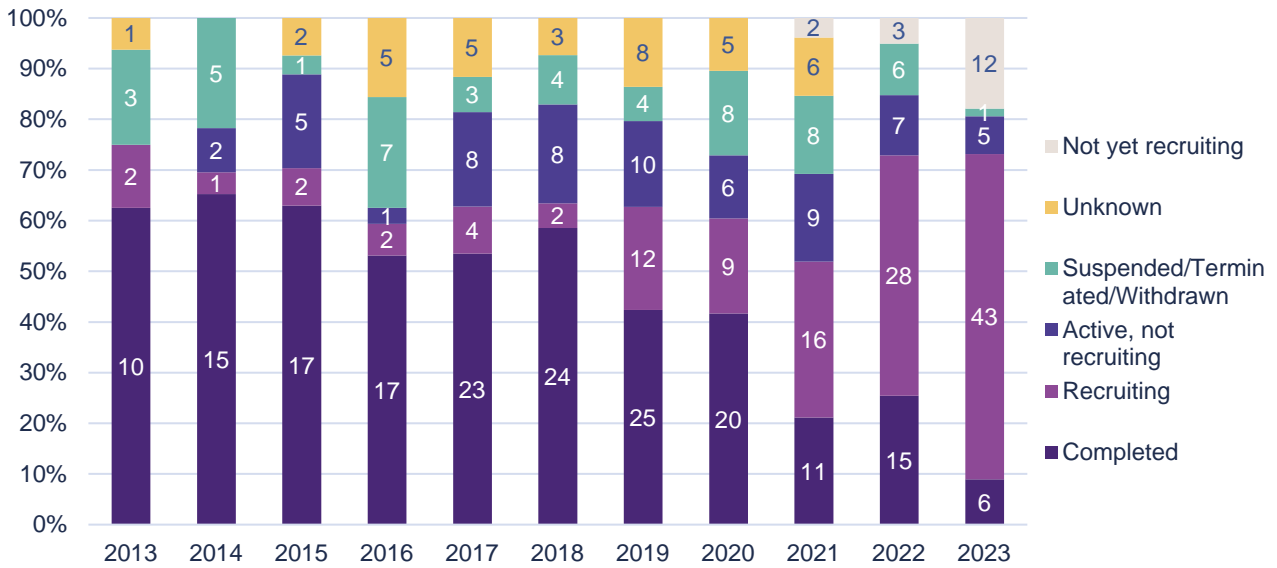
As of March 2024, the status of these studies showed that 38% ($n = 211$) were completed, while around 40% ($n = 227$) were active, including studies not yet recruiting, those with ongoing recruitment, or those where enrolment had been concluded (Figure 4, panel c).¹³ Of these active studies, the majority (81.4%, $n = 162$) began within the last five years (2019–2023) (Figure 4, panel g), while the remaining studies ($n = 37$) started prior to 2019, which may suggest prolonged enrollment or follow-up periods, assuming the investigators accurately updated the current study status on the clinical trial database. About 10% ($n = 53$) of studies did not reach completion due to suspension, termination or withdrawal. Among these studies, 25% ($n = 17$) did not report reason for study discontinuation, whereas the most frequently cited issue was enrolment challenges (20%, $n = 14$) (Figure 4, panel d). Device or study design issues were mentioned as the main reason for study discontinuation in 14% ($n = 10$) of the studies, whereas 13% ($n = 9$) of studies were discontinued due to funding issues. For 25% of the sample ($n = 17$), this information was not detailed enough to be classified into categories or left blank (shown as “Unspecified reason” in the graph).

¹³ Recruitment status definitions are available at <https://clinicaltrials.gov/study-basics/glossary>

Figure 4 Characteristics of EFS-like studies



(g) Study status per starting year

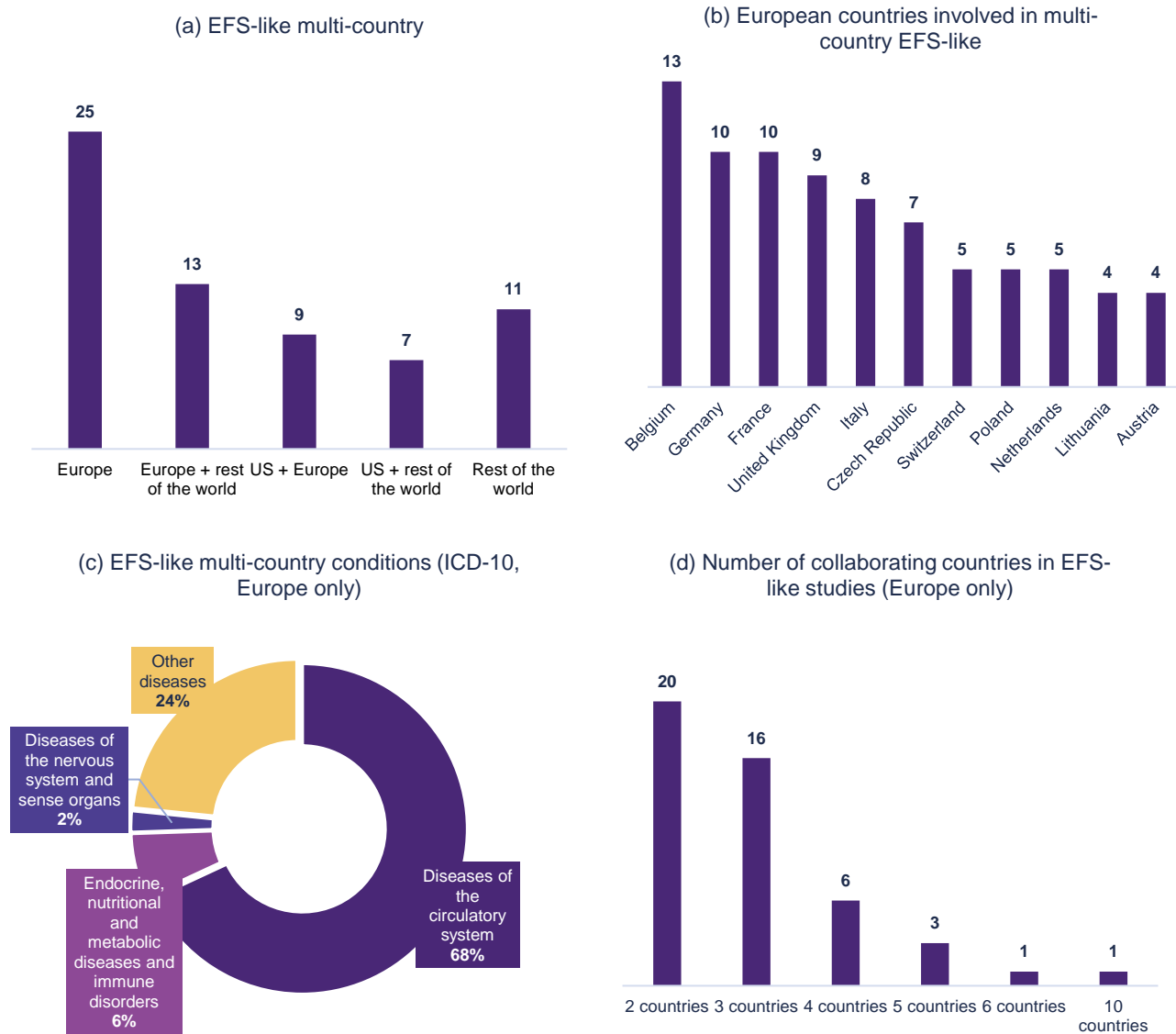


The primary endpoints are categorized in Figure 4 panel e), highlighting two main areas of focus: safety and efficacy. Primary endpoints related to safety, including device- and procedure-related adverse events, were employed in 66% (n = 369) of studies. Efficacy endpoints, assessing device effects, were investigated in 48% (n = 268) of studies, whereas 28% of studies overall included primary endpoints related to technical or device performance. Figure 4 panel f) presents the duration of each study – calculated in months from trial start date to trial final completion date - depending on the status. For completed or interrupted studies, this represents the actual duration; for ongoing studies, the estimated duration at the time of study registration is reported. Completed studies report an average duration of slightly less than two years (23.7 months), while interrupted studies last, on average, 27.8 months. In contrast, estimated durations are significantly longer, with ongoing studies currently recruiting reporting an average estimated duration of 51.6 months (over four years).

Finally, Figure 5 focuses on multi-country EFS-like studies. In total, 65 studies were identified as multi-country, i.e., studies that have been conducted in multiple centers, located in more than one country. This phenomenon is particularly prominent in Europe, where 47 studies (72%) involve more than one European countries (Figure 5, panel a). Within Europe, Belgium (13 studies), Germany, and France (10 studies each) are the most frequently involved countries (Figure 5, panel b). Additionally, the most common inter-country collaborations in European studies occur between Germany and Switzerland, Belgium and Israel, and France and the US, each with four occurrences. Other collaborations are more varied, with partnerships appearing two or three times, reflecting a dispersed pattern without dominant connections. Compared to the overall sample, multi-country studies show a stronger focus on devices addressing circulatory system diseases, accounting for 68% of the studies analysed (Figure 5, panel c). Figure 5, panel d), illustrates the extent of collaborations among countries in EFS,

revealing that most studies involve two or three countries (36 cases). Larger collaborations are less frequent, emphasizing the relatively localized nature of these studies.

Figure 5 EFS-like multi-country studies

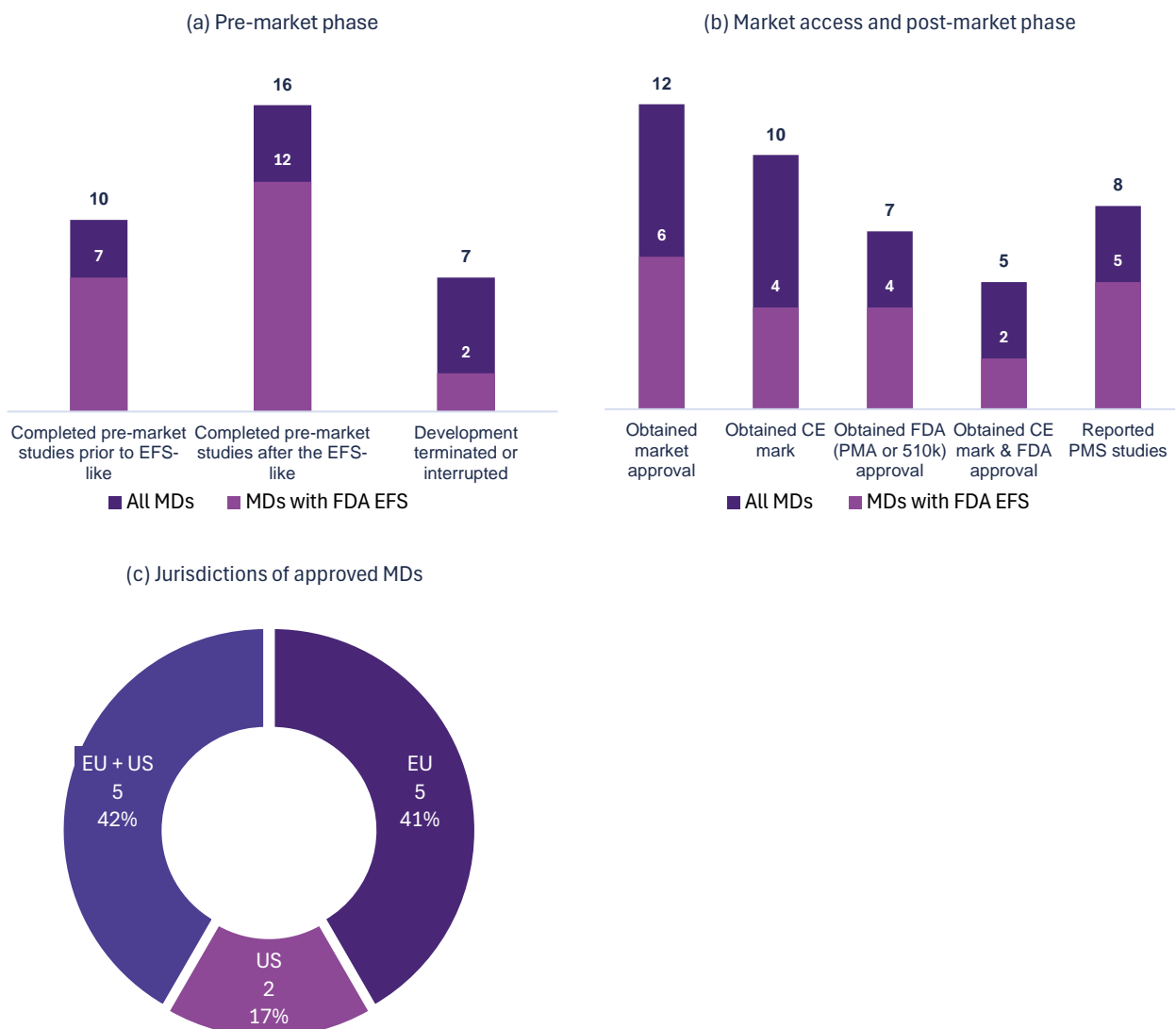


3.2. Case studies on consortium partners EFS

A total of 33 devices sponsored by the technology developers that are partners of the HEU-EFS consortium were investigated based on studies extracted from the EFS-DB. From the data collected, companies reported one case where a device investigated under the FDA EFS program was missing from the database, and another instance where an FDA EFS was excluded despite the device itself being listed. Based on these findings, we estimate the EFS-DB accuracy in identifying FDA EFS (i.e.,

absence of false negatives) to be approximately 94%. All the investigated devices are classified as risk class III, except for two devices, which are classified as class III in Europe and class II in the US. Of the 33 devices investigated, 19 underwent an EFS under the FDA's program (FDA-EFS), meaning they followed the formal FDA process for EFS envisaged by the programme. Figure 6 provides further insights into the clinical evidence generation pathways of these devices, detailing the pre-market (Figure 6, panel a), market access and post-market (Figure 6, panel b) phases.

Figure 6 Evidence generation pathway of MDs investigated through the survey and interviews with consortium partners



Regarding the pre-market phase, 10 devices reported another pre-market clinical study conducted prior to the corresponding EFS-like, while 7 devices underwent such a study when limiting the sample to FDA-EFS cases. First-in-human are the most common pre-market study prior to an EFS-like, occurring in 3 cases, followed by a previous EFS in 2 cases. After completing an EFS-like, 16 devices

proceeded to another pre-market study, often (8 cases) a pivotal study. Additionally, 7 devices had their development interrupted or terminated. The interviews conducted with the partners highlighted that in three cases termination resulted from device-related issues, where the device failed to perform as expected. In one case, development ceased because competing devices demonstrated superior results, rendering the technology redundant. Another device was discontinued due to the ineffectiveness of the underlying approach. Finally, one device was terminated despite obtaining CE marking, as long-term clinical data proved insufficient robustness and one didn't report the actual reason for termination.

Twelve devices obtained regulatory approval: 5 in the EU only, 2 in the US only (one via Premarket Approval (PMA) and one through 510(k)),¹⁴ and 5 devices in both the EU and the US (Figure 6, panel b). Restricting the analysis to devices that underwent an FDA-EFS, 6 devices reached the market, 2 only in the US, 2 in Europe and 2 devices both in EU and the US. Finally, 8 devices went through post-market surveillance studies, of which 5 had previously conducted an FDA-EFS. Finally, the partners reported three cases of safety issues with the devices under investigation in the form of field safety notices (considering any jurisdiction), out of which two instances included a recall from the market.

¹⁴ FDA PMA approval is the most stringent regulatory process through which the U.S. Food and Drug Administration evaluates the safety and effectiveness of Class III high-risk medical devices, requiring extensive clinical and non-clinical data to ensure they meet rigorous standards before being marketed (FDA, 2023).

4. Discussion and recommendations

Early Feasibility Studies have been proposed as a means to streamline and enhance the generation of clinical evidence for MDs, aiming to foster innovation in medical technology and reduce time to market for new technologies, while upholding ethical standards and acceptable levels of patient risk. However, despite their suggested role, little is known about the extent to which EFS are currently conducted, where and how they fit into manufacturers' overall evidence generation plans, and whether they indeed enhance evidence quality or accelerate the time to market for novel technologies.

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. The database showed a growing trend in the number of EFS-like studies both globally and in Europe. The United States created a favourable environment for the conduction of EFS through the introduction of a dedicated program since 2013. Despite the lack of a formalised program, several EFS-like studies are approved by national Competent Authorities and conducted in Europe, confirming the potential relevance of a clear, transparent, and homogeneous framework for EFS in Europe.

The cross-sectional overview of studies revealed a notably high concentration of EFS-like studies within the same centres, as over 25% of the studies identified globally were conducted in only 10 centres, most of which were based in the US. This degree of concentration might reflect the high level of requirements that clinical investigation sites must meet to successfully plan and conduct an EFS. Compared to other clinical investigations for devices at more mature stages of development, higher requirements may be necessary. These requirements may include institutional capabilities, such as advanced technology infrastructure, efficient support structures for clinical studies, and strong institutional commitment. They also may encompass operational capabilities, including the capacity to enroll patients, robust data collection infrastructure, risk management capabilities, high-quality standard operating procedures, and audit mechanisms. Additionally, high levels of clinical competencies may be required, involving experienced investigators, access to training facilities, multidisciplinary teams, and emergency preparedness expertise.

Approximately two-thirds of the studies reported safety endpoints as the primary outcomes, which is unsurprising given the initial focus on safety in EFS. However, fewer studies than anticipated, considering the intrinsic nature of EFS, reported using other primary outcomes such as technical success, technical performance, or ergonomics, either alone or in combination with safety or efficacy endpoints. It remains unclear whether this is due to incomplete or imprecise reporting, or because our intentionally broad definition of EFS also included other pilot studies on devices which were closer to

their final design. Nonetheless, even for studies confirmed to be part of the US EFS program, it was not always possible to extract information on the unresolved design issues that formed the basis for justifying the study, or how the EFS was intended to guide further device development.

The proportion of studies that were terminated early and did not reach completion was relatively low in the sample. This might suggest a generally good capacity for managing EFS by the proposing centres and clinicians. However, this observation could be confounded by the lack of updates regarding study status in the databases, which is difficult to verify. For example, it is unclear whether studies that have been active for an extended period, such as those initiated before 2019, experienced prolonged enrollment or follow-up times, or if their termination was simply not recorded in the databases. When exploring the reasons for study terminations with technology producers within the HEU-EFS consortium, these were reported to be due either to the failure to confirm the proof of concept or to device-related issues, such as the device not performing as expected or producing results that were not superior to those of competing devices. 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.

Identifying EFS from clinical trial database proved to be challenging for a number of reasons. First, without a clear method to identify EFS in the databases, study selection relied on assumptions, such as the number of enrolled patients and basic design information, which may not apply to all EFS. Second, for the identified studies, the quality and detail of information in the extracted fields varied greatly, limiting the ability to extract relevant information consistently across studies and raising doubts about the reliability of the data. Third, another limitation of extracting information from clinical trial databases was that sponsors can update study details over time, while maintaining the same trial registration number. As a result, studies that would have been included as EFS-like at registration may have gone undetected if later updates no longer met the applied eligibility criteria. For example, that would be the case if a study that was registered as an EFS later evolved into a pivotal study with a different name, larger sample size and more confirmatory study designs (e.g., controlled studies). While the history of changes can be reviewed on ClinicalTrials.gov, this aspect significantly complicated the process of study identification and data extraction. Finally, other databases lacked the same level of detail, making it challenging to integrate the different data sources, resulting in missing data for studies identified through less informative databases. All together, these challenges undermined the capability to derive reliable and insightful information on EFS from clinical trials databases, and to reconstruct the evidence generation processes for the identified devices.

Based on the above considerations, a number of recommendations can be made:

- **Promote multistakeholder dialogue on EFS.** The amount and growing trend of early-stage, small scale clinical investigations in Europe provides the justification for promoting a structured and comprehensive dialogue, within and beyond the HEU EFS project, on EFS between all stakeholders involved in the development and regulation of medical devices.
- **Improve quality and availability of data on EFS.** This study has highlighted the challenges in identifying and extracting information on EFS conducted in Europe and globally. Efforts should be made to promote more transparent and systematic collection of EFS data, along with their integration into the clinical development pathways of medical devices. EFS data should be embedded into existing data flows, and managed according to the FAIR principles, to ensure that data is easy to locate, access, integrate, and reuse for various purposes, including research and innovation. Further research within HEU-EFS will generate recommendations on how to best incorporate information flows on EFS within the EU regulatory processes and data structures. For example, the possibility of integrating EFS data into EUDAMED module on clinical investigations, currently in development shall be explored. Since EFS are already recognized under ISO 14155, the inclusion of an EFS-specific option in European Commission templates and forms would be also a logical step forward.
- **Implement monitoring and evaluation systems for EFS.** Transparent and reliable monitoring and evaluation systems should be established to determine whether EFS can effectively enhance the quality of evidence, shorten the time-to-market for valuable innovations without compromising patient safety, and ultimately improve patient outcomes. Such data and evidence would provide National Competent Authorities with essential tools to monitor EFS as a critical component of evidence generation for medical devices. The Monitoring and Evaluation tool should also be used, with appropriate performance indicators, to assess whether the development of an EU-EFS program can also foster innovation and increase the competitiveness of the European market. Within the HEU-EFS project this aspect will be covered in WP5, aiming to design and implement an EU EFS Performance Dashboard aiming to monitor the performance of the EU EFS Program.
- **Investigate the necessary requirements and competency set for centres to successfully manage EFS.** This study has highlighted that most early-stage, limited clinical investigations for medical devices worldwide are conducted by a relatively small number of investigational centres. To promote a European EFS program, it is essential to identify the minimum set of competencies, as well as the organizational and structural characteristics, required for centres to successfully plan and conduct EFS. Within HEU-EFS, this aspect will be covered in WP3,

Task 3.1, which aims to develop eligibility criteria for accessing the future EU EFS Program, including eligibility criteria for clinical sites.

In this report, we have gathered unprecedented data on EFS-like studies in Europe and demonstrated how this data could potentially improve decision-making and policy formulation in medical device research. We also outline a roadmap toward an enhanced monitoring and evaluation system for EFS, which is essential for implementing a transparent, cost-effective, and accountable EFS program in Europe.

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