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PERSPECTIVE

Recommendations for the design and implementation of an Early Feasibility Studies program for medical devices in the European Union

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ABSTRACT

Introduction: Early Feasibility Studies (EFS) are among the pre-market clinical investigations allowed by the International Standard for Clinical investigation of medical devices (MD) for human subjects. The Food and Drug Administration (FDA) introduced an EFS program in the US in 2013. The European Union (EU) MD Regulation, that entered into force in May 2021, opened the possibility of EFS in the EU. However, European countries at present have no standardized procedural framework for EFS. In this paper, we address the desirability of a European EFS program.

Areas covered: Characteristics of EFS conducted so far are reviewed, and perceptions of an expert, multidisciplinary panel of key stakeholders are explored regarding desirability and feasibility of a European EFS program and critical factors favoring or hampering its implementation.

Expert opinion: Implementing an EFS program in the EU would contribute to creating a favorable environment for early-stage clinical investigations, with positive effects on the quality and timeliness of clinical evidence for novel MDs, and attractiveness of the European system for pre- and post-market clinical research. Based on discussion with experts, also leveraging on the US experience, three dimensions should be considered for effective design and implementation: process, resources, and ethical issues.

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KEYWORDS
Clinical evidence; early feasibility study; European Union; Health Technology Assessment regulation; medical devices regulation; medical devices; pre-market clinical investigation

1. Introduction

European regulation of medical devices (MDs) has always been considered less stringent than that applied in the United States (US) [1]. However, recent years have witnessed a marked turnaround. The new European Union (EU) Medical Device Regulation (MDR) [2], in force since May 2021, is expected to make the regulatory framework in Europe more restrictive as it strengthens clinical evidence requirements, while the American Food and Drug Administration (FDA), from 2010, has undertaken a broad review process of its pre-market device program, following complaints that regulation provided disincentives to manufacturers to conduct research and seek market approval, thus potentially delaying access to novel MDs for American patients [3]. Indeed, between 2004 and 2009 clinical studies for MDs conducted in the US listed on ClinicalTrials.gov were reported to have dropped from 87% to 45% [4], prompting the FDA to seek measures to alleviate barriers to clinical studies for innovative MD producers [5].

Among the initiatives put in place by the FDA to improve the balance between necessary regulatory oversight and unnecessary regulatory burden, was the establishment of new and modified policies to create a collaborative environment for early clinical investigation of MDs in the US. In February 2011, the FDA's Center for Devices and Radiological Health (CDRH) proposed the Innovation Pathway, a priority review program for pioneering MDs characterized by improved collaboration between the FDA and MD innovators; in October 2011, the FDA began to pilot a Network of Experts Program to overcome the internal lack of experience and expertise needed to review emerging, innovative medical technologies by engaging with top scientific experts, members of professional health-care societies, when deemed necessary; finally, in November 2011, with the double intent to recoup the US leading role in pre-market research for MDs and accelerate access to medical technologies, the FDA solicited sponsors of innovative device technologies to apply to a pilot program for early feasibility study (EFS) investigational device exemption (IDE) [6]. In 2013, guidance on *Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies* was finally issued [7].

As described in the guidance document, EFS are limited exploratory clinical investigations which take place early in the development phase of a device, typically before the device design has been finalized, in a small number of patients. Differently from traditional feasibility studies, which aim to capture preliminary safety and effectiveness results and support the planning of larger pivotal studies, the purpose of EFS is more related to demonstrating proof of concept and optimizing device design and procedure through iterative feedback loops during early clinical experience, when further information cannot be obtained through additional preclinical testing or when appropriate nonclinical tests are unavailable. Notably, the FDA EFS program is not aimed to create an

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Article highlights

- Early Feasibility Studies (EFS) are limited clinical investigations of medical devices (MD) conducted in a small number of subjects early in development to evaluate the device design concept with respect to initial clinical safety and functionality and to guide device modifications through iterative feedback loops during early clinical experience.
- EFS are among the pre-market clinical investigations allowed by the International Standard ISO 14155:2020 for Clinical investigation of MDs for human subjects.
- The American Food and Drug Administration (FDA) launched an EFS program in 2013. European countries at present have no standardized procedural framework specific for EFS. The new European Union (EU) MD Regulation, that entered into force in May 2021, opened the possibility of EFS programs in the EU.
- A European EFS program would contribute to create a favorable environment for early-stage clinical investigations, with positive effects on both the quality and timeliness of clinical evidence for novel MDs, and the attractiveness of the European system for pre- and post-market clinical research.
- Recommendations are proposed for the design and implementation of a European EFS program based on discussion with officers of the Italian Ministry of Health and a panel of experts, also leveraging on the US EFS experience.
- Three dimensions are of key importance: process, resources, and ethical issues.

accelerated pathway to market approval, but rather it seeks to create a favorable environment for the conduction of EFS, therefore leading to higher quality and timely evidence generation. Successful EFS can be extended and subsequently transitioned into pivotal trials. Since the devices investigated in EFS are at such early stages of development, one of the main characteristics of the EFS program is that the FDA may accept a higher degree of uncertainty and require less preclinical data to support study initiation [3]. A greater emphasis is placed on monitoring and patient protection measures as compared to studies at later stages of device development. In addition, following the recognition of the specific nature of the studies, the FDA EFS program has been shaped according to key principles, including interactive dialogue between FDA, sponsors, and innovators prior to and during the EFS IDE submission; predefined phases and times for the submission review process; and flexible, risk-based management of device and/or clinical protocol modifications during the study. The latter envisages different procedures depending on the nature of the change, and whether these changes had been previously identified and foreseen during the interactive review process between the sponsor and the FDA. Briefly, there are three main procedures to manage modifications. First, changes that do not imply significant design variation and do not affect the interpretation of the results can be made through 5-day notification, without requiring FDA approval. Second, approval of anticipated or proposed device, or protocol changes can be obtained contingent on the completion of an agreed-upon test plan and acceptance criteria so that, after successful completion of testing, the sponsor can begin to study the modified device without additional FDA action (contingent approval). Third, interactive review of IDE supplements and amendments, involving the continuation of informal discussions with FDA during the 30-day IDE supplement review cycle, may be used to address deficiencies or where changes to the clinical protocol do not meet the criteria for a 5-day notice (interactive review process). The program's main characteristics and timelines are summarized in Figure 1.

Part of the 2014–2015 CDRH Strategic Priorities [8], the EFS program has been successful in attracting early-stage clinical investigations to the US: since its implementation, the number of EFS IDEs received by the FDA increased from 26 in 2014 to 73 in 2018, and the number approved annually increased from 24 to 53 [9]. The CDRH 2018–2020 Strategic Priorities report cited reduced time and cost as advantages of the EFS program and predicted for the near future increased initiation of first regulatory approval processes by manufacturers in the US – and thus faster access for patients [10]. During the COVID-19 pandemic, the interest in EFS remained high, with 61 studies submitted and 49 approved [11].

In the 2020 edition of the International Standard ISO 14155 Clinical investigation of medical devices for human subjects – Good clinical practice, EFS have been included among the possible types of pre-market clinical investigations to assess initial clinical safety, performance, or effectiveness of MDs [12]. This opens the possibility of implementing EFS programs in Europe. More recently, the Medical Devices Coordination Group (MDCG) – an expert group composed of representatives of all Member States supporting the Commission in ensuring a harmonized implementation of MD and in-vitro diagnostics Regulations – released guidance that explains the appropriate regulatory pathways for clinical investigations under the MDR. The guidance clarified that pilot stage clinical investigations such as EFS conducted to support conformity assessment (i.e. gather preliminary safety and/or performance data), are directly regulated by the MDR ex article 62 and do not fall under the Member State national regulatory pathways ex article 82 [13].

Despite the possibility to implement EFS programs, European countries at present have no standardized procedural framework for this type of study. Consequently, EFS are either put forward as individual requests for compassionate use or submitted as traditional feasibility studies. This in turn may act as an incentive for applicants to overstate the potential benefits (or understate the potential risks) of the technology and forces bodies in charge of assessing the request for the study to apply evaluation criteria that are different from those which would be appropriate for EFS. In addition, in countries like Italy, the conventional process to pre-market study authorization is relatively 'static' in that it is based on the one-off submission of the study documentation by the sponsor, without any previous interactions and with only one subsequent round of revisions and requests for integrations by the competent authority [14]. Similarly, after study initiation, current procedures to implement changes to either the protocol or the device are likely to be inappropriate for these types of studies, where such modifications are more common compared to more mature clinical studies. In fact, in many cases, changes to the study protocol or device may indeed be one of the expected outcomes of an EFS (for instance, if the purpose of the

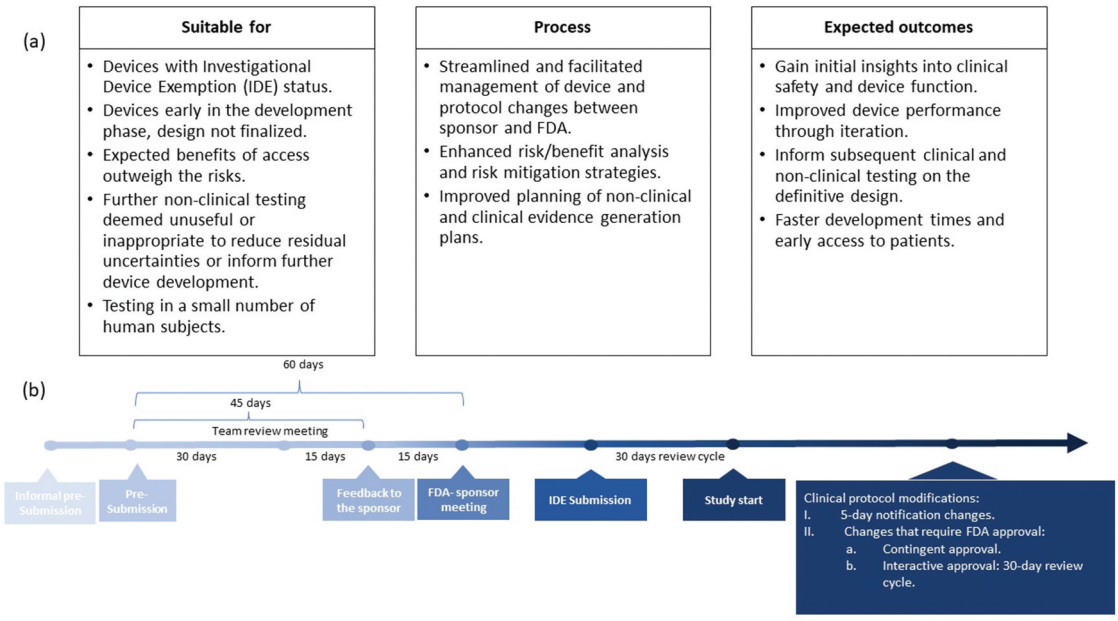

Figure 1. Main features (panel a) and timeline (panel b) of the FDA Early Feasibility Studies.

study is to establish the optimal coating material for a device between two previously identified alternatives). So, it is not uncommon that clinical investigations not approved in European countries as feasibility studies are resubmitted and approved by the FDA as EFS.

In the long run, the absence of an ad hoc, standardized framework for early evidence generation might reduce European countries' attractiveness for clinical studies and first approvals, and therefore it is crucial to stimulate debate and create awareness among European policymakers.

The aim of this study was to investigate the characteristics of the EFS program implemented by the FDA and explore perceptions of key stakeholders involved in the regulatory approval of novel MDs regarding the desirability and feasibility of a European EFS program and the critical factors that would favor or hamper its implementation.

2. Materials and methods

The research was conducted through several consecutive steps presented in Figure 2 and described in detail below. A mix of methodologies was used, both qualitative (i.e. one-to-one interviews, focus groups, surveys) and quantitative (i.e. data collection and design/implementation/elaboration of EFS databases). Both in preparing the questions (open-ended, neutral) and in conducting the interviews/group discussion (in a neutral, open, and non-judgmental way, without sharing research team personal opinions and views) we referred to the

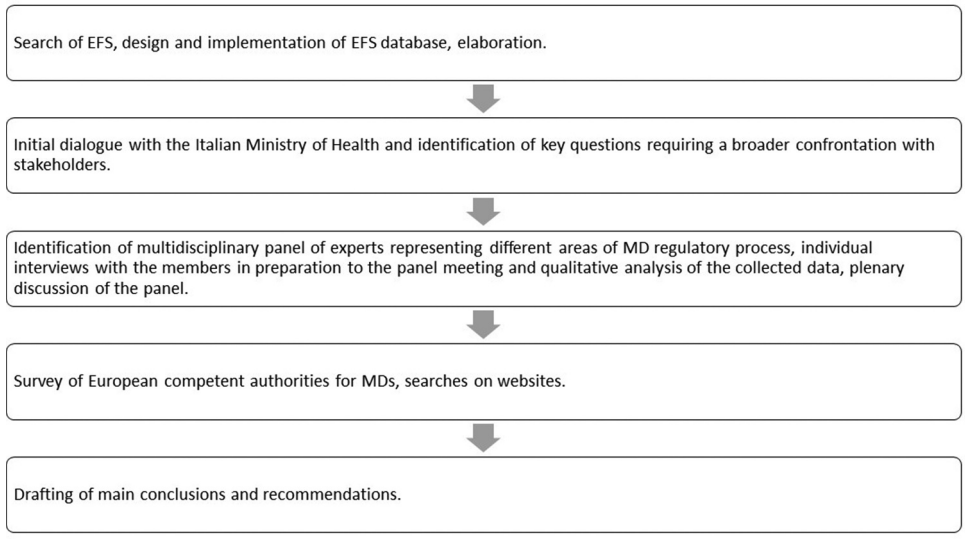

Figure 2. Steps of the methodology.

standards and best practices for qualitative research proposed by Cresswell and Poth [15].

First, to gain insight into the characteristics of EFS, in March 2019 we conducted a search of the studies registered on ClinicalTrials.gov by using the keywords 'early feasibility' with no restrictions on status, condition, disease, or country. We selected EFS involving the use of MDs – alone or in combination with drugs – and excluded those involving drugs only. The main goal of this preliminary search was to identify the prevalent clinical areas where EFS are conducted to inform the subsequent research phases. The search was updated in April 2022 to include all EFS registered through December 2021 and complemented by a search on the World Health Organization International Clinical Trials Registry Platform (ICTRP), a literature search on PubMed, Google, and American Heart Association/American Stroke Association (AHA/ASA) journals, and with searches on main news websites (i.e. Cardiac Interventions Today citoday.com, Cardiovascular Business cardiovascularbusiness.com, Cardiovascular News cardiovascularnews.com, Endovascular Today evtoday.com, and PRNewswire www.prnewswire.com) using the same keywords. For all identified EFS, we analyzed study details provided by ClinicalTrials.gov and searched all available documentation. In cases of major doubt, we requested information from device manufacturers. We designed an ad hoc database that was fed with the following information extracted from the retrieved documents: clinical trial number, study title, status at the time of the search (e.g. recruiting, completed, suspended, terminated), results, conditions, interventions (i.e. device, drug, radiation, biological, behavioral, procedure, other), primary and secondary outcomes, sponsor/collaborators, number of patients enrolled, sex, age, study phase, study type (i.e. observational or interventional), allocation (i.e. randomized or non-randomized), intervention model (i.e. single group, sequential, parallel, crossover assignment), masking (i.e. open, double, triple), primary purpose (e.g. prevention, treatment, supportive care), observational model (i.e. case-only, case-control, cohort), time perspective (i.e. prospective or retrospective), registration date, start date, and completion date, and location. Moreover, we grouped the conditions and diseases according to the chapters of the International Classification of Diseases, 9th revision – Clinical Modification (ICD-9-CM).

As a second step, we conducted qualitative interviews with Italian Ministry of Health (MoH) officials and an expert panel (Figure 2) to collect and synthetize opinions on the appropriateness and feasibility of an EFS program, and to identify recommendations for its implementation. We focused on Italy as a case-study as it is second in number of medical technology companies and the fourth largest MD market in Europe [16], which makes it an optimal testing ground for implementation of an EFS program at the European level.

Between March 2019 and February 2020, meetings were held with the director and members of the Office for Clinical Investigations at the Italian MoH, Directorate General for Medical Devices and Pharmaceutical Services, which is the competent authority for MDs in Italy. These meetings had the objective of familiarizing participants with the main characteristics of the EFS program in the US, and eliciting opinions from public officers regarding the opportunity to implement a similar program in Italy. The meetings also sought to identify key aspects to address when designing and implementing an EFS program to explore with a broader set of stakeholders. The interviews were conducted by two of the authors (GC, PhD, female; and CF, PhD, male), health economists, experienced in conducting qualitative interviews and group discussions. A junior health economist (RF, female) served as observer and note taker. The moderators conducted the interviews in a neutral, open, and non-judgmental way, and did not share their personal opinions and views in order not to influence participant answers. From these meetings, four open-ended, neutral questions were drafted covering (1) the desirability and main advantages of an EFS program in Europe, and specifically in Italy; (2) potential challenges related to the implementation of an EFS program and main ethical considerations; (3) elements requiring special consideration during the application process for an EFS; and (4) the types of devices that would be suited for an early feasibility study and minimum eligibility criteria (Table 1).

Subsequently, in February 2020 a purposive sample of 10 experts was selected among clinical investigators, biomedical engineers, academics, members of scientific and professional associations, members of ethics committees, developers of new technologies, including representatives of the industry. To involve the most fitting stakeholders, we selected experts from the main therapeutic areas identified in the EFS database (i.e. sectors where such studies were most frequent): cardiovascular, diabetes, and neurology. All the identified members agreed to participate in a panel meeting. Due to travel limitations imposed by COVID-19, the original full day, in-person workshop in March 2020 was re-organized as a two-hour web conference postponed to July 2020. To maximize efficiency for the reduced time available for the panel discussion, preliminary materials, validated by the MoH, were sent to all participants in advance in June 2020. These materials included a briefing document and three video lessons recorded by GC, CF, and RT, summarizing the goals of the initiative, the main features of the FDA EFS program and the four questions to be addressed by the panel, without unveiling the authors' views and opinions. Before the web panel meeting, one of the authors (GC) conducted individual online interviews with each of the experts with the aim to have feedback in advance on the four questions and to identify the main aspects to discuss during the panel. Consent to video-record the interviews was obtained, and the recordings were professionally transcribed. Transcript data were then analyzed using qualitative

Table 1. Questions regarding the possible implementation of an EFS program in Europe discussed with the panel.

Q1 – In your opinion, can a procedural innovation like the EFS program promoted by the FDA be useful in the Italian context and what critical aspects can be overcome thanks to it?
Q2 – What challenges are posed by the implementation of an EFS program? In particular, what ethical aspects need to be carefully considered due to the higher risk profile linked to the early development phase of the investigated devices?
Q3 – Which parts of the application form require more attention compared to traditional feasibility or pivotal studies?
Q4 – What types of devices might benefit most from the implementation of an EFS program? Is it possible to define a set of minimum admissibility criteria?

content analysis by identifying recurring themes and sorting them into categories. The July 2020 plenary meeting with panel members and the MoH was moderated by GC, where key points derived from individual interview analysis were presented and discussed to work toward consensus on the main aspects involved in evaluation of the feasibility, design and implementation of an EFS program. During both individual interviews and the board meeting, the moderator asked neutral questions and did not share her own nor research team opinions so as not to influence opinions and answers. The remarks emerging from the first phase of the interviews and panel discussion were then synthesized and shared with the MoH and panel members for comments and integrations.

As a last step, we designed an ad hoc survey to investigate how other European competent authorities for MDs were preparing to meet the MDR requirements and whether they had started designing or implementing national EFS programs. In December 2020, we invited all 27 competent authorities, including the UK, to complete the survey, which remained active until January 2021. In the absence of replies, we searched relevant websites for mention of national EFS programs.

3. Results

3.1. Characteristics of EFS

Overall, we identified 198 EFS registered by December 2021, with 152 on ClinicalTrials.gov and the remaining found through other sources. The number of studies, by start date, increased over time and peaked in 2021 (Figure 3).

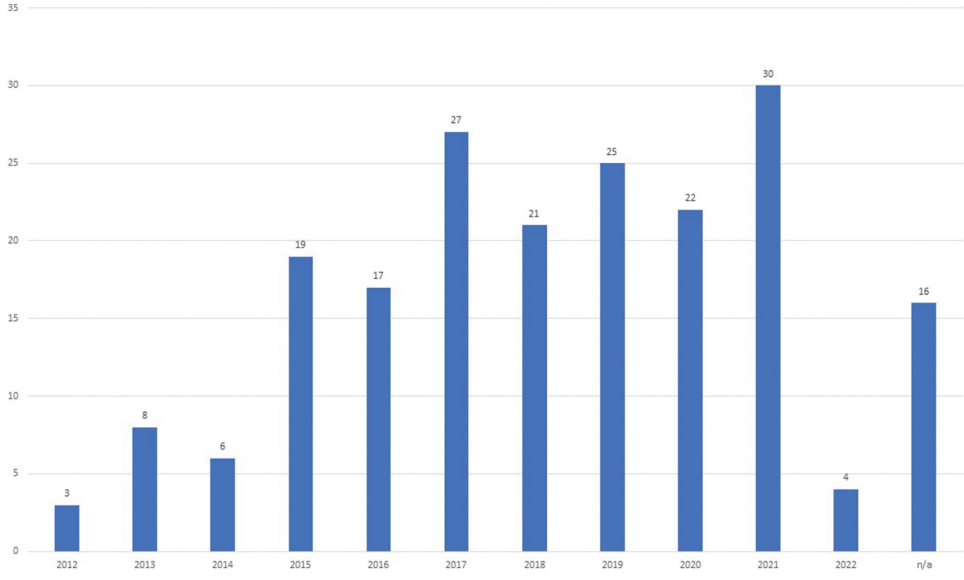

Figure 3. Time trend of EFS.

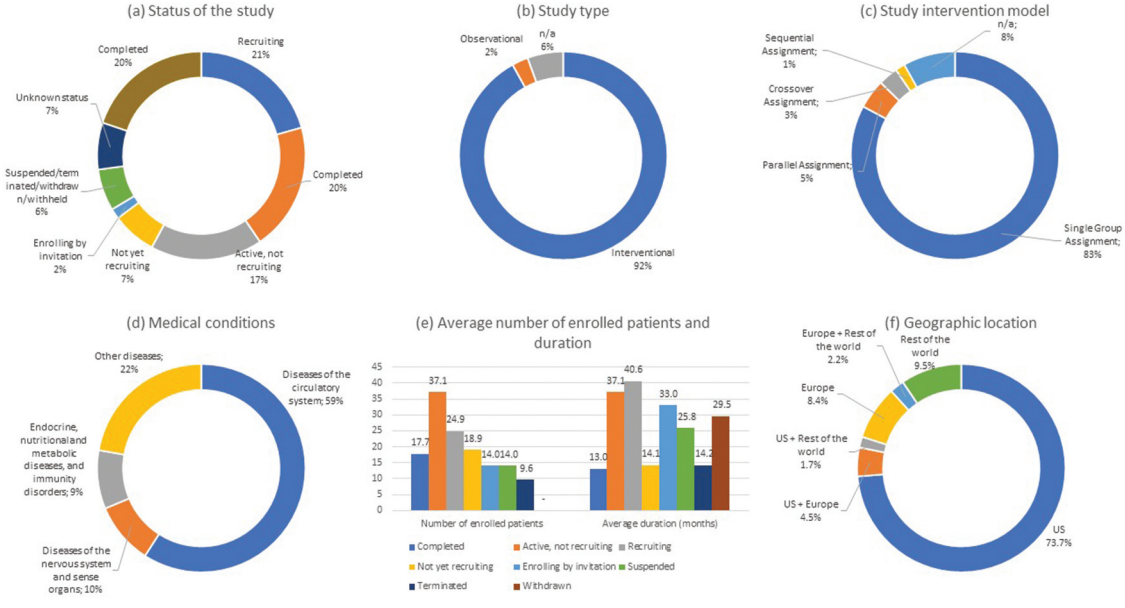

Figure 4. Main characteristics of EFS.

Approximately 58% of the studies were ongoing or about to be initiated at the time of the search, 25% were completed and 8% abandoned (Figure 4 panel a). Roughly 92% of the EFS are interventional (Figure 4 panel b) and 83% are single group assignment (i.e. studies in which all participants receive the same intervention/treatment) (Figure 4 panel c). More than half of the studies focused on diseases of the circulatory system (59%), followed by diseases of the nervous system (10%) and endocrine, nutritional, and metabolic diseases – in particular diabetes – (9%) (Figure 4 panel d). On average, completed studies enrolled 17.7 patients and had a duration of 13 months; terminated EFS were stopped after 14.2 months after enrolling 9.6 patients (Figure 4 panel e). More than three-fourths (73.7%) of the studies were conducted in the US and 6.2% joint with other countries (Figure 4 panel f). European countries seem to have limited experience with EFS, with only 27 studies conducted. Germany is the most experienced, with nine studies conducted, followed by France and Poland (six) and Italy (five). For studies starting in 2021 and 2022, that are currently recruiting patients, the location is often not available.

3.2. Presence of European EFS programs

Our survey received five complete responses from European competent authorities for MDs: Italy and Sweden, the only two countries with previous EFS experience, Bulgaria, Finland, and Slovenia. All declared that they have not implemented EFS programs or produced national regulations/laws/rules for these types of studies. Searches conducted on the websites of non-replying competent authorities highlighted the existence of rules for the conduction of pre-market clinical investigations (e.g. traditional feasibility studies, first-in-human, pivotal studies) in all European countries. Nevertheless, none of them have implemented formal EFS programs or collaborative pre-submission frameworks with EFS-like iterative interactions with study sponsors.

Concerning the actions taken in preparation for full application of MDR, complementary national regulations have been adopted in Bulgaria, Finland, Slovenia, and Sweden, and new administrative procedures and reorganization activities have been implemented by the Slovenian and Swedish competent authorities. The Italian Ministry of Health has not taken any action among those proposed (i.e. complementary national regulations, new administrative procedures, reorganization, national regulations for some types of clinical investigations for human subjects not mentioned in the MDR) because the national regulations transposing the European Directives are currently under review based on MDR requirements.

3.3. Suggestions for the implementation of an EFS program by the expert panel members

In this section, we present the results of the discussion with the expert panel members and their suggestions for the implementation of a European EFS program.

3.3.1. Desirability and main advantages of a European EFS program

Overall, all the members of the panel agreed that an EFS program would be highly desirable in Europe and unanimously supported the implementation in Italy of a pioneering framework for EFS to be used as a pilot experience for Europe. Indeed, both during the individual interviews and the panel discussion, several potential contributions for a European EFS program were identified, subsequently grouped into two broad themes. The first relates to the definition of a dedicated administrative procedure and an ad hoc, standardized framework for the successful initiation and conduction of EFS in Europe, to maximize the efficiency of evidence generation processes. The introduction of clearer rules for the submission and management of EFS was considered favorable as it would allow greater certainty for the sponsors regarding the requirements to initiate a study, documentation to be produced, procedures in place, and especially the timing of each step in the process from first contact with the competent authority through definitive study evaluation and decision. Such a program would also help overcome the limits of the traditional pathway characterized by poor interaction between the competent authority and sponsors during the application process for a study. The possibility of instituting continuous, dynamic dialogue within an established procedural framework was perceived as better suited to promote real exchange on and mutual understanding of the characteristics of the innovation and the proposed evidence generation plan. Such dialogue was seen to foster reciprocal knowledge and trust between manufacturers, investigators, and regulatory authorities. In addition, mirroring the FDA EFS program, the possibility to introduce specific procedures for managing changes to the study protocol or modifications to investigational devices was also perceived to increase flexibility, in keeping with the early stage of development of the technology and the ultimate purpose of EFS.

The second theme relates to the ability of an EFS program in Europe to attract R&D investment and strengthen the biomedical sector's competitiveness, especially for micro, small, and midsize enterprises. The board members also highlighted that early experience with new technologies on the part of clinicians and sites facilitates the subsequent undertaking of pivotal studies, generating a multiplier effect for personnel skills and competencies and attracting capital investment.

Importantly, among the panel there was consensus that these types of studies should not supplant informative nonclinical testing or in any way reduce the acceptability level of clinical studies, i.e. in terms of the amount of successfully conducted preclinical tests needed to initiate a clinical study, the required level of evidence on device safety, or the expected risk–benefit ratio for the patient. Rather, EFS should enhance the efficiency of evidence generation processes by limiting non-informative investigations and maximizing returns of studies in terms of information gathered to reduce uncertainties regarding the devices investigated.

3.3.2. Potential challenges related to the implementation of an EFS program in Italy and main ethical considerations

Several potential challenges, ranging from administrative and bureaucratic issues to cultural and ethical considerations, were

identified which would need addressing to ensure successful implementation of an Italian EFS program. First, a clear legal and procedural framework delineating the role and nature of EFS from the Italian Government was considered of vital importance to provide required flexibility and facilitate the initiation and execution of these types of studies. Second, the Italian EFS program would necessarily need to accommodate and function within the system of Internal Ethics Committees (IECs) in Italy. According to most members of the panel, important aspects to address regarding IECs include their heterogeneous nature in terms of risk aversion, quality, and timing of the approval processes, as well as the availability of resources and technical expertise, especially concerning clinical investigations of MDs. More in general, panelists raised a cultural issue regarding the poor propensity of IECs to positively assess requests for EFS. Possible explanations given were again the lack of technical skills to correctly understand and assess an EFS, and the lack of a clear definition of the medical-legal responsibilities for these early-stage studies, which may lead to a general conservative approach to avoid excessive risk-taking. A similar issue concerns the need for a proper insurance system, able to address the nature of these studies and correctly evaluate the risks associated with their implementation. Third, an FDA-like EFS program would require dedicated, highly skilled staff who follow the applicant from the initial dialogue phase, several weeks before the submission of the study application, and throughout its implementation. Indeed, this type of 'follow-up' is far more complex and time consuming compared to the procedures currently in place and therefore would require appropriate resizing of any administrative structure dedicated to the program. In addition, since EFS studies usually involve highly innovative devices with novel mechanisms of actions, evaluation of ethical aspects is likely to be more complex and uncertain, requiring a high level of expertise from both applicants and assessors. In fact, EFS inherently carry a higher risk profile, which all actors involved in the authorization process (i.e. IECs, competent authority) should be competent to assess and correctly balance against the potential benefits of the technology. Building the necessary technical competency would require significant investment, to expand dedicated staff for the competent authority, IECs and study applicants. However, the design of a network of external collaborators such as independent research centers or universities or members of professional scientific associations to be involved by competent authorities as external assessors could provide a suitable and independent structure to support the program.

3.3.3. Elements requiring consideration during the application for an EFS

It was generally agreed that no further documentation should be required of applicants when applying for an EFS compared to other pre-CE mark studies (e.g. traditional feasibility studies), as the standard documentation already satisfies all information (e.g. related to patient safety and study ethics) needs to assess the application for a study. However, some parts of the documentation may require more attention, such as patient protection measures, informed consent, or selection criteria for experimenting centers and patients. First, as an essential precondition, applicants should clearly justify the suitability of the EFS to answer the planned research questions and why further preclinical testing would not be appropriate or informative for the development of the product. Assessment of the adequacy and comprehensiveness of preclinical evidence should also include any possible in-silico application (i.e. computer simulation used to form patient virtual cohorts for testing the safety and/or efficacy of new drugs and of new medical devices [17]) which may contribute to further reduce uncertainty regarding device performance prior to its use in human subjects. Second, it was argued that all patient protection measures should be enhanced. Analysis of the risks and potential device failures should consider the early development stage of the technology and provide a thorough analysis of the whole spectrum of potential device failures and their consequences on patients. For each of the identified risks, particular attention should be devoted to defining an appropriate risk-mitigation strategy to minimize the additional risk incurred by the patient during the study. Given the likely complexity and novelty of the device under investigation, risk analysis should also include evaluation by highly specialized non-clinical experts (e.g. biomedical engineers) to verify the technical characteristics of the devices, the appropriateness of the construction materials and production processes, and the congruity between the description of the device and its mechanism of action with the expected performance.

While the safety and risk analysis would require more emphasis due to the intrinsic nature of EFS and the device under investigation, minor importance was given to statistical considerations such as calculation of the required sample size and the power of the study, given the fact that the general aim of EFS is not to obtain statistically significant estimates of the device safety or performance. Naturally, for the study to meet the required ethical standards, the applicants should also clearly show that the identified risks are offset by greater expected benefit for the patient.

Another relevant part of the application that may need more consideration in EFS is the informed consent form given to patients. This should clearly detail the potential risks to patients from the experimental device compared to their current condition or any other alternative procedures, the additional risks related to the non-definitive design of the device and any other aspects that may be relevant for the patient to make an informed decision.

The nature of EFS also requires careful consideration of the criteria for selecting the investigating centers participating in the study and the patients to be enrolled. Regarding the selection of the sites, it was noted that the way these studies are managed may be different as opposed to more mature studies and requires both greater clinical and management expertise and the right 'cultural' approach. For example, EFS may require closer follow-up of patients and higher capacity to promptly respond to any adverse events, but they also require the capacity to culturally manage a high rate of failures (e.g. higher mortality or adverse events) compared to studies with more defined device designs and patients often

in better condition. In general, high volume, teaching and research hospitals were deemed the most appropriate setting for the conduction of EFS.

Selection criteria for patients to enroll in an EFS may also require specific considerations in the application. On one hand, severely ill patients with no available alternative treatments would likely ensure a positive risk–benefit ratio in EFS applications. On the other hand, patients' conditions should not be too compromised, to allow data collection, which is informative for the purposes of the study. Therefore, the enrollment of lower-risk patients was also discussed, although whether ethical standards would be met in this case should be verified on a case-by-case basis, after considering the existing risk profile of the device under investigation and available alternatives.

3.3.4. Types of devices that would be suited to an early feasibility study and minimum eligibility criteria

One general aspect that emerged from the panel discussion is that it would be difficult to pre-specify a minimum set of criteria to decide which candidate devices are admissible for EFS. In addition, the definition of a list of devices eligible for EFS, to be periodically updated by the MoH, was not considered advisable given the high pace of innovation that would require continuous updating of the list. However, two broad principles achieved agreement, which basically reiterate that mentioned above. First, the use of the device on human subjects should be regarded as the only way to further product development, and all available types of preclinical tests, including bench, animal, and in-silico models, should be proven to be inappropriate to collect the required evidence. Second, the potential benefits to patients should offset the potential risks related to their condition or any other available therapeutic option. This means that devices that are designed to treat severe conditions and unmet needs would be more likely to be approved for EFS. Related to this latter aspect, EFS were considered an efficient and structured way to collect clinical evidence in cases where the criteria for allowing individual compassionate use are met.

Regarding the characteristics and the stage of development of the devices, it was argued that devices with a high degree of novelty (i.e. disruptive innovations) and high potential to improve existing clinical standards were generally regarded as better candidates for EFS. However, discussion also centered on whether it would be ethical to consider the potential benefits accrued to future patients as one of the criteria to evaluate the admissibility of a device for EFS.

Beyond their use to assess innovative devices in the early phases of development, the admissibility of other types of devices was also discussed. For example, other potential candidates for EFS applications might include more mature technologies used for a novel indication, or even devices introducing incremental innovations compared to previous generations. In all cases, however, compliance with the two broad principles mentioned above, i.e. the inappropriateness of further non-clinical testing and an (expected) favorable risk–benefit ratio would still need to be met.

3.4. Key recommendations for the implementation of a European EFS program

Based on the discussion with the Italian MoH and the panel of experts, also leveraging on the US experience, we formulated several key recommendations for the design and implementation of a European EFS program and grouped them into three dimensions: process, resources, and ethical issues (Figure 5).

4. Discussion

This paper provided a broad overview of the characteristics of the Early Feasibility Studies program implemented by the FDA and the views and perceptions of key stakeholders on the desirability, feasibility, and challenges of implementing an FDA-like EFS program in Europe, and specifically in Italy.

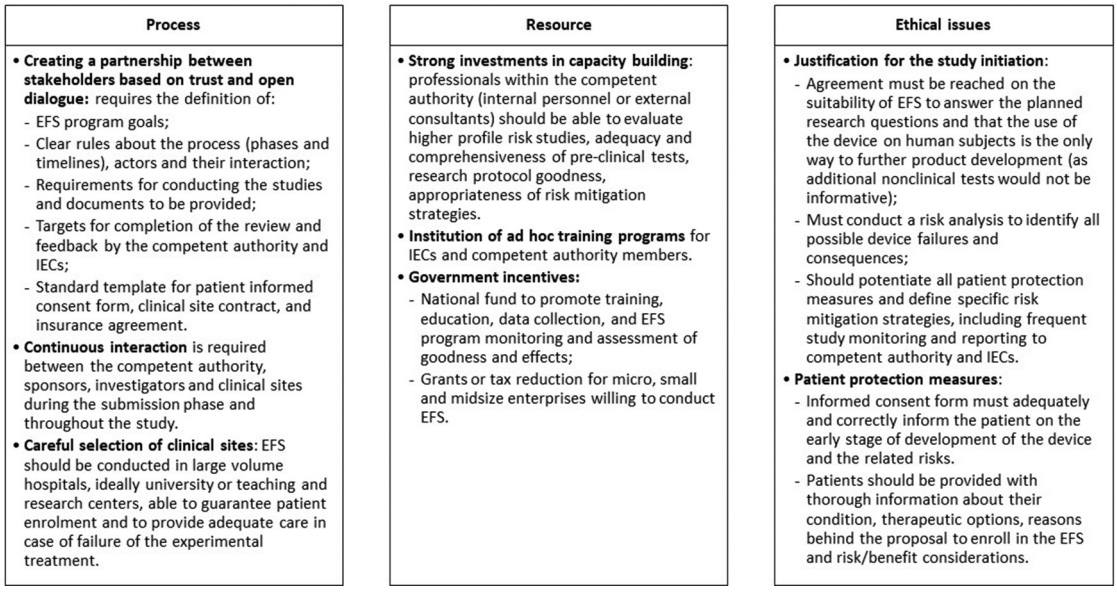

Figure 5. Recommendations for the successful implementation of a European EFS program.

Europe is the second largest market for medical technologies after the US [16] and exhibits an excellent level of innovativeness: in 2021, nearly 15,320 patent applications for medical technologies were filed with the European Patent Office (EPO), 41% of which were from European countries [18]. Nonetheless, full application of MDR will inevitably have consequences for the European industrial sector, for example in terms of higher development costs [1]. This in turn may affect the competitiveness of the European MD sector, and the expected uptick in regulatory requirements in Europe may push manufacturers to relocate their global clinical development strategies in countries with a more favorable environment, and then use the evidence generated to support their CE Mark application in Europe. This may reduce the attractiveness and role of European investigation centers and ultimately affect the possibility for European patients to obtain timely access to innovative medical technologies. In a similar fashion to the developments that led the US to review their pre-market device program, a European-wide EFS program may contribute to counterbalance such trends.

Because of the early stage of device development at the time of EFS, and the distinctive features of these studies as opposed to more mature studies, great emphasis needs to be put on promoting transparent and honest dialogue between the parties – innovators, competent authorities, clinical investigators, IEC, and assessors – involved before and after study authorization. Eventually, such dialogue would also facilitate deeper knowledge and reciprocal trust between manufacturers, competent authorities and IECs that was deemed key to successful implementation of the program. The promotion of dialogue among parties is in line with the overall approach adopted at the EU level to improve evidence generation processes and avoid unnecessary delays in providing market access to innovative health technologies. The MDR explicitly envisages the possibility for manufacturers of class III and certain class IIb devices to consult an expert panel on questions of clinical development and investigation [2]. Similarly, the new European Union Regulation on Health Technology Assessment (HTA) (Regulation (EU) 2021/2282) [19], approved in January 2022 with full application by January 2025, provides for health technology developers to engage in early dialogue with European HTA bodies as one of the four pillars of cooperation among EU Member States on this matter.

Recent European health policies have been characterized by a tendency toward centralization and harmonization. For instance, the EU Regulation on MDs [2] and HTA [19] established coordination groups. A similar harmonized approach would be desirable for the implementation and management of a European EFS program. To overcome the fragmentation in the regulatory process that has historically characterized the EU, by harmonizing and sharing processes, procedures, approaches, and methods, we envisage the creation of a European EFS Coordination Group. This would also help to capitalize on competencies and knowledge. Because EFS are not widely understood, even less so in the EU where they are not formally recognized, bringing together the jurisdictions, institutions, and scholars who have worked on this issue would be a great advantage for Member States.

Given the low quantity of evidence normally available for MDs, combining all efforts would be beneficial for manufacturers, regulatory agencies, and ultimately patient safety. The spontaneous birth of the International Medical Device Regulatory Forum (IMDRF), a voluntary group of MD regulatory agencies of the US, the EU, Australia, Brazil, Canada, China, and Japan, to accelerate international MD regulatory harmonization and convergence is a good omen. To further enhance collaboration, homogenization, and harmonization of EFS, a permanent working group could be established within the IMDRF.

The formal recognition of EFS among the pre-market clinical investigations allowed in Europe would add a missing piece in the evidence generation plan that the MDR requires over the whole technology life cycle [20], from preclinical pre-market (e.g. toxicology and biocompatibility tests, in silico trials, early HTA) to clinical pre-market (e.g. first-in-human exploratory studies, EFS, comparative effectiveness studies) to post-market phases (e.g. long-term registries, observational studies). EFS may be particularly informative in the pre-market phase studies, as information obtained during their execution can guide device modifications and eventually condition the continuation or suspension of the product's development. The concept of generating evidence across the various stages of medical technologies' life cycle is quite common and several approaches have been proposed, the two most prominent being the Total-Product-Life-Cycle [21], endorsed by the FDA, and the IDEAL (Idea, Development, Exploration, Assessment, and Long-term study) framework [22], originally developed for surgical interventions and several years after adapted for MDs through the IDEAL-D framework [23].

The establishment of an EFS program would require considerable organizational and financial effort as compared to the procedures currently in place for pre-market authorizations. Therefore, adequate mechanisms to monitor the performance of the EFS program, and whether it achieves planned objectives should also be established. In the US, a public–private partnership between the FDA and industry called Medical Device Innovation Consortium (MDIC) was created with the objective of further enhancing the efficiency of EFS conducted in the US [24]. To that end, several performance metrics were defined, specifically time to FDA IDE approval, time to site IEC approval, time to contract approval, and time to first subject enrolled by site. Performance metrics baselines were computed thanks to the 2017 MDIC Metrics Program, that collected data from 13 EFS sponsors on study and site performance from studies performed in 2015–17 and the so-called '60/60/60' goal (i.e. the time to execute the EFS Clinical Trial Agreement, achieve IEC approval, and enroll the first patient) was defined [25]. The analyses showed good performance on the time to EFS IDE protocol approval and site internal review panel approval, but cited several administrative barriers, for example regarding the times required for site contracting and patient enrollment [24,26]. To achieve the performance goal, MDIC created a network of sites and sponsors to favor a learning environment and share best

practices, and developed an EFS tool kit comprised a Master Clinical Trial Agreement template, contract language library & negotiation tool, patient Informed Consent Form template, and background information for IEC and research staff and for patients [27]. Registration of the EFS in EUDAMED, the European database of MDs currently under implementation, will allow to establish ad hoc metrics and monitor the performance of these studies.

In this respect, our database on EFS has some limitations: first, since registration on databases such as ClinicalTrials.gov is not mandatory for small clinical trials to determine feasibility and certain trials to test prototype devices, we were not able to identify the actual number and characteristics of all EFS that have been conducted over the years. This explains the reason why our data underestimate the number of approved studies reported by FDA officers Farb and Dreher [9], who rely on FDA CDRH data. Moreover, as EFS are not officially recognized by European Competent Authorities, eventual EFS approved as traditional feasibility studies are unlikely to be labeled EFS in publications and might have not been identified by the searches. Therefore, our database might lack some relevant articles.

5. Expert opinion

The European Union Regulation on Medical Devices entered into force in May 2021. It embraces clinical evidence generation across the entire lifecycle of MDs, from preclinical pre-market to clinical pre-market to post-market stages. Each stage is prodromal to the next and characterized by an appropriate level of clinical evidence [20]. Consistent with international standards for MDs [28], the evidence generation process normally starts with preclinical, toxicology, and biocompatibility tests aimed to optimize design, prototype development, and manufacturing engineering. This stage is followed by a clinical, pre-market phase, typically starting with exploratory studies intended to answer specific questions that may condition the continuation or suspension of the product's development program.

At this stage, a relevant option may be represented by early feasibility clinical investigations. EFS are pre-market studies recognized by the International Standards for clinical investigation of MDs for human subjects, that 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 asmall number of subjects when this information cannot practically be provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable. [12]

EFS may be particularly important as information obtained during their execution can guide device modifications.

European countries have no standardized procedural framework for EFS. In the absence of a specific framework, in Europe EFS are submitted either as individual requests for compassionate use or as traditional feasibility studies, and the competent authorities in charge of assessing the requests apply evaluation criteria neither specifically designed nor appropriate for EFS. So, it is not uncommon that clinical investigations not approved in Europe as traditional feasibility studies are resubmitted and approved as EFS in the US, under the FDA EFS program launched in 2013, with the aims of increasing early patient access to potentially beneficial medical devices in the US; reestablishing or increasing US participation in the early clinical evaluation of innovative medical devices; enhancing collaboration among developers, industry, regulators, and investigators; and utilizing the Investigational Device Exemption regulations to protect study participants during the EFS.

In December 2021, the European Parliament and the Council of the European Union approved a Regulation on Health Technology Assessment entering into force in January 2022 that will fully apply as of January 2025 [19]. The objective of the Regulation is to establish a common framework for joint clinical assessments of health technologies, improve the functioning of the EU internal market and promote the health of EU patients.

The approval of the EU Regulation on HTA, that will introduce centralized assessments on clinical dimensions, poses to Member States the challenge of embracing a comprehensive and shared vision of clinical evidence generation. EFS are the missing element in the European clinical pre-market stage. A discussion among Member States and the development of a shared framework for EFS, that employs agile procedures, enhances collaboration and trust among stakeholders, standardizes evaluation processes and criteria, and provides patient protection measures, are strongly recommended. The absence of a European structured framework for EFS will preclude European countries from early-stage R&D investment, reduce the attractiveness of European investigation centers, and ultimately affect the possibility for European patients to obtain timely access to innovative medical technologies. A European-wide EFS program may contribute to counterbalance such trends.

Declaration of Interest

The authors have no 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. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Tarricone R, Ciani O, D'Acunto S, et al. The rise of rules: will the new EU regulation of medical devices make us safer? Eur J Intern Med. 2020;80:117–120.

•This reference describes the key points of the EU Regulation on Medical Devices.

2. 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. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745.
3. Shuren J. Continuing America's leadership: the future of medical innovation for patients. Statement of Jeffrey Shuren, M.D., J.D., Director, Center for Devices and Radiological Health, Food and Drug Administration Department of Health and Human Services, before the Committee on Health, Education, Labor and Pensions, United States Senate. 2015 Apr 28. Available from: http://www.help.senate.gov/imo/media/doc/Shuren3.pdf.
4. Holmes DR Jr, 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(17):1908–1915.
5. Eydelman MB, Nguyen T, Green JA. The US food and drug administration's new regulatory toolkit to bring medical device innovation back to the United States. JAMA Ophthalmol. 2016;134(4):353–354.
6. Maisel W. Innovation at the food and drug administration's device center. J Am Coll Cardiol Intv. 2012;5(7):797–798.
7. US Food and Drug Administration, Center for Biologics Evaluation and Research. 2013. Investigational device exemptions (IDEs) for early feasibility medical device clinical studies, including certain first in human (FIH) studies: guidance for industry and food and drug administration staff. Available from: http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf.

••This reference describes the key features of the FDA EFS Program and provides a guidance regarding Investigational Device Exemptions for EFS.

8. Center for Devices and Radiological Health (CDRH). 2014. 2014 – 2015 strategic priorities. Available from: https://www.fda.gov/media/88017/download.
9. Farb A, Dreher ML. An update from FDA on CDRH's EFS program, edition 5, June 6, 2019. Available from https://mdic.org/wp-content/uploads/2020/07/Edition-5.pdf.
10. Center for Devices and Radiological Health (CDRH). 2018. 2018 – 2020 strategic priorities. Available from: https://www.fda.gov/media/110478/download.
11. Dreher ML, Rouabhi O, Farb A. Early feasibility study program during the COVID-19 pandemic, edition 26, 2021 Mar 23. Available from: https://mdic.org/wp-content/uploads/2021/03/EFS-Express-26.pdf.
12. ISO 14155:2020 clinical investigation of medical devices for human subjects – good clinical practice. Available at: https://www.iso.org/standard/71690.html?browse=tc.
13. Medical Device Coordination Group (MDCG). 2021. Regulation (EU) 2017/745 – questions & answers. MDCG 2021-6, Available from: https://ec.europa.eu/health/sites/default/files/md_sector/docs/mdcg_2021-6_en.pdf.
14. Italian Ministry of Health, Directorate General for Medical Devices. 2021. Notifica di indagini cliniche svolte con dispositivi medici non recanti la marcatura CE (pre market). Available from: http://www.salute.gov.it/portale/ministro/p4_8_0.jsp?lingua=italiano&label=servizionline&idMat=DM&idAmb=SC&idSrv=ICPRE&flag=P.
15. Creswell JW, Poth CN. Qualitative inquiry and research design choosing among five approaches. 4th ed. Thousand Oaks: SAGE Publications, Inc.; 2018.
16. MedtechEurope. 2021. The European Medical Technology Industry in figures 2021. Available from: https://www.medtecheurope.org/wp-content/uploads/2021/06/medtech-europe-facts-and-figures-2021.pdf.
17. Pappalardo F, Russo G, Musuamba Tshinanu F, et al. In silico clinical trials: concepts and early adoptions. Brief Bioinform. 2019;20(5):1699–1708.
18. European Patent Office (EPO). 2022. European Patent Office: Patent Index 2021. Available from: https://www.epo.org/about-us/annual-reports-statistics/statistics/2021/statistics.html.
19. Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32021R2282&from=IT.

•This reference illustrates the vision of the European Commission on the pan-European collaboration on HTA.

20. Tarricone R, Ciani O, Torbica A, et al. Lifecycle evidence requirements for high-risk implantable medical devices: a European perspective. Expert Rev Med Devices. 2020;17(10):993–1006.

••This reference provides recommendations for the appropriate level and timing of clinical evidence throughout the lifecycle of high-risk implantable medical devices.

21. Hausman ED, Altaie SS. Regulatory aspects of total product life cycle. Diabetes Technol Ther. 2004;6(6):761–766.
22. McCulloch P, Altman DG, Campbell WB, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009;374(9695):1105–1112.
23. Hirst A, Philippou Y, Blazeby J, et al. No surgical innovation without evaluation: evolution and further development of the IDEAL framework and recommendations. Ann Surg. 2019;269(2):211–220.
24. DR H Jr, Mack MJ, Leon M, et al. The medical device innovation consortium and its goal to further the efficiency of early feasibility studies in the United States. J Endovasc Ther. 2019;26(3):423–424.
25. MDIC. 2018. 2017 program summary, Available from: https://mdic.org/wp-content/uploads/2020/06/EFS-Metrics_MDIC-Website-2018.pdf.
26. MDIC 2019. Early feasibility studies: metrics update 2019. Available from: https://mdic.org/wp-content/uploads/2020/06/APF-EFS-Final-20190903c.pdf.

•• This document presents the measures developed by the FDA and the Medical Device Innovation Consortium to evaluate EFS performance and identify weaknesses.

27. MDIC. 2020. The complete MDIC EFS tool kit now available for sponsors and clinical research sites, edition 22, 2020 Nov 3. Available from: https://mdic.org/wp-content/uploads/2020/10/EFS-Express-22.pdf.
28. ISO 10993 biological evaluation of medical devices series. Available from: https://www.iso.org/search.html?q=10993.