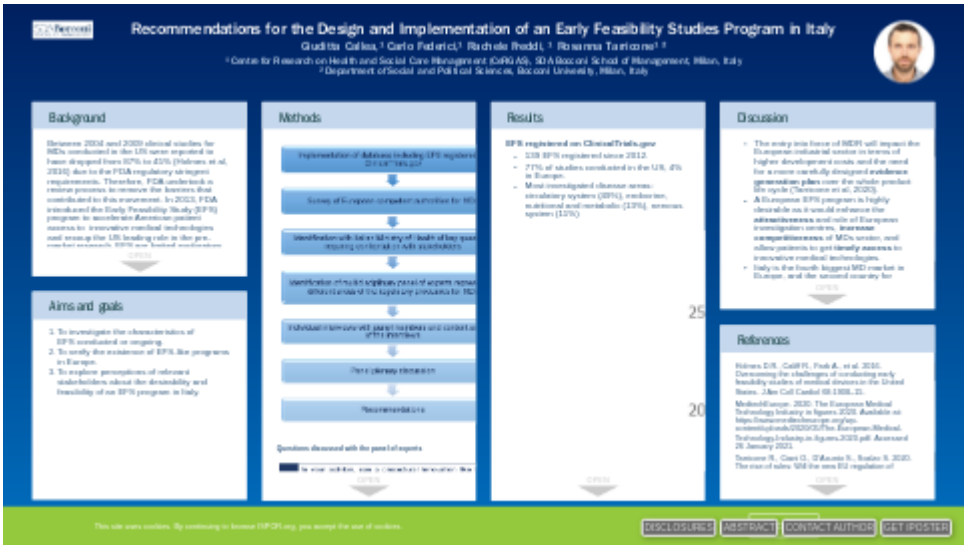
Recommendations for the Design and Implementation of an Early Feasibility Studies Program in Italy



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BACKGROUND

Between 2004 and 2009 clinical studies for MDs conducted in the US were reported to have dropped from 87% to 45% (Holmes et al, 2016) due to the FDA regulatory stringent requirements. Therefore, FDA undertook a review process to remove the barriers that contributed to this movement. In 2013, FDA introduced the Early Feasibility Study (EFS) program to accelerate American patient access to innovative medical technologies and recoup the US leading role in the pre-market research. EFS are limited exploratory clinical investigations taking place early in the development of devices, in small number of patients, typically before the device design has been finalized. Their purpose is related to demonstrating proof of concept and optimizing device design when further non-clinical testing is deemed inadequate to the scope.

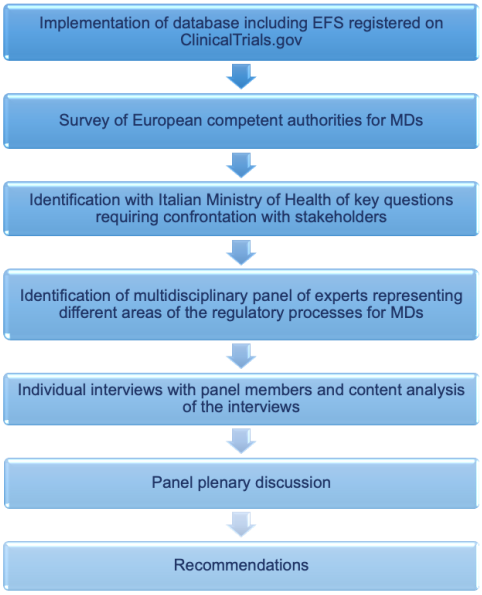
Currently European countries do not have a standardized procedural framework for EFS, that are either put forward as individual requests for compassionate use or submitted as traditional feasibility studies and evaluated with inappropriate criteria.

The new European Regulation on MDs (MDR), that will become fully active in May 2021, is expected to make the regulatory framework in Europe more restrictive. A European FDA-like EFS program would be desirable as it may contribute to a more streamlined and efficient process for evidence generation and therefore constitutes a viable option to meeting the requirements of the MDR while acknowledging the specificities of devices development and reducing the burden for technology developers.

AIMS AND GOALS

1. To investigate the characteristics of EFS conducted or ongoing.
2. To verify the existence of EFS-like programs in Europe.
3. To explore perceptions of relevant stakeholders about the desirability and feasibility of an EFS program in Italy.

METHODS



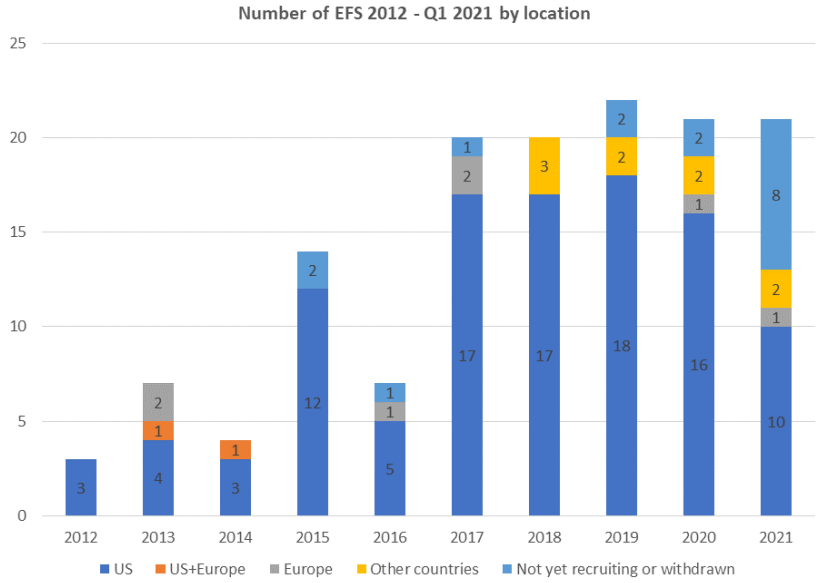
Questions discussed with the panel of experts

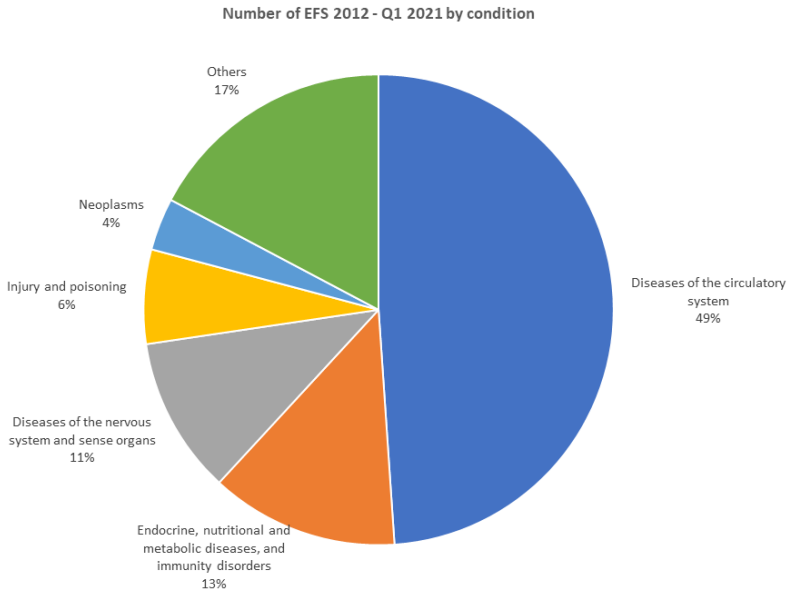
Q1	In your opinion, can a procedural innovation like the EFS program promoted by the FDA be useful in the Italian context and which critical aspects can be overcome thanks to it?
Q2	Which challenges are posed by the implementation of an EFS program? In particular, which ethical aspects need to be carefully 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 type of devices might benefit most from the implementation of an EFS program? Is it possible to define a set of minimum admissibility criteria?

RESULTS

EFS registered on ClinicalTrials.gov

- 139 EFS registered since 2012.
- 77% of studies conducted in the US, 4% in Europe.
- Most investigated disease areas: circulatory system (49%), endocrine, nutritional and metabolic (13%), nervous system (11%)





Presence of European EFS programs

- 5 responses to the survey from competent autority in Italy, Bulgaria, Finland, Slovenia, and Sweden.

- No EFS programs implemented.

Recommendations for the implementation of an EFS program

Process

- To create partnership between stakeholders based on trust and open dialogue.
- To promote continuous interaction between competent authority, industry, investigators and clinical sites.
- To carefully select clinical sites.

Resources

- To invest in capacity building.
- To establish ad hoc training programs for internal ethics committees and competent authority members.
- To create government incentives for small and medium-sized enterprises.

Ethical issues

- To clearly justify the suitability of an EFS initiation and the reason why further pre-clinical testing would not be informative for the development of the product.
- To use enhanced patient prtection measures.

DISCUSSION

- The entry into force of MDR will impact the European industrial sector in terms of higher development costs and the need for a more carefully designed **evidence generation plan** over the whole product life cycle (Tarricone et al, 2020).
- A European EFS program is highly desirable as it would enhance the **attractiveness** and role of European investigation centres, **increase competitiveness** of MDs sector, and allow patients to get **timely access** to innovative medical technologies.
- Italy is the fourth biggest MD market in Europe, and the second country for number of medical technologies companies (MrdtechEurope, 2020), hence it stands as an optimal testing ground for a higher scale implementation of the EFS programme at the European level.

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DISCLOSURES

CONFLICTS OF INTEREST: The authors have no conflicts of interest to declare.

ACKNOWLEDGEMENTS: The study received an unrestricted grant from the Directorate General of Medical Devices and Pharmaceutical Service, Ministry of Health, Italy

ABSTRACT

OBJECTIVES: Early Feasibility Studies (EFS) are limited exploratory clinical investigations taking place early in the development of devices, in small number of patients, typically before the device design has been finalized, when further non-clinical testing is not possible or meaningful. An EFS program was introduced by the US Food and Drug Administration (FDA) in 2013 to accelerate access of American patients to medical technologies and recoup a leading role in the pre-market research. The aim of this study was to explore perceptions of relevant stakeholders about the desirability and feasibility of an EFS program in Italy and of critical factors favoring or hampering its implementation. **METHODS**: Qualitative research methods (i.e., exploratory and confirmatory focus groups) involving an expert panel of clinicians, biomedical engineers, members of ethics committees, academics, and industry representatives were used to collect opinions on the appropriateness and feasibility of an EFS Italian program. **RESULTS**: The expert panel agreed that an EFS program would maximize the efficiency of evidence generation process, strengthen competitiveness and attract R&D investments in the biomedical area. Potential challenges relate to the need for a clear legal framework and high level of technical competencies to evaluate studies. A particular attention must be given to ethical aspects, safety and risk analysis. Any device could be eligible, but potential benefits should offset risks, and the use of the device on human subjects should be regarded as the only way to further product development. **CONCLUSIONS**: An Italian EFS program is highly desirable, however it requires trust and open dialogue between stakeholders, strong investments in capacity building, and patient protection measures to be successful. If successful, it could be scalable to the European context.