Harmonised approach to **E**arly **F**easibility **S**tudies for Medical Devices in the **E**uropean **U**nion **(HEU-EFS)**

WP3
Methodology development: rationale, processes and procedures

DELIVERABLE 3.1

Eligibility criteria for EFS

Co-funded by the European Union

Disclaimer:

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Project Acronym	HEU-EFS
Project Title	Harmonised approach to Early Feasibility Studies for Medical Devices in the European Union
Project Coordinator	Giuditta Callea giuditta.callea@unibocconi.it
Grant Agreement Number	101112185
Project Duration	October 2023 – October 2027 (48 months)
Deliverable Number	Deliverable 3.1 Eligibility criteria for EFS
Work Package	3
Task	3.1
Lead Beneficiary	NIPH, UB, Edwards
Status	Completed
Dissemination Level	Public
Type	R – Document, report
Due Date of Deliverable	28-02-2025
Actual Submission Date	20-03-2025
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File History				
Version	**Date**	**Status**	**Authors**	**Review**
1.0	16-12-2024	V1.0	Carmen Furno, Benedetta Brancadoro (GEMELLI), Nicolas Martelli, Ornella Tangila Kayembe, Tess Martin (AP-HP), Alexandra H.C. Poulsson, Marit Erna Austeng (NIPH), Lise Kvistgaard Jensen (SDU CIMT), Benedetta Brancadoro, Carmen Furno, Carlo Trani (GEMELLI), Laura Sampietro-Colom, Daniel Beltrán (HCB), Adrián Valledor (FCRB), Maria Luisa Buzelli, Helen Banks (Bocconi), Kevin Drisko, Karin Fricke (Edwards), Manon Gielkens, Sebastiaan de Jongh (Medtronic), Jeff Sturm (Abbott), Marta Bragagnolo (GHH), Claudia Louati, Yasemin Zeisl (EPF)	Full consortium: Monica Tocchi, Eleonora Russo, Donatella Mariani (Meditrial), Sebastian Kuhn (UMR), Nancy Zhang, Cinzia Santin, Cristina Isaia (W.L.Gore), Els Boone (Abbott), Tom Melvin, Majella Geraghty (TCD), Franco Zurlo UB, Marta Kerstan (J&J) , Fanny van der Loo (Edwards)

File History				
Version	**Date**	**Status**	**Authors**	**Review**
2.0	30-01-2025	V2.0	Nicolas Martelli, Ornella Tangila Kayembe, Tess Martin (AP-HP), Alexandra H.C. Poulsson, Marit Erna Austeng (NIPH), Laura Sampietro-Colom, Adrián Valledor (FCRB), Maria Luisa Buzelli, Helen Banks (Bocconi), Kevin Drisko, Karin Fricke (Edwards), Yasemin Zeisl, Claudia Louati, Estefania Callejas de Luca (EPF), Marta Bragagnolo (GHH)	Rosanna Tarricone, Giuditta Callea (UB)
3.0	06.02.2025	V3.0	Alexandra H.C. Poulsson, Marit Erna Austeng (NIPH), Laura Sampietro-Colom, Adrián Valledor (FCRB), Nicolas Martelli, Ornella Tangila Kayembe (APHP), Maria Luisa Buzelli, Helen Banks (Bocconi), Kevin Drisko, Karin Fricke (Edwards), Yasemin Zeisl, Claudia Louati, Estefania Callejas de Luca (EPF), Marta Bragagnolo (GHH)	Full Consortium: Nancy Zhang, Cinzia Santin, Cristina Isaia (W.L.Gore), Els Boone (Abbott), Tom Melvin, Majella Geraghty (TCD), Franco Zurlo UB, Marta Kerstan (J&J) , Fanny van der Loo (Edwards)

File History				
Version	**Date**	**Status**	**Authors**	**Review**
3.5	26.02.2025	V3.5-3.9	Alexandra H.C. Poulsson, Marit Erna Austeng (NIPH), Laura Sampietro-Colom, Adrián Valledor (FCRB), Nicolas Martelli, Ornella Tangila Kayembe (APHP), Maria Luisa Buzelli, Helen Banks (Bocconi), Kevin Drisko (Edwards), Manon Gielkens (Medtronic), Sebastiaan de Jongh (Medtronic)	Jeff Sturm, Alessandra Denaro (Abbott), Fanny van der Loo (Edwards), Benedetta Brancadoro, Carmen Furno, Carlo Trani (GEMELLI), Cinzia Santin (W. L. Gore)
4.0	20.03.2025	V4.0	Alexandra H.C. Poulsson, Marit Erna Austeng (NIPH), Helen Banks (UB)	Giuditta Callea (UB)

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ABBREVIATIONS

AI	Artificial Intelligence
APHP	Assistance Publique Hôpitaux De Paris
ASTM	American Society for Testing and Materials
ARQ	Attività Regolatoria e Qualità (Regulatory and Quality Activities)
CA	Consortium Agreement
CEC	Clinical Events Committee
CFS	Certificate of Financial Statements
CI	Clinical Investigation
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organizations
CRU	Clinical Research Unit
CTA	Clinical Trial Assistant
CTOs	Clinical Trial Offices
CTUs	Clinical Trial Units
CS	Common Specifications of MDR
DEC	Dissemination, Exploitation and Communication
DHT	Digital Health Technologies
DMP	Data Management Plan
DoA	Description of Action
DSMB	Data and Safety Monitoring Board
EC	European Commission
EEA	European Economic Area
EFS	Early Feasibility Studies
EMA	European Medicines Agency
EPF	European Patients Forum
EU	European Union
EUDAMED	European Database for Medical Devices
FDA	Food and Drug Administration

FDA EFS Program	FDA Early Feasibility Program
FEA	Finite Element Analysis
FIH	First-In-Human
GA	Grant Agreement
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
GHH	Global Heart Hub
GSPR	General Safety and Perform Requirements, MDR Annex I
HEU-EFS	Harmonized Approach to Early Feasibility Studies for Medical Devices in the European Union
HTA	Health Technology Assessment
HTAR	Health Technology Assessment Regulation
HTD	Health Technology Developer
ICF	Informed consent form
IDE	FDA Investigational Device Exemption
IEC	Independent Ethics Committees
IHI	Innovative Health Initiative
IRB	Institutional Review Board is a group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research.
IRCCS	Istituto di Ricovero e Cura a Carattere Scientifico, which translates to Institute for Hospitalization and Scientific Care.
ISO	International Organization for Standardization
IVDR	In Vitro Diagnostic Regulation
JCA	Joint Clinical Assessments
J&J	Johnson & Johnson
JSC	Joint Scientific Consultation
KOLs	Key Opinion Leaders
MD	Medical Device
MDD	Medical Device Directive

MDCG	Medical Device Coordination Group
MDCG guidance	Medical Device Coordination Group (MDCG) guidance https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en
MDIC	Medical Device Innovation Consortium
MDR	Medical Device Regulation
MIM	Mutual Insurance Mechanism
NCA	National Competent Authority
NIPH	Norwegian Institute of Public Health
NB	Notified Body
PAG	Patient Advisory Group
PROM	Patient Reported Outcome Measure
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
ROL	Result Ownership List
RP	Reporting Period
SAE	Serious Adverse Events
SOP	Standard Operating Procedures
SME	Small and Medium Enterprise
TCD	Trinity College Dublin
UB	Bocconi University
UMR	Philipps-Universität Marburg
UTC4	Unità Trials Clinici (Trial Coordination Unit)
vs.	Versus
WET	Well Established Technology
WP	Work Package

EXECUTIVE SUMMARY

The Harmonised approach to Early Feasibility Studies for Medical Devices in the European Union (HEU-EFS) project aims to develop a sound, widely applicable, and harmonised framework for EFS implementation at the EU level. This framework is to be integrated in the clinical evidence generation cycle for medical devices (MDs), including digital health technologies (DHTs), compliant with EU Regulations (Medical Device Regulation (MDR), HTA Regulation (HTAR), and AI (Artificial Intelligence) Act).

Leveraging the results of research and analysis of pre-market clinical investigations (CIs) approval pathways, including the Food and Drug Administration (FDA) EFS Program, and EU regulatory framework and international standards, the consortium members have developed recommendations on eligibility criteria for EFS in the EU. To ensure wide applicability of the HEU-EFS methodology, a fully inclusive approach was adopted, involving the Advisory Board and the Patient Advisory Group (PAG) in the discussions.

The proposed eligibility criteria will be applied during the pilot phase of the project that has been designed to validate the functioning of the future EU-EFS Program in practice, to reveal possible areas for improvement, and recommend any adjustments. Therefore, the recommendations are to be considered functional for the pilot phase. The final eligibility criteria will be reviewed and updated in light of the *ex post* evaluation of the pilot EFS studies and will be included in the EU-EFS Program final Guidance for the HEU-EFS project.

ELIGIBILITY CRITERIA AND RECOMMENDATIONS FOR EU-EFS FRAMEWORK TO BE TESTED BY PILOT USE-CASES

The eligibility criteria relate to technologies that are proposed to undergo an EFS, medical conditions and populations to be included in and EFS, the level of pre-clinical evidence necessary to start an EFS, and clinical sites and clinical expertise needed to conduct an EFS. The eligibility criteria presented are not ranked.

Technology

The characteristics that MDs, including DHTs, must meet to be eligible for an EFS pilot are shown below. Three general device scenarios have been identified as most applicable to conduct EFS under the EU-EFS program are presented in Box 1

Box 1 Eligibility criteria for technologies undergoing an EFS.

General criteria: **High-risk devices (Class III and Class IIb), including DHTs**, for which clinical investigation data is needed to support a future conformity assessment.

Technology specific criteria:

1. **Breakthrough Device/Unmet Need** – utilised to collect early clinical data when no equivalent device exists.
2. **Anatomical understanding –** utilisation of the EFS to better understand physiology and anatomical limitations of the device under development.
3. **New/Expanded intended uses or indication for use** – the application of an existing/approved device in a new patient population or application.

Medical conditions and populations included in EFS.

Recommendations regarding medical conditions, unmet needs, and population to be recruited for EFS are presented in Box 2.

Box 2 Eligibility criteria for medical conditions and populations included in EFS.

1. **Limit the study population in EFS** to a small number of patients, ideally **not more than 15**.
2. **Phased or iterative enrolment** (e.g., 1-2 patients, with testing and evaluation before continuing to the next) is recommended.
3. **Limits to medical conditions** suitable for EFS are not recommended.
4. A focus on **patient groups** and **conditions** with no **existing effective treatment.**
5. **Align patient population with study objectives:** To ensure the selected patient group reflects the goals of the study.
6. **Consult patients/patient** representatives during the **design of an EFS.**
7. **Benefit-risk analysis:** Evaluate the **benefits for the eligible patient population** of the EFS through a benefit-risk analysis.
8. **Prioritise patient safety:** Aim for **high patient safety** despite the potential for high-risk MDs in EFS.
9. In line with restrictions set out under the MDR identify **which patient groups ought to be excluded from EFS**, or be duly justified for inclusions (e.g., incapacitated subjects, minors, pregnant women and breastfeeding women)

10. **Transparency: Patients involved** in the EFS should be **kept informed** about trial results and updates, especially if there are changes/modifications to the EFS.

Level of pre-clinical evidence

The evidential requirements and types of tests to be conducted prior to initiating an EFS are presented in Box 3.

Box 3 Level of pre-clinical evidence necessary to initiate an EFS.

1. Pre-clinical testing should be **compliant to GSPR** in **the EFS framework** unless duly justified or relevant data is gathered through the EFS.
2. **Pre-clinical testing** shall be **performed as far as possible,** unless:
    a. a justification is provided for limitations in the testing, e.g. where **further testing is not possible** due to anatomy, physiology etc. and will be **answered through the EFS**, or
    b. **testing can be performed in parallel to EFS,** e.g. full number of cycles in a biomechanical test (to estimate a 10–15-year lifetime in use).
3. Allow for **leveraging data** from **similar devices or previous versions.**
4. **Open communication with the NCA** during the EFS is essential to facilitate **design changes as the EFS progresses,** since **pre-clinical testing will not be finalised,** and the design will remain in a continuous iterative phase**.**
5. An **iterative approach** in the EFS is important **to accommodate** potential **design changes.**
6. **Guidance** on the required pre-clinical evidence needed to start an EFS is important for start-ups to **promote innovation** in Europe and aid SMEs in moving from ‘bench to bedside’.

Clinical sites and clinical expertise need to conduct an EFS

Box 4 shows the requirements that should be met by clinics selected for the EFS, and the minimum level expertise for all parties involved in CIs such as clinicians, administrators, sponsors and investigators.

Box 4 Eligibility criteria for clinical sites and clinical expertise.

1. An **increase in regulatory competence** is beneficial for all parties involved in planning and conduction of EFS. Clinical sites may have **dedicated units or personnel** specifically tasked with **coordinating regulatory submissions and contracts.**
2. Clinical site should ensure **compliance with ICH-GCP standards and ISO 14155:2020** is necessary in EFS.
3. Personnel involved in EFS must have **an extensive understanding on how to report serious adverse events** in line with requirements of the MDR.
4. **Clinical site** needs to have the **capacity and equipment** to offer adequate **emergency care and support systems** during and, where needed, after the EFS.
5. Ensure **independence or transparency of conflict of interest for clinical staff** working on the EFS. Clearly communicating this to patients can be an important step to building trust and confidence in an EFS participation.
6. Clinical staff should have **experience in the therapeutic field** of the investigational device and/or have **research experience with similar devices or early phase CI**. The **site should have the required population** needed within the agreed recruitment period.
7. In EFS **training for the clinical personnel** has to be ensured at a high-level. Training methods may include **simulators, procedural videos, hands-on practice, and pre-clinical work (e.g., animal or cadaver models)** are valuable tools for building to enhance readiness and confidence.
8. Clinics should **involve proctors and clinical specialists**: As their guidance is highly beneficial to **train the clinical staff**.
9. **Regulatory harmonisation** for EFS pathway across NCAs is necessary as **clinical sites have experienced a lack of harmonisation.** In addition, a need for **ongoing dialogue between sponsors, clinical staff and National Competent Authorities** (NCAs) is essential.
10. **Quality markers** may be useful as **a guidance for the clinics planning EFS** and for the NCAs, when evaluating of CI applications.

1. Introduction

The overall aim of the 'Harmonized Approach to Early Feasibility Studies for Medical Devices in the European Union' (HEU-EFS) project is to develop and validate a sound, widely applicable methodology for EFS in the EU/EEA, compliant with EU regulations. To achieve this objective, work package 3 (WP) is responsible for developing eligibility criteria to access the future EU-EFS Program. These criteria include technologies, medical conditions, population to be included in EFS and unmet needs, the level of evidence required to initiate an EFS, requirements to qualify as an EFS clinical site, and the clinical expertise needed to run an EFS.

The objective of this report is to identify the eligibility criteria that will guide the pilot EFS (WP7) in the project which will test the functioning and propose improvements to the HEU-EFS methodology. This will ultimately inform our future recommendation for an EU-EFS program. The eligibility criteria are based on both an overview of the requirements described in current regulations such as the MDR and HTAR, and the needs from health technology developer (HTDs) engaged in clinical development, the experience from clinical sites who run EFS, regulatory experience of the Health Technology Assessment (HTA) Bodies and patients' perspectives. Any changes in the regulatory framework that may affect the project during the project period will also be taken into consideration.

The EU AI act (Regulation: 2024/1689) will impact any MD which is software driven by machine learning (ML) and digital devices or AI. This new regulation must be taken into consideration in the EU-EFS future framework.

The MDR framework for CIs serves as the foundation for the establishment for HEU-EFS methodology and thereby ensures that the safety requirements of MDR are followed.

ISO 14155:2020 'Clinical investigation of medical devices for human subjects — Good clinical practice' defines that EFS are limited CIs, early in the development of a MD to evaluate the device design concept and understand initial safety and performance. EFS are typically performed before the device design has been finalised, for a defined intended use, to evaluate an innovative device for a new or established intended use or for an already approved device for a new intended use.

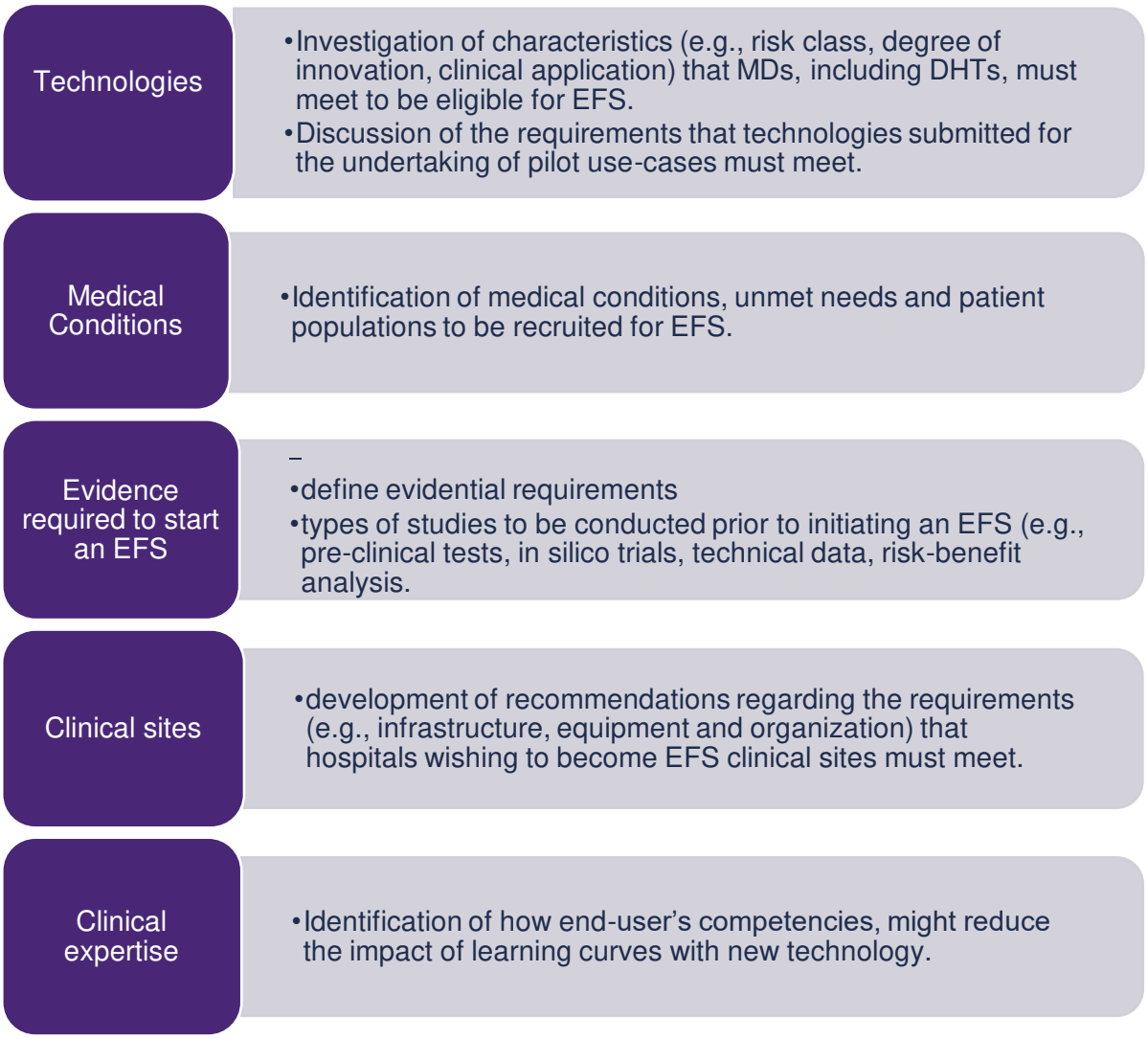
WP1 and 2 of the HEU-EFS project have already completed four reports [1-4]. These reports provide an overview of EU regulations, CI in the EU/EEA, international standards, and guidelines. An analysis of EFS-like studies since 2013, to understand their main characteristics

[4]. Finally, a report mapping the EU and international research projects on DHTs has been published [2]. These reports form a foundation for the work in WP3.

In particular, this current report presents the recommendations which have been developed based on the scoping literature reviews and the early feasibility studies database (EFS-DB), both conducted as part of WP1 and an overview of EU regulatory framework of WP2. We have performed a more focused review of the MDR and its guidance documents, ISO 14155:2020 and FDA EFS Guidance for the Investigational Device Exemption (IDE). To establish the eligibility criteria for EFS all the partners in the Consortium were consulted. Working groups (WG) of the contributing partners were established based on their expertise and feedback and suggestions were gathered in Task 3.1 of WP3. In addition, we conducted questionnaires with Consortium clinics, and interviews with Consortium HTD Partners.

Consistent with the HEU-EFS project' objective of patient-centricity, the project's Patient Advisory Group (PAG) have contributed to the findings through active participation in two focus groups where the eligibility criteria were discussed. This deliverable is broken down into detailed tasks which focus on eligible technologies, patient conditions and the population included in EFS, the level of evidence required to move to clinical investigations, and requirements for clinical sites and expertise needed for the conduct of EFS to provide criteria and recommendations for each, within the current regulatory framework. Details of Task 3.1. are shown in Figure 1.

Figure 1 Subtasks in the deliverable.

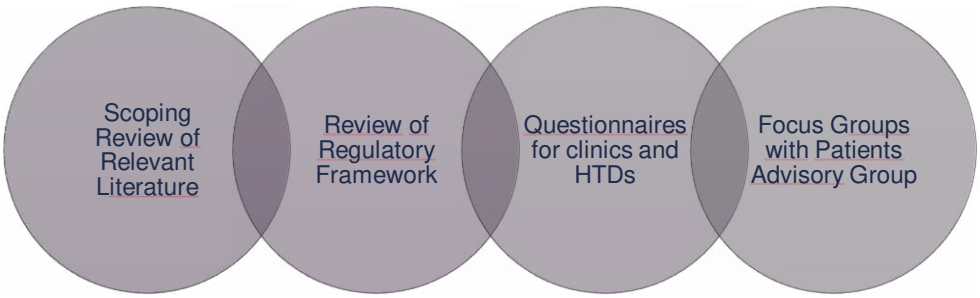


2. Methods

WP3 is central to the whole HEU-EFS project and therefore started by involving all the 22 partners of the project to identify resources and define the more detailed scope of Task 3.1. Once this was established, the leader and co-leaders of the WP took on the role of subtask leaders. A call went out to all the relevant partners in the Consortium to volunteer for WGs for each subtask, shown in Figure 1, as either hands-on, internal subtask-reviewer or reviewer. Each WG with its subtask-leader undertook the work of their chapter in this deliverable following the methodology described below.

Each subtask leveraged the results of previous literature and regulatory mapping done as part of WP1 and WP2 to gather the relevant foundation for their activities. Where additional information was needed this was gathered from the relevant sources as described below and in Appendix II Methods.

Figure 2 Schematic representation of research methodology.



An in-depth review of MDR, Medical Device Coordination Group (MDCG) guidance, relevant standards such as ISO 14155:2020 and ISO 14971:2019 – 'Medical devices — Application of risk management to medical devices', the ISO 10993 series of standards for 'Biological evaluation of medical devices', Medical Device Innovation Consortium (MDIC) Blueprint and the FDA EFS Program was conducted to identify specific requirements and develop the recommendations in the following Chapters.

Two questionnaires targeted to Consortium Partner clinics and larger HTDs were developed based on the aforementioned literature and regulatory reviews and partner input. Two focus groups with Patient Advisory Group (PAG) members were organised to identify patient perspectives on the developed eligibility criteria. The focus groups of the PAG covered all the

areas described in Figure 1. Finally, the eligibility criteria were presented in workshop with the HEU-EFS Advisory Board. A more detailed Methods Section for all Subtasks can be found in Appendix II Methods.

3. Eligibility criteria for technologies which could benefit from an EFS

3.1 Introduction

As previously mentioned, the concept of an EFS is to gain further understanding on an early development stage of a MD in a small number of subjects. This approach was originally developed by the FDA in 2011 and following a two-year pilot, expanded into a full program complete with a released FDA EFS Program guidance document (Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies) in October 2013 [5]. In the FDA EFS Program, studies are suitable for a variety of device types that undergo premarket approval or notification as well as De-Novo classification devices and Humanitarian devices. The FDA approach in the FDA EFS Program is risk based. Oversight of IDEs, of which an EFS is a sub-type, is the responsibility of the FDA for "Significant Risk Devices" while oversight of "Non-Significant Risk Devices" is managed by reviewing Institutional Review Boards (IRBs). Significant risk devices are described in 21 CFR 812.3(m) as a device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject.
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject.
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject.
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

While it is possible for a non-significant risk device to undergo an EFS study, these non-significant risk devices would normally fall under a lower risk classification and would frequently be brought to the market without conducting a pre-market CI, therefore, the primary focus of EFS studies evaluated by FDA would be the significant risk device category.

In Europe, device classification follows a different scheme than in the USA and while theoretically all devices could be investigated in an EFS in Europe, certain types of devices are better served in the EFS setting. The MDR has a risk-based approach to clinical evidence

generation for MDs. High risk devices are subject to a thorough evaluation for CI under MDR, whereas low risk devices generally undergo a short validation for CI by the NCAs. In simple terms high risk devices such as implantable class IIb and III devices require clinical investigations for a future conformity assessment (for market access/ CE-certificate), where a CI application must be evaluated and approved by the NCA and Independent Ethics Committees (IEC) in accordance with MDR Article 62. In the EU-EFS pilots it may therefore be advantageous to have a focus on these high-risk devices with a small cohort of subjects, ideally not more than 15. Where further CI will be needed for the conformity assessment.

Article 70(7) governs CI for low-risk devices, such class I devices or non-invasive class IIa and non-invasive class IIb devices, where a sponsor may start the clinical investigation unless otherwise stated in the national law, immediately after the validation date, with IEC approval in the Member State concerned.

Establishing guidelines for the type of devices suitable for EU-EFS studies is the goal of this task and are articulated in the following Section.

3.2 Results

Through discussion among the Consortium Partners, including the PAG, and reflection upon the existing criteria for devices eligible for EFS as established by the FDA, it is proposed that primarily high-risk devices including DHTs for which CI data would be needed to support a future conformity assessment at a later stage would be suitable for EFS within the EU. From these discussions, three general device scenarios were highlighted as most applicable for the conduct of EFS under the EU-EFS program.

It is the responsibility of the HTDs to justify the need to conduct such CIs within the clinical evaluation plan (MDR Article 61(1) and Part A of Annex XIV) of which EFS is a subset. There is synergy noted between the aforementioned subset of devices and the devices identified in the recent Health Technology Assessment Regulation (HTAR) (EU) 2021/2282, Orphan devices clinical evaluation pilot MDCG 2024-10 and the scope for the MDR Expert Panel Scientific Advice as defined in Article 54 (1) of Regulation (EU) 2017/745.

3.2.1 Unmet need/breakthrough devices

An area of MD development suitable for EFS are those for which the technology is serving an unmet need or described as breakthrough in the FDA EFS Program. In general, when treating an unmet need there is a need for slow progression through the development process as typically no viable alternatives previously exist. The known treatment effects and risks of the

device within the target patient population are often limited but offset by potential benefits. The importance of addressing unmet medical needs has been previously identified in the HTAR, Orphan devices clinical evaluation pilot supporting the implementation of MDCG 2024-10, and Expert Panel Scientific Advice, and is described in detail in Table 2. When targeting an unmet medical need, a small CI with proper oversight, such as an EFS, and appropriate risk minimisation measures would be an opportune starting point when initiating the clinical experiences with a novel device. Similarly, a device can be defined as breakthrough when the potential of the device is to provide or diagnose a safer or more effective outcome for a life-threatening, highly debilitating, or high-prevalent human disease/condition than existing technologies. In this scenario, an EFS would be an opportunity to gather early information about the safety and/or performance profile of the device before proceeding into larger confirmatory clinical studies.

The so called “first-in-class” devices could also come under this category, where treatment options may already exist, but the new technology significantly improves patient outcomes compared to existing alternatives. The figure below shows the areas of medical devices which are focused on in the HTAR where the aim is to achieve faster market access for health technologies across the EU in a centralised and harmonised system. When considering the areas described above, it might be useful to have the union wide perspective from the HTAR in mind. These devices have come into focus under the HTAR, where delivering innovations to patients in Europe is in focus further described in Table 1.

Table 1 Medical devices that are the focus of HTAR as described in Article 7(4).

HTAR	Devices
Article 7(4)	(a) unmet medical needs; (b) first in class; (c) potential impact on patients, public health or healthcare systems; (d) incorporation of software using artificial intelligence, machine learning technologies or algorithms; (e) significant cross-border dimension; (f) major Union-wide added value. (a) unmet medical needs;

3.2.2 Anatomical understanding

One primary reason for a device design to not be considered finalised, is when the knowledge of the anatomy/physiology is limited, specifically the interaction between the device and the human body. In these cases, a small CI may be conducted to confirm findings from prior bench testing, learned from prior in vivo (animal) studies, in silico trials, or derived from literature. Animal models may not adequately represent human anatomy or disease states thereby limiting the interpretation of device safety and performance in those studies. Further, bench test and in vitro modelling or in silico trials may have been conducted using defined anatomical and physiologic parameters, though these tests have inherent limitations. Therefore, EFS are needed as population for which the target device is intended may vary from the general population and have specific nuances that need to be understood or defined beforehand. Obtaining a better understanding of the anatomy within a specific patient population through a small, controlled CI is expected to reduce future procedural risks by developing an enhanced characterization of anatomical features which could interact with the successful use of the investigational device.

3.2.3 New/expanded intended uses

MDs, including DHTs, would benefit from an EFS when the device has been authorised for use within one indication, but a population outside of the previously defined population may benefit from the use of the device. In such circumstances, an EFS study would allow the sponsor and user to assess if the benefits observed for the initial intended use are observed in the alternative intended use and outweigh the risks of treatment in the new intended use. An example of this scenario could be where a device (e.g., glucose monitor) is approved for use in a specific disease phenotype (Type I diabetes) but could provide a benefit in an alternate disease phenotype (Type II diabetes). Another example of this type of expansion could be when a device has been authorised for use within one indication/anatomy and is investigated into a new anatomy, for example a stent used in the coronary vasculature having the indication extended to a below-the-knee application.

A subset of this type of expansion of indication could be when patient anatomy exceeded those defined in the instructions for use by either suggesting smaller devices or larger devices. Often, as the device size changes, mechanical forces on the device will also be impacted, and, in such scenarios, applicable engineering assessments shall be conducted initially to support expansion of the device use into the CI setting. Examples of this type of development activity often occur in the cardiovascular space when devices are designed for an adult population,

but the sponsor identifies patient populations or genders through their clinical experience that have e.g., vascular anatomies larger or smaller than the original device configuration.

A slight extension of conducting an EFS on a new size or configuration of device is when an additional design feature has been incorporated into the existing device and the sponsor justifies that further clinical experience is needed to ensure the benefit-risk balance has been maintained or improved with the addition of the design enhancement. Examples of this could include the addition of coatings to mitigate known risks, modifications to the device to enhance usability, or incorporation of digital technology in, or adjacent, to an existing device.

3.2.4 Focus groups with the PAG and recommendations

The PAG focus groups evaluated the aforementioned eligibility criteria for EFS from a patient-centric perspective. Within the discussion section below, the main findings are presented, structured around patient needs, safety, and inclusivity, as reported by the PAG in relation to technologies suitable for EFS studies within the EU. The suggested criteria in detail above have been developed to provide guidance on the scope of technology most suitable for inclusion in an EFS within the EU, but other scenarios may be appropriate when justified by the sponsor, then reviewed and approved by the NCA and IEC. Ultimately, the EFS study should be established with a patient population no larger than 15 subjects, conform to all principles of CI conduct as noted in relevant standards such as ISO 14155:2020 and have a high level of oversight (e.g., Data and Safety Monitoring Board (DSMB), Clinical Events Committee (CEC), Stopping Rules) to ensure that following the treatment of each subject, the potential benefits continue to outweigh the potential risks.

Discussions with the PAG showed that benefit-risk assessments of the technology used in an EFS are interpreted in a highly personal way and can vary between patients. Since risk appetites and perceptions of benefits may vastly differ from patient to patient, it is important that patients are well informed about the technology tested in the EFS as well as what is known about its safety and performance. This is particularly important considering that EFS are relatively high-risk in nature as first-in-human studies of devices for which less evidence may be available compared to the data needed in a larger CI. From the focus groups, information presented to patients to help them make an informed decision about participating in an EFS should include:

- Comprehensive information about the device, its intended use, indications for use, mechanism of action and functioning, and how it differs from available treatments if there are any, including clear identification of the use of AI and digital health tools in

EFS protocols, ensuring that patients understand how these technologies work and how their data will be used.

- Evidence and experience from relevant comparable devices, such as previous iterations of the same device.
- Information on number of participants previously or currently treated with the device. While this number will be low for EFS, understanding this information may help the patients' decision-making and building trust.
- Expected short-, medium- and long-term outcomes and impacts on the individual participant and at large on the patient population.
- Risks and benefits of the device and participation in the EFS. Participants must be aware of what an EFS is and transparency about all possible risks and benefits is important, including the fact that the device design is potentially still being developed and not yet finalised in an EFS.
- Research objectives/questions, design and methodology of the EFS, including information on the use of control groups. Some patients have limited or no alternative treatment options and seek CIs to specifically get access to treatment, possibly as a last resort; therefore, it is important that patients are clearly informed about the objectives, design and methodology when considering and consenting to participation in an EFS.

3.3 Summary and discussion

Three general device scenarios were identified as recommendations as most applicable for the conduct of EFS under the EU-EFS program. The PAG has contributed to the work and given a valuable perspective on the type of devices that may undergo EFS. These scenarios compliment type of devices that receive an opinion from the Expert Panels (MDR Article 54) and consequently the type of devices which fall in the scope of a Joint Clinical Assessment (JCA) under HTAR (Article 17.4). The recommendations are the product of the work conducted:

- Unmet Need/Breakthrough Device – utilized to collect early clinical data when no predicate exists.
- Anatomical understanding – utilization of the EFS to better understand physiology and anatomical limitations of the device under development.

- New/Expanded Intended Uses – the application of an existing/approved device in a new patient population or application.

3.4 Conclusions

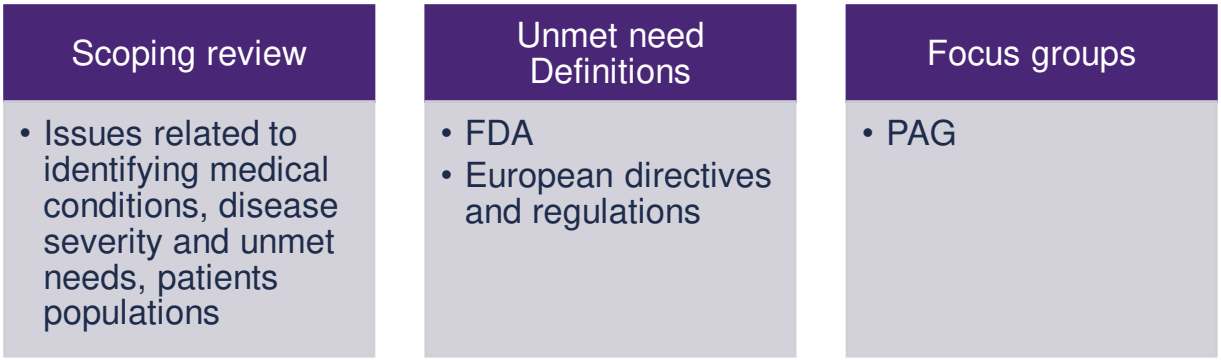
It is proposed that class IIb and class III devices, including DHTs, for which CI data is needed to support a future conformity assessment would be the most suitable for EFS studies within the EU. It is the responsibility of the HTD to justify the need for an EFS within the clinical evaluation plan. The developer can further support the need for an EFS on a developing technology based on the need to better understand physiology and anatomical limitations of the device under development. This is also the case where an existing/approved device is applied an existing/approved device in a new patient population or application, and/or the initial CI activities related to a breakthrough device or a device serving an unmet need.

4. Eligibility criteria for medical conditions, disease severity and populations included in EFS

4.1 Introduction

. When drafting a protocol for an EFS, assessing the medical conditions and disease severity of target population is a key step, with important implications for patient eligibility and selection for an EFS. Table 3 below shows the method used in this section to define the medical conditions, disease severity, patient populations and unmet clinical needs to be targeted in EFS pilot uses cases.

Figure 3 The methodological approach taken.



4.2 Results

4.2.1 Scoping literature review relevant for identifying medical conditions, disease severity and unmet needs in EFS

Medical conditions and disease severity

The literature review brought up some considerations for assessing the disease severity of target population. An argument put forward in the literature is to consider the importance of enrolling patients whose health is not severely compromised for safety reasons. This to avoid posing additional risks and allow data collection throughout the study. However, patients with serious conditions who lack other treatment options, where the devices tested can potentially alleviate or lead to an improved health condition and thereby benefit from the device, are a patient population which can be more relevant for the EFS studies [6, 7]. To manage risks for

patient harm and injury, once the population has been selected, Holmes et al. (2016) suggest focusing on medical liabilities through proper contractual agreements [7, 8]. Another factor when it comes to eligibility of medical conditions and severity of diseases in target patients refers to their relevancy. Before enrolling patients, sponsors need to ensure that the population that will eventually be recruited at chosen clinical sites can help in answering the CIs research question(s), and that this population is also in line with objectives for a larger study at a later stage, such as a traditional feasibility or pivotal study [9].

Unmet need

The assessment of unmet needs was also a common topic discussed in the literature. Within the discussion on unmet needs, quite recent papers focus on the lack of a common definition and provide an overview of existing definitions [10, 11]. For instance, a scoping and grey literature review performed by Vreman et al. (2019) identified 16 definitions which, although they consider common characteristics (including alternative treatments, burden of disease and population size), differ from one stakeholder to another [11]. Along the same line, Jommi et al. (2023) conducted a comparative analysis of the definitions of unmet needs across several countries (Belgium, France, Italy and the UK) and found that most of the available literature advocates a broader definition of need, which should incorporate additional factors, including socio-economic burden of disease, the broader effects of existing treatments and their acceptability [10]. The current definitions of unmet need from European Commission (EC) Directive on the Community code, Medical Device Unit at DG SANTE and the FDA are shown below in Table 2.

Table 2 Current definitions of unmet need.

Organisation or framework	**Definition**
According to Article 83 of the proposed EC Directive on the Community code relating to medicinal products for human use	"A medicinal product shall be considered as addressing an unmet medical need if at least one of its therapeutic indications relates to a life-threatening or severely debilitating disease and the following conditions are met: • There is no authorized medicinal product in the EU for such a disease, or existing treatments leave significant morbidity or mortality unaddressed. • The use of the medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population. Designated orphan medicinal products (…) shall be considered as addressing an unmet medical need."
The Medical Device Unit at DG SANTE proposal for Unmet need for medical devices, JSC Selection	"'Unmet medical needs' as regards MD and IVD should be understood as a condition for which there exists no satisfactory method of diagnosis, prevention, treatment, monitoring or compensation in the European Union or, even if such a method exists, in relation to which the device concerned will be of major therapeutic advantage to those affected."
US FDA Patient-focused-drug-development-glossary	"An unmet medical need is a condition or symptom whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (e.g., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs

Despite the aforementioned definition, and even though many authors refer to unmet clinical needs, a single definition has yet to be agreed upon.

The EC has invited a more inclusive and less restrictive definition of unmet. The EPF (EPF, Patient-centred-vision-for-unmet-medical-needs) has proposed the following: Define "unmet medical needs" starts with listening to patients and understanding the profound impact of their conditions and treatments on their lives. Collaboratively shaping legislation and definitions with patients at the heart of the process fosters true health innovation, ensuring that medicinal products are developed and evaluated in ways that genuinely enhance patients' lives.

Unmet needs versus disease severity

Regarding unmet needs and disease severity, some authors and guidance argue that device development should be guided by the current unmet needs to lessen any significant gap in healthcare [5, 9, 12, 13]. From a different perspective, Eichler et al. (2015), argue that a medical need should not lead to any prioritizations, but rather only a benefit-risk analysis should determine whether to conduct a study [14]. Callea et al. (2022), published a study where they consulted a panel of experts and found two necessary conditions for EFS; the inability of pre-clinical or nonclinical testing and an expected favourable benefit-risk ratio for the population included [6]. Their focus was on devices aimed at fulfilling unmet needs or treating severe medical conditions where an EFS could be the next stage in the development.

Patient safety

The identified literature highlighted other factors that should be considered with regard to patient eligibility in an EFS. A factor to consider when establishing criteria for the patient population to be selected refers to the number of patients for an EFS, which FDA guidance and various authors recommend should not exceed 15 patients, ideally 5 to 10 [5, 12, 13, 15, 16]. In addition to restricting the number of participants in EFS, another measure to mitigate risk is staged enrolment of 1-2 subjects with evaluation before enrolling further patients [16]. In the EU, MDCG 2024-3 guidance provides some measures to evaluate and reduce risk, particularly in relation to early clinical studies of high-risk devices, including limiting patient numbers, testing and evaluation on the first patient before continuing to the next [15].

Risks for patients

A benefit-risk analysis for the patient population should be performed in the development of an EFS[17]. According to the literature, the primary goal for the adoption of new technologies, and thus of an EFS, should be a positive ratio between risks and benefits for the patient, thus

leading to better outcomes, such as morbidity reduction, health-related quality of life, survival rates [17, 18]. In line with these areas, Campbell et al. (2018) categorize patient benefits into five main areas which include [19]:

- Safety: patients suffer fewer complications, adverse events, etc.;
- Clinical benefits: patients receive more efficacious treatment that lasts longer;
- Experiential benefits: patients receive treatments that keep them in the clinics for a shorter period and require fewer follow-up visits;
- Psychological benefits: patients receive treatment for which they experience immediate results;
- Quicker recovery: patients receive treatment that enables them to return to their daily activities more quickly.

Although higher uncertainty may remain regarding the benefit-risk- ratio of a device before the conduct of an EFS, in general, target population may benefit from the study from its beginning, as it provides earlier access to a new technology, especially when there are limited or no alternative options [9].

Issues related to informed consent and patients related outcomes.

Finally, a criterion for selection may refer to the patients' ability to provide informed consent. It is key that patients understand the nature of the study, e.g., potential increased risks inherent to an EFS, as these are the early-stage clinical trials. Provisions for patients who are unable to directly provide consent must also be considered. Additionally, the informed consent form (ICF) must contain clear information about the risks associated with the procedure and device that can help treating their conditions. The patients must be made aware of the inherent risk associated with the nature of the study due to the limited available data and clinical experience with the device. *"For example, the form should note that even if there is limited or no expected personal benefit to the study subject, future patients with the disease or condition may benefit from the information obtained during the early feasibility study" [5].* To mitigate the risks associated with the study and enhance patient protection during an EFS, Herrmann et al. (2022) suggests including safety endpoints [16]. They also suggest making use of patient reported outcomes (PROMs) to better study the target population, for instance, by using symptomatic scales that can be considered as study endpoints [16].

4.2.2 PAG focus groups

The focus groups with the PAG aimed to assess and refine the criteria designed to help sponsors identify key factors for selecting target patients while ensuring safety, maximizing

benefits, and aligning with clinical goals. The focus group marked a crucial step in enhancing patient-centric approaches in the design of EFS. Below is a summary of key insights shared by patients, highlighting considerations for patient selection in EFS and recommendations for sponsors to streamline and improve the EFS process.

- Patient understanding: Feedback emphasized the necessity of simplifying the information provided to patients to help them make informed decisions. Among the suggestions for increasing patient understanding, the group suggested simplifying ICFs while keeping them comprehensive and employing patient-friendly language, diagrams, and visuals. ICF should also be viewed as a process rather than a one-off point of engagement, as patients should be kept informed about any relevant updates or changes to allow them to re-affirm their consent.
- Inclusiveness in patient selection: Although the limited number of patients enrolled in EFS, patients considered the importance of having a diverse group of participants enrolled to enhance the study validity.
- Changes in patient's lifestyle and legal considerations: Sponsors should think ahead about the impact of the study on patients' lifestyle (e.g. ability to walk, perform daily task independently) associated with using investigational devices, which could help define criteria for selection.
- Patient preferences: Including patient preferences in the informed consent process may ensure better alignment between the research goals and the patient's expectations.
- Transparency: According to participants, keeping patients informed about trial results and updates is key, especially if they are modified or discontinued. This is also part of a meaningful and continuous informed consent process for patients that allows patients to be aware and actively consent to changes and updates.

This collective input has further guided the refinement of the criteria for identifying patients for EFS, ensuring that the content reflects a balanced approach to patient safety and inclusivity.

4.2.3 Suggested criteria for identifying patients for EFS

Based on the findings collected and the information gathered through internal discussions and the focus groups with the PAG, a list of criteria with key questions for identifying patients for EFS was developed as a practical tool for sponsors when identifying patients for EFS and summarised in Table 3.

Table 3 Checklist for sponsors for defining patient selection criteria.

Characterisation of the context in the design and planning stages of an EFS	**What is the aim of the study, prior testing, device design stage?**	
	Is the patient population selected adequate for a larger study (e.g. traditional feasibility study/pivotal study)?	
	Does the population align with the intended indication of the device?	
Benefit-Risk-ratio [6] and EC MDR Expert Panel guidance for CECP	**Patient risks**	What are the risks that patients are likely to face? Consider the following areas to assess the risks: • Procedure-related risk (e.g. adverse events) • Device-related risks (e.g. adverse events) • Psychological / emotional risks (e.g. due to stress, side-effects, no positive effects) • Adverse biological responses • Unforeseen risks (e.g. long-term complications) • Post-procedure living restrictions For the risks listed, express the likelihood of the risk and the duration, and assess the subject tolerance for risks. Consider the impact that digital health elements and artificial intelligence may have on patient outcome, where relevant.
	Patient benefits	What are the benefits this device would bring to the patient population? Consider the following areas to assess the benefits: • Safety • Clinical benefits • Quicker recovery • Psychological benefit • Experiential benefit For every benefit, you may also express the probability of the benefit and the duration of the positive effect. You may also want to consider the impact that digital health elements and artificial intelligence may have on patient outcome, where relevant. Does the choice of study endpoints reflect the identified benefits?
	After analysing the risks and benefits, do the benefits outweigh the risks?	

Selection of study participants	• **Would this device address a significant gap in healthcare?** • **Is there an alternative treatment option?** • **If alternative treatments are available, would this device offer improvements with respect to current options?** • **What are the options in place for study participants to be treated?**
Disease severity level	What is the acceptable level of disease severity for patients to participate in the study? Consider the following questions to assess the severity: • Does the patient's disease stage align with the intended device indication? • Is the patient stable enough to avoid posing additional risks? • Is the patient's disease stage advanced enough to justify the risks associated with the intervention? • Would patient comorbidities negatively impact the collection of data from the study (e.g. if a patient has to withdraw from the study for health reasons)?
Patient understanding	• Have patient friendly language, visuals and / or diagrams been used to communicate complex studies details effectively to patients? Is consent fully informed, based on comprehensive, clear, and unbiased information about the device and anticipated benefit/risk? • How are health literacy considerations and informed consent processes integrated into patient selection criteria to ensure that participants fully understand the implications of participation?
Transparency and patient feedback	• Have patients been kept informed about the study progress, any modifications or discontinuations? • Has patient feedback been collected throughout the trial to ensure ethical and inclusive study management?

4.3 Summary and discussion

Results from the scoping literature review showed no limits to medical conditions and patient severity levels suitable for an EFS. This was also confirmed during discussions among partners of the HEU-EFS project and the PAG. The development of criteria for identifying patient populations, their enrolment in EFS and unmet needs is crucial for the success of an EU-EFS program. Well-defined criteria for patient population are essential not only for answering the study's research questions, but also for ensuring the findings are applicable to a larger population in later stages of development. Key recommendations for patient selection include:

- Limit the study population to a small number of patients, ideally not more than 15. Staged or iterative enrolment (e.g., 1-2 patients, with testing and evaluation before continuing to the next) is encouraged but may be adjusted where there is more than one site involved in the study.
- Align targeted patient population with study objectives and goals. A best practice for this is to engage patients/patient representatives as active co-creators of study objectives and goals to better define unmet needs and reflect real world situations.
- Evaluate the benefits for the eligible patient population through a benefit-risk analysis, increasing willingness to accept higher risks due to the nature of the study.
- Ensure that the study does not compromise patient safety.
- Make information on the study accessible to patients using lay language, to ensure they fully understand the uncertainties and risks of the devices and studies and the benefit-risk ratio.
- While no limits on medical conditions suitable for EFS are recommended, unmet needs should be considered when selecting devices for development, particularly for severe conditions lacking effective treatments.
- Transparency: Keeping patients involved in the EFS process and informed about trial results and updates is key, especially if they are modified or discontinued. This is also part of a meaningful and continuous informed consent process for patients that allows patients to be aware and actively consent to changes and updates.

4.4 Conclusion

The focus groups were instrumental in refining criteria and ensuring patient perspectives were properly integrated. By summarizing essential aspects of patient selection, this chapter supports the development of safe, patient-centred medical devices.

5. Required level of pre-clinical evidence

5.1 Introduction

The aim of this section is to describe the level of evidence required before an EFS can be undertaken and to discuss the types of pre-clinical tests necessary to provide this level of evidence. Our focus has been on pre-clinical or non-clinical testing which are well described in the MDR, specified in the General Safety and Performance Requirements (GSPR), MDCG guidance and detailed international standards. In addition, as the FDA EFS Program is well established this has also been evaluated. EFS Program was established as a pathway to gain more evidence where for example pre-clinical testing of a novel device is not able to further inform device design, functionality and/or safety. Early clinical testing is needed to identify "…*appropriate modifications to the device or the procedure to use the device, to optimize operator technique, to refine the intended use population, and to refine non-clinical testing and development of subsequent clinical study protocols*," as described by Weiss and Farb [20]. We have also conducted interviews with HTDs in the Consortium, who have the hands-on experience with the FDA EFS Program. Through the interviews we have looked into the type of testing required in the USA compared with what a NCA will require for a CI in the EU or European Economic Area (EEA) and if this then differs for an EFS. Finally, we have had two focus groups with the PAG to ensure a patient-centric approach to the level of evidence needed.

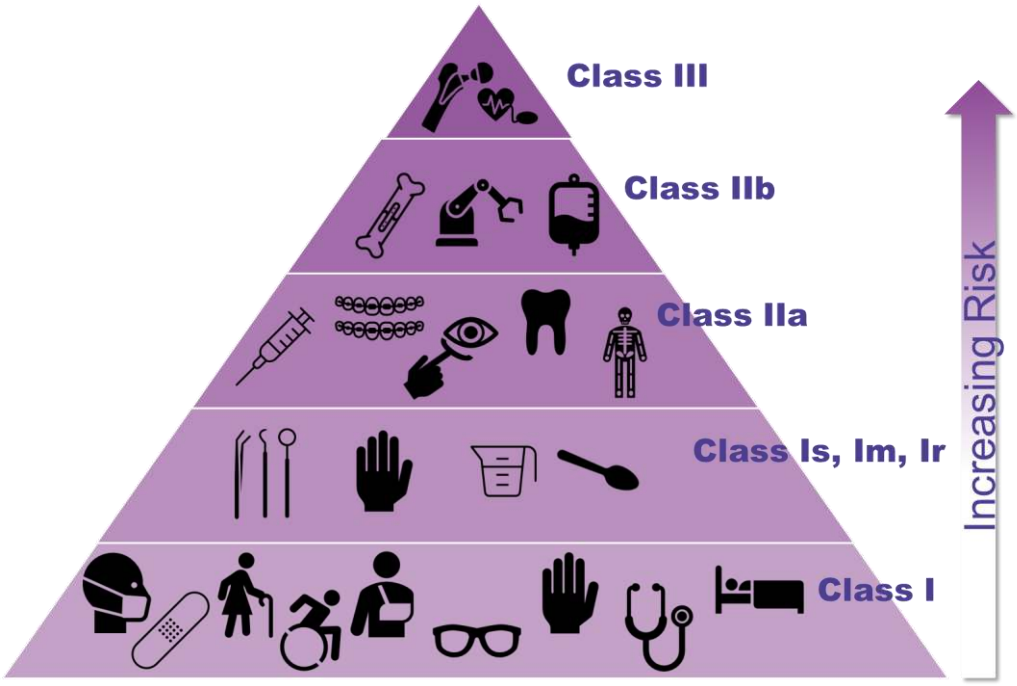
5.2 Results

5.2.1 Results of Regulatory Review

MDR Article 61(4) states "*In the case of implantable devices and class III* devices, clinical investigations *shall be performed* […]" and stipulates certain exemptions which are further supplemented in Article 61a(6). Additionally, Section 3.1 of this report describes this in more detail. Our focus for the EU-EFS program is on MDs which will require a CI as part of their conformity assessment. As low-risk devices (class Im, Is, Ir, IIa and non-implantable IIb), as shown in Figure 4, can leverage other data rather than perform CI in order to fulfil the requirements in the conformity assessment process. We, therefore, propose that only devices (including DHTs) for which CIs are needed to support a future conformity assessment would

be suitable for the pilot EFS studies (WP7), specifically high-risk implantable devices (class IIb and class III) as shown in Figure 4.

Figure 4 A simplified schematic of the devices and risk classes under MDR.



Although the MDR provides a robust regulatory framework for MDs in the EU, it does not describe EFS specifically. To supplement the regulation, the MDCG has developed guidance documents providing more detail on how to interpret the regulation. For this deliverable we have focussed on MDCG 2021-08 'Clinical investigation application/notification documents which detail the application and notification documents for CIs for the MDR CI pathways.

5.2.2 General Safety and Performance Requirements (GSPR) of the MDR

Annex I of the MDR sets out the GSPR, these are the requirements that the HTDs have to comply with in order to prove the safety and performance of their device. The sponsor should describe which standards or Common Specification (CS) have been used in order to claim compliance, and where the evidence can be found, unless the gathering of this evidence is the goal of the CI. Where there are deviations from the checklist a justification must be provided, which is up to the NCA evaluating the CI application to accept. In the MDR Annex XV, Chapter 2 on Documentation regarding the Application for CI, 2.7 describes that a list detailing the fulfilment of GSPR, standards and CS in part or fully shall be provided. MDCG 2021-8 Annex

6 contains the checklist to show compliance with GSPR that primarily covers pre-clinical testing requirements, where pre-clinical test such as those shown in the Table 4 below need to be fulfilled.

Table 4 Description of types of pre-clinical testing that may be required for a device before an EFS can be initiated.

	Pre-clinical testing	Standards
1	Mechanical or Bench testing	Device specific standards
2	Laboratory (in vitro, ex vivo)	ISO 10993 and device specific standards
3	Simulated Use (*in silico*, Finite Element Analysis (FEA))	Device specific standards
4	Animal testing	ISO 10993 and device specific standards
BIOCOMPATIBILITY - testing of all materials in direct or indirect contact with the patient or user		
5	Physical	ISO 10993 and device specific standards
6	Chemical	ISO 10993 and device specific standards
7	Microbiological	ISO 10993 and device specific standards
In addition to		
8	Electrical Safety	IEC 60601-1-11:2015, device specific standards
9	Electromagnetic Compatibility	ISO 14117:2019, device specific standards,
10	Software Verification, Validation and Testing	IEC 62304:2006, device specific standards,
11	Sterilisation and sterility testing	ISO 11737 series and sterilization type specific standards, ISO 11139:2018 device specific standards,
12	Stability and Packaging, Including Shelf-Life.	ISO 11607 series, ISO/TS 16775:2021, device specific standards,
13	Usability	IEC 62366-1:2015, device specific standards,
Testing standards specific to the device		

There are a wide range of ISO and ASTM (American Society for Testing and Materials) standards available, and some are device specific while others are general. For example, the ISO standards for sterilisation methods and packaging are universal. The ISO 10993 series of standards describe specific pre-clinical tests that are required to prove the safety of the device. ISO 10993-1:2018 has a table which illustrates the tests that are needed dependent on the type of contact (skin, mucous membrane, wound, through the blood, or implanted and where) and the duration of this contact, allowing the type testing to be determined for each individual device. The ISO 10993 series cover for example chemical characterisation, cytotoxicity, sensitisation, irritation, systemic toxicity, hemocompatibility, genotoxicity testing, but are not limited to these.

5.2.3 ISO 14971 – Risk management for medical devices and its use in CI

The MDR does not refer to ISO 14971 specifically, however, it is expected that to claim compliance to the GSPR risk management is performed in accordance with the 2019 version of ISO 14971 – 'Medical devices — Application of risk management to medical devices' which is harmonised to the MDR. ISO 14971 provides the foundation for risk management for HTDs from the design phase through production and use, and finally to disposal, described in Table 5. The risk management system can then be used to achieve compliance to the GSPR through risk mitigation, whereby hazards associated with a device can be evaluated as far as possible through pre-clinical testing. To start a CI, the sponsor must show compliance or justification for non-compliance to the relevant GSPRs.

Table 5 Annex I GSPR 3 – Risk management system for medical devices.

Annex I, General Requirements 3
"Developers shall establish, implement, document and maintain a risk management system. Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic updating. In carrying out risk management developers shall: (a) establish and document a risk management plan for each device; (b) identify and analyse the known and foreseeable hazards associated with each device; (c) estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse; (d) eliminate or control the risks referred to in point (c) in accordance with the requirements of Section 4; (e) evaluate the impact of information from the production phase and, in particular, from the post-market surveillance system, on hazards and the frequency of occurrence thereof, on

estimates of their associated risks, as well as on the overall risk, benefit-risk ratio and risk acceptability; and
(f) based on the evaluation of the impact of the information referred to in point (e), if necessary**,** amend control measures in line with the requirements of Section 4."

5.2.4 Pre-clinical testing needed in the FDA EFS Program

The FDA's EFS program does not outline explicit eligibility criteria but provides detailed guidance on its scope and the circumstances under which an EFS might be conducted.

More details are described in Section 3.1and in Deliverable 1.1 [1]. FDA EFS Program focuses primarily on innovative, high-risk devices intended for the Pre-market Access (PMA) pathway and requiring CI.

For novel devices the FDA also has the Breakthrough Devices Program, which is a voluntary program for devices that promise to provide "*more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions*". Devices in the FDA's Breakthrough Device Program have accelerated approval for transformative technologies, and may also be suitable for the EFS pathway.

The CIs undertaken as part of the EFS program allow for clinical evaluation of investigational devices that have not been cleared for marketing and normally aim to collect both safety and performance data. An investigational device under the FDA is not the same as an investigational device in the MDR, see Table 6 and Appendix I Nomenclature. For the European context it is important to be aware of this and that the MDR allows for the NCAs to determine if a device in the design stage can be implanted.

Table 6 A comparison of the term 'Investigational Device'.

MDR Investigational Device (Article 2 (46)) and Article 62(4l)	FDA Investigational device IDE program (21 CFR 812.)[5]
'Investigational device' means a device that is assessed in a clinical investigation; […] conform(s) to GSPR apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subjects. This includes, where appropriate, technical and biological safety testing and pre-clinical evaluation, as well as provisions in the field of occupational safety and accident prevention, taking into consideration the state of the art;	Investigational device which has not reached its final design can potentially contain changeable parameters or design changes can be investigated. This use of a device early in development is allowed though the EFS program (21 CFR 812.) where the device is registered as an investigational device exemption

The FDA has teams responsible for technology areas (e.g. orthopaedics, cardiovascular) who provide feedback on the device during the review process. The use of specialised teams means that they are more familiar with the type of pre-clinical testing for their field of devices and request specific testing to be performed before an EFS can start. The FDA thereby allow the type and timing of pre-clinical testing to be more open when the device design is not finalised [13]. The FDA review period is generally highly interactive and usually characterized by frequent exchanges with questions and requests for clarification from FDA for the sponsor. Once IDE approval has been obtained, the EFS study can begin, contingent upon, as for all CIs, the IRB approval from the study site has also been obtained [5, 9]

5.2.5 PAG focus group concerning level of evidence required to start an EFS

PAG members highlighted communication directed at the correct level, safety issues and a transfer of knowledge from earlier devices and CI.

Figure 5 Overview of the main information provided by the PAG.

The importance of evidence and lessons learned from comparable or earlier versions of devices cannot be overstated. PAG members expressed concerns over first-in-human (FIH) EFS, which may involve various unknown risks. They felt that leveraging data on the performance, functionality, historical context, recalls, and adverse safety incidents of other devices would reduce uncertainties from the patient's perspective. Additionally, they stressed the need for a clear presentation of associated risks and benefits in accessible language to help build patient confidence in an EFS. This as well as other information mentioned under eligibility criteria for technology and for clinical sites should be integrated into informed consent forms using lay language to ensure a meaningful consent process for patients.

5.2.6 Level of Evidence Required to start an EFS: HTDs perspective

The questionnaire was developed based on the results from the literature review, the regulatory review, and information gathered around pre-clinical testing in the FDA EFS program. These are large HTDs, with a range of employees from 16,000-130,000 employees. The HTDs produce a wide range of MDs from the lower risk class to high-risk devices. However, the groups involved in the Consortium are primarily focused on cardiovascular and orthopaedic high-risk devices. The questionnaire was performed to understand the HTDs perspective of the development of a new device. HTDs typically have established internal quality management systems, which strictly govern the progression from laboratory testing to animal testing, and subsequently to FIH testing.

It was confirmed that procedures are in place such as design control and design review with independent validation to govern when device development has matured enough to move into humans. The HTDs described that for novel high-risk devices, animal testing is performed before moving to EFS. In addition to device specific standards which describe for example the

mechanical tests covering parameters such as the number of cycles for fatigue testing, minimum break strength, corrosion testing, or electrical testing requirements.

The benefit-risk analysis as mentioned, is ongoing throughout the device lifecycle, and once there is an overall benefit, as described by ISO 14971, with the approval of for example internal clinician(s) the device can move towards EFS.

EFS are often instigated where additional non-clinical assessments or appropriate non-clinical tests are unavailable, and therefore translating this to the EU, the level of compliance to GSPR may vary.

Material testing with well established (WE) materials is most often fully covered before moving into EFS. Some HTDs also reported that in the development phase their regulatory department will encourage them to use WE materials in innovative devices, to avoid additional testing needed for less WE materials. However, innovative materials may elicit the need for an EFS to determine the functionality where animal testing is not adequate.

When discussing the FDA EFS Program several HTDs described that mechanical testing with a reduced number of cycles for fatigue testing could be justified based on that it would be completed during EFS or that the number of samples tested can be reduced based on previous data with similar devices. They also described that FEA, *in silico* testing is used to support and supplement mechanical data, where the modelling is as exhaustive as possible in order to predict the clinical situation and be leveraged to justify the EFS. Regarding biocompatibility, the FDA expects certain tests first (e.g., hemocompatibility, genotoxicity, mutagenicity), while further required biocompatibility testing can be performed during the EFS. This is especially important if there are major design changes, as that would require the testing to be repeated with for example the new materials.

Animal testing often includes biocompatibility tests, the biological responses to the device. Functionality testing *in vivo* may not always be possible due to differences in anatomy and physiology. Additionally, animal testing is most often performed to prove biological safety rather than the performance. Healthy animals are used in the testing, hence relevant anatomical regions can be targeted, though the testing does not replicate disease conditions.

International standards for high-risk devices are followed where relevant and often full compliance to specific standards is achieved before the start of EFS. However, in some cases, partial compliance is the goal, and a justification is provided in the CI application based on the benefit-risk analysis, in addition to the aim of the EFS being to test device functionality. For

novel devices the ISO standards may only be partially relevant, so this can also be a reason for partial compliance.

Identification of device specific standards has been recognised as a challenge for companies that are less experienced, such as SMEs. The companies interviewed are leaders in their respective fields for their type of MDs and have often supported the development of standards and have a good understanding of the relevant standards. This underscores the importance of providing clearer guidance for an EU-EFS framework. If the aim is to foster innovation in Europe, particularly among SMEs, enhanced support on transitioning from 'bench to bedside' is essential.

An EFS is performed where the device is novel, a new technology involved, or for a new intended use. However, if the technology is well established, then it can move straight to a traditional feasibility study or pivotal trial. The interviewed developers explained that the EFS are also always conducted on patients suffering from the relevant health condition. Thereby the data collected during the EFS is the start of the relevant clinical safety and performance needed for the conformity assessment. Where new technology addressing an unmet need for patients is concerned, gaining experience of the clinical impact from the start is very important.

The HTDs highlighted that MDR has brought major changes, GSPR is more detailed. For example, polymer formulations need to be documented to be compliant with REACH, with supplier certificates in the CI application. The FDA often does not require this level of detail for the EFS. The HTDs also emphasised that to justify partial compliance to GSPR in the EU is more difficult, the NCAs expect full compliance to the GSPR checklist, except for those that are to be tested in the EFS.

For the interviewed HTDs the R&D was most often based in the USA, but some have R&D in Europe. This was therefore seen as an additional hurdle in starting an EFS in the EU. The HTDs also mentioned that EFS are often conducted first in countries outside the EU and EAA, the countries mentioned were the USA, New Zealand, Australia, but also countries such as Taiwan, Singapore, Uruguay, Brazil and Kazakhstan.

The interviewed HTDs had experience from the FDA EFS program since it began and have developed further experience for this type of CIs over time. In the device development, they arrange a meeting with the FDA once they are close to starting an EFS. They have an understanding of what type of pre-clinical testing will be required, and the type of justification for partial compliance that can be accepted. Within their speciality the team at the FDA is dedicated, and therefore specialised for example in cardiovascular, even so detailed as a

'structural heart' team. The HTDs propose pre-clinical testing that will be completed before the first patient is enrolled, where biocompatibility is needed, but for example chemical, genotoxicity, and corrosion tests can be delayed. An appropriate level of safety testing must have been performed for the EFS to be approved. The FDA may require that testing be provided later, for the enrolment of more patients, but they will state what is expected. For pivotal CI all relevant preclinical testing needs to be in place. For EFS some tests can be truncated, and run in parallel, answered through the EFS or duly justified. Table 7 shows some of the key findings from the HTDs experiences with EFS in Europe.

Table 7 Experiences and impressions from EFS in Europe, key findings.

Countries in Europe where EFS has been performed (more experience under MDD)	Interactions with NCA
Germany, UK and Switzerland	Longer assessment time of applications NCA Initial applications were not approved, with rounds of more questions Reluctancy to allow for phased enrolment of patients Less specialized evaluators of applications

5.3 Summary and discussion

Currently under the MDR there is no clear path for pre-market CI of a device that has not reached a final design and so is not ready for clinical performance and safety data to be gathered for the purpose of a future conformity assessment. Pre-clinical testing is an essential part of the development of MDs, however there are some key differences identified in the approach to EFS in the USA and EU. The decentralised regulatory system in the EU means that though the MDR clearly requires certain pre-clinical testing to be performed, the interpretation of what is acceptable can diverge across the NCAs in the EU and EEA. The MDR and the MDCG guidance do not provide a clear opening to partial compliance to GSPR. Further, guidance on pre-clinical testing after the EFS has started is also not described, however, some NCAs may allow this. The FDA's acceptance of the iterative design, where the MDR sees this as a substantial modification to the CI, but can allow for an adaptive clinical investigation protocol. WP2 has identified that NCAs experience with these processes seems to be limited. In the MDR the device that is to be tested should be the final design of the device.

Therefore, it is clear that certain recommendations and criteria are needed to establish an EFS pathway in the EU, where the iterative approach is described.

Recommendations and criteria

- GSPR must be the foundation for pre-clinical testing performed for an EFS.
- EFS should be limited to high-risk devices, where a clinical investigation will be required as part of the conformity assessment. Where CS exist or the device classification indicates that clinical evidence is not needed, an EFS should not be recommended.
- Pre-clinical testing shall be performed as far as possible in accordance with the GSPR:
    - Where justification is provided for limitations, such as where further testing is not possible due to anatomy, physiology etc., or concurrent testing can be performed without causing greater risk to the patients enrolled in the EFS.
    - Allow for leveraging data from similar devices or e.g. reducing number of cycles.
    - Where certain GSPR requirements cannot be applied at the early phase of design and manufacturing processes, a justification that this would not pose undue risk to patients or alternative controls can be implemented in the EFS.
- Allow for the design to be in an iterative phase, the 'FDA's Investigational Device', where the EFS can inform changes to the device, the procedure or to the study protocol.
- Phased enrolment to an EFS allows for patient safety to be assured, and changes to be made where necessary
- Pre-clinical testing is a challenge for start-ups, to promote innovation in Europe an EU-EFS framework must provide more guidance especially to SMEs on how to move from 'bench to bedside'.

5.4 Conclusion

The criteria for pre-clinical testing of MDs through the GSPR are well established under the MDR. However, a clear distinction must be made about which tests are needed and when they must be performed. Shelf-life and stability are examples of testing that may not be necessary

for an EFS to start. It is also important to be aware that though a lot of emphasis is put on animal testing, the MDR, GSPR and ISO 10993 do not require that a device is tested for its functionality in animals. The anatomical and physiological differences, that the animal is not suffering from the health condition leads to limitations in the data that can be gathered through these tests. Where these clear limitations are shown, even though the testing has been performed as far as possible there is a clear need for an EFS. Allowing the FDA's approach in EU-EFS framework would enable a smoother approach for novel devices to reach the European market.

6. Eligibility criteria for clinical sites and clinical expertise

6.1 Introduction

This section describes the requirements of clinical sites for CIs and details the qualifications, obligations and duties needed for the various roles in a future EU-EFS program.

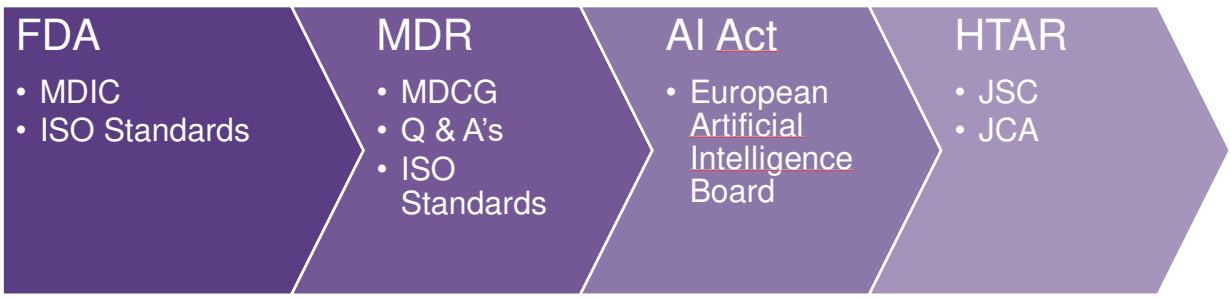
The MDR defines the responsibilities of sponsors, investigators and acting personnel, and makes reference to training requirements for each role needed. We have therefore used the MDR as the primary source and compared the wider European framework set out by MDR with the FDA's EFS program to gain a better understanding of what is needed for a future EU-EFS program. Furthermore, we have investigated the perspective and the needs described by the clinics that conduct CI and HTDs through questionnaires and focus groups with the PAG.

6.2 Results

6.2.1 Review of regulatory frameworks and guidance available for Clinical Investigation

An overview of the terminology for CI and roles in MDR, FDA, HTAR and ISO standards is shown in Table 9 in Appendix III. The findings show that the majority of terminology overlaps across the three main regulatory references, MDR, FDA and HTAR (Figure 6).

Figure 6 An overview of the regulatory framework for CIs.



The FDA EFS program clearly describes the pathways available to gather required pre-market clinical evidence. The clinical site and clinical expertise may need to change and adapt dependent on the different stages in the clinical development shown in Table 8 below.

Table 8 Comparison between the different stages of CI of medical devices, based on the FDA EFS program.

	EFS	Traditional Feasibility	Pivotal
Device design	Device -breakthrough device, -design stage, -new intended use, -finalised design FIH testing	Near final device design	Finalised device design which will be used in conformity assessment
Evidence available	Pre-clinical data: limited, appropriate pre-clinical tests are unavailable.	Additional pre-clinical data available	Pre-clinical testing completed, analysed and used to inform CI
Aims	Obtain initial clinical insights for: -the clinical safety specific to device; -of the procedure; -successfully delivered, implant; -operator technique - usability; -the clinical safety of the device (e.g. SAE) - performance intended purpose (e.g., mechanical function, measurements: -device failures; -patient characteristics (e.g., limitations in anatomy); -therapeutic parameters	Obtain initial clinical safety and effectiveness information for a near final or final device design or capturing data to guide the development of a pivotal study	Obtain safety, performance and sometimes effectiveness data to support marketing application

6.2.1.1 MDR and MDCG on CI

There are three main regulatory pathways for EFS under MDR, Article 62, 70 (7) for low-risk devices and Article 82 which offers an opening for national interpretation. A CI performed to gather clinical evidence for the conformity assessment to gain certification in the EU is described in Art. 62. For the purpose of developing an EU-EFS framework, we have explored the existing pathways and how they can be adapted for the purpose of EFS.

An overview of the MDR guidance and MDCG guidance, is shown in Table 12, and provide a more in depth understanding and details of the requirements in MDR. EFS should follow Article 62 (MDCG 2021 6 Rev.1 Q&A), however when not performed with the goal of a future conformity assessment Article 82 also can be applied. This article (Article 82) opens for member states to lay down national legislation. Though some NCAs have decided not to differentiate Article 82 from the other regulatory pathways for CI under MDR and may require an application for CI that are not performed for a future conformity assessment. Some member states have included EFS under Article 82, as "any investigation in humans", while others have included ITTs (Investigator Initiated Trials).

Regulatory pathway interpretation can therefore vary regarding EFS in the EU/EEA thereby leading to uncertainty as to how sponsors should approach EFS in Europe. For more detailed information on MDCG documents on CI, sites and roles see Table 12.

MDR on obligations of sponsors, investigators and requirement to sites

Our results show that MDR describes the responsibilities of the sponsors and investigators in CIs thoroughly, however not specifically for EFS. Likewise, the role and safety of the subjects are thoroughly described in MDR for CIs in general. In Table 10 the definitions and responsibilities of the roles such as sponsors, subjects, investigators, sites, referencing the specific MDR article is presented. These definitions should be taken into account for a future EU-EFS program.

MDR on the role of the NCA and ethics committees

The member state delegates the authority to a NCA to have the responsibility for and assess CI. The MDR requires that the member states where a CI is to be conducted involve ethical committees to evaluate the sites and clinical expertise (Article 62). The MDR addresses ethical considerations in the Recital 65 and in Article 62 on CI investigations (see Table 11 in Appendix III). A thorough review of the existing member states practices and recommendations on ethical approval of CIs will be undertaken as part of WP6.

ISO 14155 and ISO 14971 on roles on obligations of sponsors, investigators and requirement to sites

The need to follow ISO 14155:2020 in CI is described in the MDR in Recital 65. ISO 14155 and ISO 14971:2019 on risk management, are integral for MD development, as they are both harmonised with the MDR. ISO 14971 forms the foundation for all risk management in the MD lifecycle, constantly evaluating the risk of harm at every stage. For CI the benefit-risk analysis from ISO 14971 is used by the sponsors to ensure patient safety.

ISO 14155 describes the roles of sponsors, principal investigator (PI) and other investigators in more detail for CI than MDR. The roles, duties and obligations for the sponsors and investigator regarding “sites” in clinical investigation is thoroughly described in ISO 14155, although there is no mention of sites in connection to EFS. ISO 14155 describes training in a CI to be the responsibility of the sponsor. This training should be offered to users and investigators.

6.2.1.2 AI Act, Regulation 2024/1689

The use of artificial intelligence in the EU will be regulated by the AI Act. This new regulation is still in the process of being adapted into national legislations; however, it is expected to be fully adopted in the coming years. The aim of the AI-Act is to regulate the use of AI in a way that ensures safety and fundamental rights, while promoting innovation within a harmonised framework. Developers and providers of AI/ML medical devices will need to comply with both the MDR and the AI Act. The regulation focuses on human-centred and ethically responsible AI, in line with the EU Charter of Fundamental Rights [21]. The AI Act assigns AI applications to four risk categories; applications with unacceptable, high, limited and lastly minimal risk applications, but the interaction with the risk-classes of MDR is still under interpretation. This new regulation will interact with how medical devices such as DHTs are introduced to the market and will have to be considered in the future EU-EFS program. Further exploration with a scoping review on the interaction between MDR and the AI- act is to be performed in WP 2.

6.2.1.3 FDA – EFS – clinical sites and guidance in use

FDA is described in detail in Delivery 1.1 [1]. and previously in Sections 3 and 5.

a. Medical Device Innovation Consortium, US (MDIC)

Blueprint for Early Feasibility Study Success: A report of the Early Feasibility Study working group of the Medical Device Innovation Consortium (MDIC)[9]. This Blueprint document from 2016 on EFS in the US identifies barriers to EFS and proposed possible solutions and tools to facilitate EFS. It argued that there was a trend of transferring initial clinical research activities and EFS outside the US in response to a more stringent legal, regulatory, and financial environment in the USA. The situation described by the MDIC in the US in 2016 is similar to the current situation in Europe. Holmes et al showed that the number of CI had reduced over the last five years from 87% to 45% between 2004 and 2009 [7]. Deliverable 1.3 showed that there has been an increase in EFS after the introduction of the FDA EFS Program.

6.2.2 Clinical Investigations Sites and Expertise, Clinic-Questionnaire

The clinical sites who responded to the questionnaire represented various profiles involved in the conduction of a CI, including investigators, project managers, statisticians, hospital IEC members, members of a non-profit academic private CRO, and members of clinical trial units. A summary of the findings for each topic is presented below.

6.2.2.1 Clinical Investigation Sites
6.2.2.2 Infrastructure requirements

Clinical sites conducting EFS and FIH studies should have organizational structures and resources adapted to their operational purpose and the conduct of clinical trials. While some sites have dedicated units for clinical investigations, most rely on existing institutional infrastructure and equipment, prioritizing practical improvements over the construction of dedicated spaces.

a. Eligibility requirements

The initiation of a clinical investigation typically requires regulatory and ethical approvals. Depending on national laws, a clinical site may also need certification from the relevant authorities to be recognized as a centre for clinical investigation. Although clinical and academic centres are well known for conducting clinical investigations due to their research focus, clinical sites seeking to conduct an EFS must demonstrate a proven track record in clinical research. This can be supported by metrics such as the number of completed clinical investigations such as EFS and FIH studies or patient enrolment targets.

b. Other areas raised by the clinics

The clinics raised that when a CRO is used, it can be a critical factor for EFS success, and therefore the selection of an appropriate CRO is important, if the clinics/centres own CRO is not involved. They emphasised that clinical sites must have confidence in the CRO partner chosen by the sponsor. Substantial experience in early-stage clinical investigations and an in-depth understanding of the complexities concerning high-risk clinical investigations such as EFS.

Despite ongoing efforts to enhance clinical investigation capacity, many sites continue to face challenges, including resource constraints (e.g., funding, staffing, and facilities), regulatory gaps, and limited expertise in assessing clinical investigations.

A particularly concerning issue raised during interviews was the perceived lack of limited expertise of IECs in assessing EFS. Many interviewees also perceived the clinical investigation approval processes of NCAs as lengthy and complex. Some respondents expressed concerns

about inefficiencies, noting that regulatory timelines for clinical investigation submissions were not always consistently met, which could contribute to delays in study initiation.
To mitigate these delays, some institutions implement parallel processing approaches, where contract negotiation and approval occur simultaneously with IEC and NCA submissions. This ensures that both processes align upon study approval, expediting patient enrolment.
Addressing these issues requires multidisciplinary collaboration, harmonized practices, and a deep understanding of relevant regulations to improve efficiency and ensure patient safety.
Addressing these limitations through coordinated strategies is essential to advancing early-phase studies more effectively. The findings from the clinic questionnaires are summarised below.

Clinical Investigation Sites

- Should hold regulatory and ethical approvals required in their country to conduct the CI.
- Should ensure data compliance with ICH-GCP standards and ISO 14155:2020.
- Should possess equipment, facilities and procedures to ensure patient safety.
- Should have experience in the therapeutic area of the investigational device.
- May have dedicated units or personnel specifically tasked with coordinating regulatory submissions and contracts.
- Should have proven track record of experience in conducting EFS/ early-stage studies, or generally CI:
    - Access to previous EFS records via recognized databases.
    - Metrics such as the number of completed trials or patient enrolment targets to support track record in conducting clinical research
- When selecting working with a CRO, from the clinical site's perspective, they should ensure that the CRO:
    - Holds up-to-date ICH-GCP certifications and has knowledge of European regulations for medical devices.
    - Has proven experience in pilot studies and a solid understanding of the complexities specific to clinical investigations of medical devices.
- Proceed with parallel processing when applicable, where contract negotiation and approval begin simultaneously with IEC and NCA submissions.

6.2.2.3 Clinical Expertise

Based on the responses gathered, no specific qualification or certification is required for investigators conducting EFS or FIH studies, as with other clinical investigations. However, the following areas were highlighted and reflect the focus areas identified by the clinics.

- Clinical expertise in the therapeutic field of the device.
- Adherence to regulatory standards, including both national and international guidelines such as Good Clinical Practice (ICH-GCP) and ISO 14155:2020.

The personnel

- Should possess clinical expertise in the therapeutic area of the device, demonstrated through documented experience, such as years of practice or a senior physician role in the field.
- Should be qualified under ICH-GCP and meet any additional qualifications required at national level.
- Ensure that the site complies with regulatory standards, such as ISO 14155:2020.
- Should ensure that the investigation site team is qualified through education, training, and experience to take responsibility for the proper conduct of the clinical investigation.
- Should ensure that the site has the required number of eligible subjects needed within the agreed recruitment period.
- Should possess research experience with similar devices or early phase CI, documented through publications, or other adequate means. If not, they should have experience in advanced CI, such as pivotal studies in the therapeutic area, or provide justification of training and capability to conduct CI.

According to interviewees, the investigator's role is paramount to the success of an EFS. Several key factors contribute to this success, with the investigator’s expertise in the field being the most critical, followed by their availability and commitment of the investigator or dedication to the study. From the interviews performed a simplified schematic of the roles of personnel involved in CI is shown in Figure 7 with a description of their responsibilities.

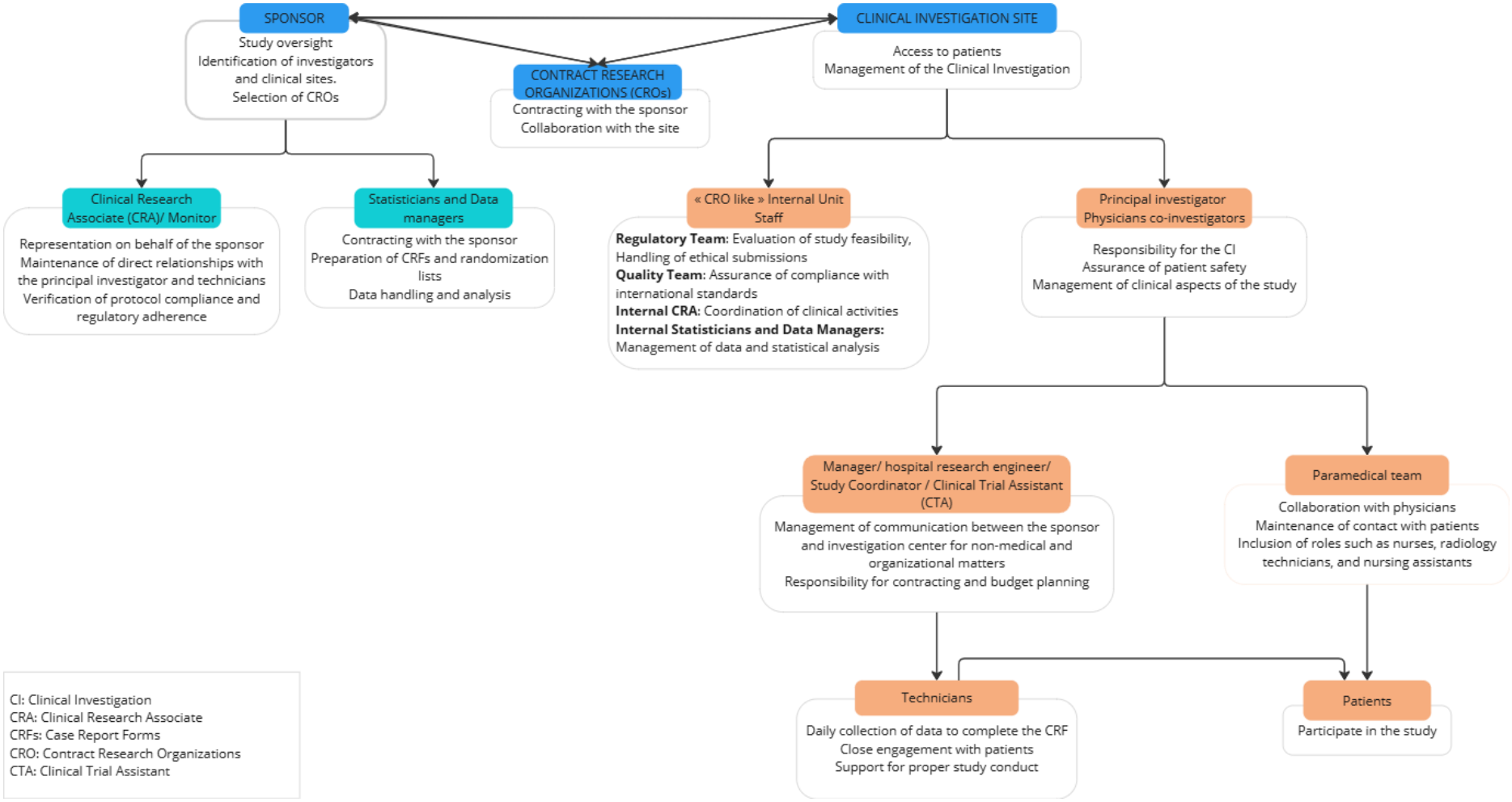
The clinics highlighted that investigators should be skilled clinicians with a solid understanding of the therapeutic field of the device under study, study design, patient safety, and the physio-pathological considerations related to the device being tested. Additionally, they stated that technical expertise is crucial; investigators must be proficient in handling the device, making the learning curve a critical consideration in the initiation of an EFS. Training provided by sponsors is essential to ensure readiness, and a successful EFS.

Further the clinics stated that the learning curves vary depending on the complexity of the device, the procedure, and the investigator's experience. The clinics put forth two areas of focus for training and minimising learning curves as training plays a pivotal role in preparation of investigators for initial interventions:

- Training methods: Simulators, procedural videos, hands-on practice, and pre-clinical work (e.g., animal or cadaver models) are valuable tools for building proficiency and confidence.
- Proctors[1] and clinical specialists: Their guidance is highly beneficial, although selecting proctors with both technical and clinical expertise can be challenging.

[1]A proctor acts only as a supervisor to evaluate the technical and cognitive skills of another physician. A proctor does not directly provide patient care, has no physician-patient relationship with the patient being treated.

Figure 7 A simplified map of personnel and their roles in CI from the clinics' perspective, for EFS some of these roles would not be relevant.

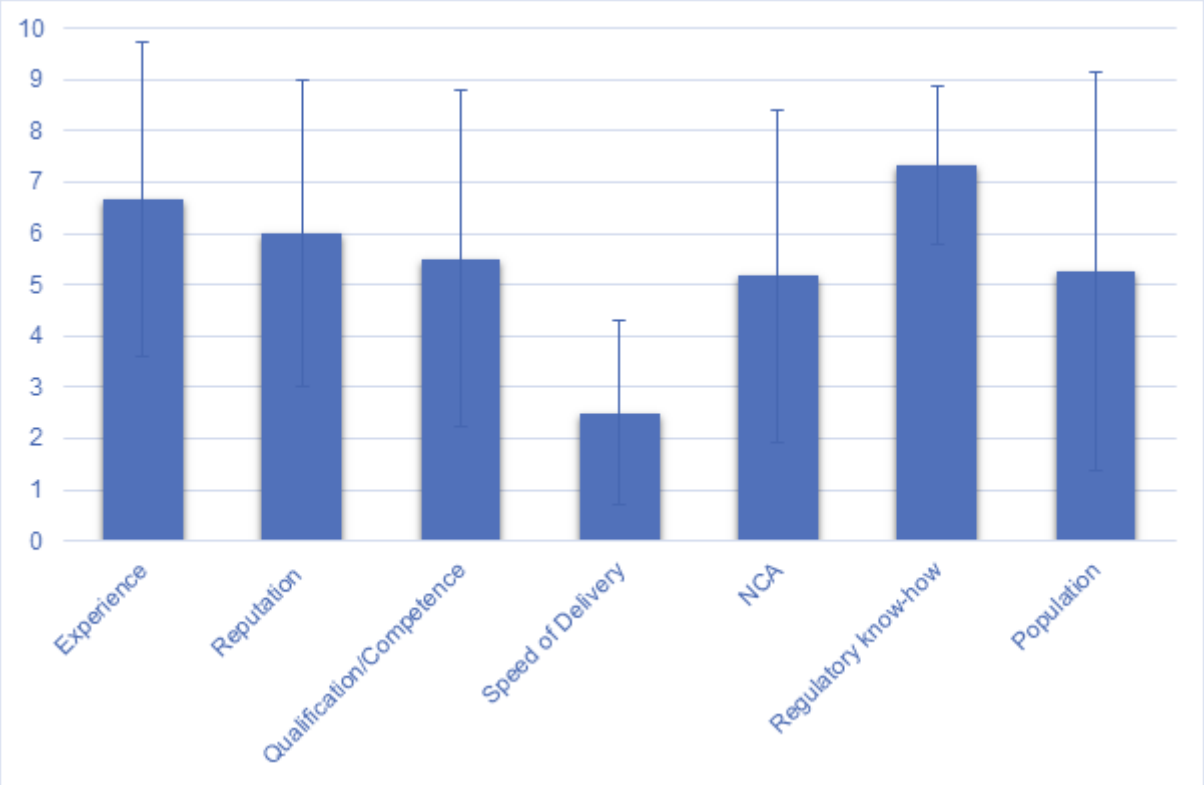


6.2.3 Results from the HTDs - Clinical Investigations, Sites and Expertise – Questionnaire

The major impression given by the HTDs, overlap as well in gross with the information given by the clinics, and has a strong focus on qualified and experienced sites and personnel, with specific knowledge in the given medical field. The personnel must be qualified by training, education and have relevant experience appropriate to the study device. The training provided by HTDs before the start of an EFS was described in detail, where for example clinicians and operation room personnel can be involved from early development, and models will be made to better understand intricate anatomies before EFS are started. Reduction of learning curves is proactively work with from many aspects and throughout the clinical development.

The HTDs also value that the sites have shown interest in feasibility studies or have extended experience with EFS. Site facilities are a necessity (e.g., product delivery, storage and accountability) in addition to sufficient resources, and position to work within the regulatory requirements. Sites need not to pursue conflicting studies, avoid a conflict of interests. The choice of site in relation to reputation would depend on the study needs and goals. An overview of some of these aspects ranked from 1-10, where 10 is the most important, is shown in Figure 8.

Figure 8 HTDs opinion on sites, competence and other aspect for EFS ranked from 1-10.



For questions related to timelines, the HTDs focussed on activation time. Speed to delivery was less important. In further question on NCA and regulatory know-how, the HTDs underlined importance of experience, and that it could possibly lead to the prioritising of some countries over others.

6.2.4 Results from the PAG workshop focus groups concerning Clinical Sites and Clinical Expertise

A preference for reputable clinical sites with advanced technology, experienced staff, and robust infrastructure to ensure high patient safety and care emerged among PAG members. This was contrasted with the concern that these sites may be less accessible for patients as there are fewer of them. The consensus, nevertheless, was that such high-quality sites can increase confidence among patients when participating in an EFS, with some willingness to trade off proximity to the site. One comment noted that the higher the health benefit for the participant, the more willing they may be to accept long distances. Another key aspect in this context is that some patients with reduced mobility may be unable to travel far, highlighting the need to consider specificities of the targeted conditions and related patient characteristics. Some participants noted that it is important for patients to understand that clinical trials are primarily a research endeavour and do not equate access to treatment.

When discussing available support, follow-up, and facilities in a clinical site, the following needs were identified by the PAG:

- Access to emergency care.
- A clear, dedicated contact point that participants can reach in case of questions or concerns, ideally a person that is closely involved in the study and participants trust.
- Regular check-ins with participants to ensure their wellbeing and understanding of the process; in cases where access is an issue, remote monitoring may be considered. This can ensure that patients remain informed about trial updates and modifications, maintaining trust and engagement.
- The site's ability to manage and address different situations, including emergencies and unforeseen events with participants, during and after an EFS.
- Personalised support for participants, such as mental health support, accessibility and mobility support to ensure that the different needs of patients are met during and after the EFS.

Adequate compensation of patients for their participation was considered another crucial requirement that any clinical site conducting an EFS or CI should offer to recognise the value

of patients' and their carers` time and effort and cover associated costs, e.g. travel, time off work.

The clinical site should also be transparent and clear about meeting all ethical and legal requirements and standards when communicating with patients, according to workshop focus group results. Further, the need for independent ethical committees to oversee an EFS/clinical investigation was raised.

Regarding clinical expertise the PAG members expressed a clear preference for clinicians/investigators with a high level of expertise and specialisation in clinical investigations and EFS, as this would raise patient confidence in the study. Linking to the discussion on clinical sites, focus groups participants recognised that the number of such specialised clinicians may be relatively low and willingness to travel may increase accordingly.

A central point of discussion was the independence and trustworthiness of clinicians conducting the EFS. PAG members recognised that clinicians interact closely with developers during a study. While studies may not be entirely separable from commercial factors, PAG members stressed the importance of a genuine interest of clinicians in patient benefits and health outcomes over commercial interests. An objective presentation of information about the medical device and study by the clinician was also considered crucial, as clinicians may have bias in favour of a certain technology and express views that could influence patients' perception.

Finally, empathy, patience, and understanding of patients' needs are vital skills valued by patients, according to focus groups findings. While expertise is indispensable, patients' trust in an EFS can be further established through emotional intelligence and active response to patients' questions and needs.

6.3 Summary and discussion

Through the questionnaires we have gathered the experiences of running CI in the HEU-EFS partner clinics. We have also investigated these experiences aligns with the current regulatory framework and compared with the FDA's EFS program. Finally with the input from the clinics, HTDs and PAG we present the following recommendations for clinical sites and expertise:

- The requirements defined by the MDR for sponsors, sites and investigators should be followed in the establishment of the EU-EFS framework.
- Personnel involved in EFS must have an extended understanding on how to report on serious adverse events in line with requirements of the MDR.
- An increase in regulatory competence on EFS is needed for all parties involved.

- A need for ongoing dialogue between sponsors, personnel involved in running the EFS and National Competent Authorities (NCA) is needed for a future EU-EFS program.
- Clinical site for EFS must have the capacity and equipment to offer adequate emergency care and support systems during and, where needed, after the EFS.
- Clinical site support should be tailored to the individual patients recruited, such as dedicated contact points for questions and concerns, accessibility and mobility support, mental health support, etc.
- Ensure independence or transparency of conflict of interest for clinical staff working on the EFS. Clearly communicating this to patients can be an important step to building their trust and confidence in an EFS participation.
- Clinical sites should ensure data compliance with ICH-GCP standards and ISO 14155:2020.
- Clinicians involved in EFS should have experience in the therapeutic area of the investigational device.
- Clinics should have dedicated units or personnel specifically tasked with coordinating regulatory submissions and contracts.
- Should ensure that the clinics have the required number of eligible subjects needed within the agreed recruitment period.
- Clinics should possess research experience with similar devices or early phase CI, documented through publications, or other adequate means. If not, they should have experience in advanced CI, such as pivotal studies in the therapeutic area, or provide justification of training and capability to conduct CI.
- Training methods: Clinics should have access to simulators, procedural videos, hands-on practice, and pre-clinical work (e.g., animal or cadaver models) are valuable tools for building to enhance readiness and confidence.
- Clinics should involve proctors and clinical specialists: When talking about the training curves, as their guidance is highly beneficial. Although, selecting proctors with both technical and clinical expertise can be challenging.
- There is a need for increased regulatory competence on EFS and a need for ongoing structured dialogues between clinics, HTDs and NCAs for the EU-EFS framework.
- Quality markers may be useful as a guide for clinics planning EFS and for the NCAs when evaluating CI applications.

6.4 Conclusion

The PAG identified competences, duties and obligations described for the sites, professionals involved in the EFS, and the training requirement needed in MDR are the borders with which a future EFS should make out the foundation for the development of EU-EFS. . The need for a more coordinated approach to clinical investigations including EFS is needed. FDA is regarded to have regulatory framework, which is beneficiary to EFS, and their work may inspire to a future EU-EFS framework.

The PAG concluded that the eligibility criteria for EFS must prioritise patient safety, transparency, and inclusivity. By addressing patient concerns around health literacy, benefits, risks, practicalities of participation, and communication, EFS can build trust among patients. These criteria should be integrated into study design to create a patient-centred approach that balances innovation with ethical responsibility.

The clinics, HTDs and patients were aligned on many areas concerning the development of a future EU-EFS framework with the foundation of MDR, ISO 114155 and GCP. All parties also highlighted the need for more guidance and alignment across Europe.

7. Conclusion of the eligibility criteria

We have identified, evaluated and compared the current situation for EFS and how this can be accommodated to the EU-EFS framework. The required competences, duties and obligations described for the clinical sites, professionals involved in EFS, and the training requirement needed in MDR are the borders within which a future EU-EFS framework must work. FDA is regarded to have regulatory framework, which is beneficial to EFS, and their work may inspire to a future EU-EFS framework.

In Europe the MDR governs the framework for CI and a future EU-EFS program should fit within this framework. A future EU-EFS framework has many challenges, among them a decentralised regulatory framework of the EU. However, the EU has been working on better collaboration between NCAs, NBs, MD HTDs and patients, and it is clear that many changes have come and are coming in the next few years. The HTAR was implemented on January 12, 2025. Notably, with the introduction of incremental steps of implementation, where e.g. parallel advice from the MDR Expert Panels and HTA Bodies, from Q2 2025 represents a significant advancement. These Joint Scientific Consultation (JSC) on a technology under development allow the HTDs to invite their NBs to participate as an observer, thereby enhancing the planning of CIs and facilitating communication among the various parties involved in conformity assessment for high-risk MDs.

The EU Commission is currently evaluating MDR, with potential pilot-projects such as a ‘breakthrough’ device pathway. The pilot for multi-site CI applications (Coordinated Assessment), where only one application has to be submitted to one EU NCA is also about to start.

These changes in the regulatory landscape emphasise that the MDR is still under development and changes which may be beneficial for a future EU-EFS program may occur.

The technological focus of EFS should be high-risk MDs, where sponsors can conduct an EFS on a developing technology based on the need to better understand physiology and anatomical limitations of the device under development, to apply an existing/approved device in a new patient population or application, and/or the initial CI activities related to a breakthrough device or a device serving an unmet need.

Patients considered for EFS should be carefully selected to contribute to the development of safe and effective MDs that meet their needs, while maintaining high standards of patient safety and ethical conduct. The conditions evaluated in an EFS should not be restricted.

The criteria for pre-clinical testing are well established under the MDR, however, a clear harmonised distinction must be made for when testing must be performed and when in the development process testing can be performed, to allow for iterative design changes. A clear understanding of the limitations of pre-clinical testing is also important where animal testing cannot accommodate for anatomical and physiological differences. EFS must however justify where the testing does not fulfil the requirements of the GSPR. Patients should have access and the opportunity to better understand the risks associated with less compliance prior to the EFS enrolment.

Clinical sites questionnaires identified the critical role of investigators' expertise and commitment, ensuring compliance with regulatory standards and site organization. Key challenges include regulatory inconsistencies, insufficient resources, and administrative delays, requiring streamlined processes and enhanced training.

PAG members expressed a clear preference for clinicians/investigators with a high level of expertise and specialisation in CIs and EFS, to raise patient confidence in the study. Linking to discussions on clinical sites, focus groups participants recognised that the number of such specialised clinicians may be relatively low and willingness to travel may increase accordingly. A central point of discussion was the independence and trustworthiness of clinicians conducting the EFS.

The need for reputable clinical sites with advanced technology, experienced staff, and robust infrastructure to ensure high patient safety and care emerged among PAG members. Such high-quality sites can increase confidence among patients when participating in an EFS.

The HTDs also value site experience, regulatory know-how, clinical expertise and good training routines. Sites are selected provided they have the intended population per study protocol, can meet the enrolment targets, and their clinicians have corresponding experience in the medical field.

We found that there was alignment between clinics, HTDs and patients on many areas for the development of a future EU-EFS framework, building on the foundation of MDR, ISO standards and GCP.

An EU-EFS program must accommodate the criteria and recommendations laid out in this report. To promote a harmonised EFS program and more innovation for the patients in the EU

is important that all the stakeholders such as NCAs, HTDs, academia, clinical sites, clinicians, patients and HTA Bodies work together.

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9. Appendices

Appendix I Nomenclature

EFS from ISO 14155:2020	'A limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication (e.g. innovative device for a new or established intended use, marketed device for a novel clinical application). 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. An early feasibility clinical investigation does not necessarily involve the first clinical use of a device. NOTE Early feasibility clinical investigation can also be called proof of concept clinical investigation.'
EFS from the FDA	'An early feasibility study is a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication (e.g., innovative device for a new or established intended use, marketed device for a novel clinical application). It may be used to evaluate the device design concept with respect to initial clinical safety and device functionality in a small number of subjects (generally fewer than 10 initial subjects) when this information cannot practically be provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable. Information obtained from an early feasibility study may guide device modifications. An early feasibility study does not necessarily involve the first clinical use of a device.'

Investigational device	**MDR definition:** a device that is assessed in a clinical investigation; **FDA definition:** a device, including a transitional device, that is the object of an investigation. (https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-definitions-and-acronyms)
Significant risk device from the FDA Code of Federal Regulations Title 21 §812.3(m)	'Significant risk device means an investigational device that: (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; (3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.'
Conformity Assessment	'conformity assessment' means the process demonstrating whether the requirements of this Regulation relating to a device have been fulfilled

Appendix II Methods

9.1.1 Introduction

Working groups were formed to undertake the tasks covered in this deliverable, and the activities and involvement of the PAG have influenced the findings and recommendations of this deliverable. In addition, activities, findings and recommendations for WP 3 build on a number of activities undertaken in WP1 and WP2, incorporated into and furthered by WP3. The activities of WP1 and 2 including a scoping review of the literature and grey literature, a review of the regulatory framework, as well as the WP1 developed databases for Pre-market Approval Pathways database (PMAP-DB), and the EFS database (EFS-DB).

The working groups (WGs) were formed for each of the five tasks presented in this deliverable (3.1.1-3.1.5). Numerous WG meetings were held over the course of the last half of 2024 and the first months of 2025. Both internal meetings and meetings organized with project partners were held to review pertinent issues, potential criteria, address missing factors, and discuss emerging questions for each area. A further, focused, regulatory review, questionnaires and surveys were also undertaken by WP3 WGs. In addition, to gather patient perspectives, focus groups with the HEU-EFS PAG were organized to present and discuss progress toward development of the criteria and collect input from PAG. Feedback from the focus groups informed the development of criteria and recommendations. Pertinent details regarding the methodology employed by the various WGs and for the PAG contributions are outlined below.

9.1.2 Scoping review of peer-reviewed and grey literature on pre-market approval pathways and EFS, project databases

WGs reviewed the findings collected from a scoping literature review, also including grey literature searches and information gathered in the PMAP-DB and the EFS-DB, conducted under WP1. For the scoping review of the scientific literature, a total of 730 papers were identified in advanced searches covering characteristics, features, challenges and performance of pre-market approval pathways (PMAPs). Search terms were combined into four parts, joined by AND, and searched for title and abstract in Pubmed; title, abstract and keywords in Scopus; and in all fields in Web of Science (Box 5). In this search, no date restriction was used since it covers pre-market programs and not just EFS (the program started in 2013).

Box 5 Search terms used in the literature review.

(("early feasibility stud*" OR "clinical feasibility" OR "first in human" OR "iterative development" OR (("premarket" OR "pre-market") AND "clinical") OR (("preapproval" OR "pre-approval") AND "clinical") OR " CI" OR "clinical evaluation")

AND ("medical device*" OR "medical technology" OR "digital health technology" OR "digital medical device" OR "digital software")

AND ("program" OR "approval" OR "pathway" OR "regulat*")

AND (perform* OR characteristic* OR impact OR evaluation OR assessment OR effectiveness OR analysis OR consequence* OR "barrier*" OR "challenge*" OR "feature*" OR "KPI" OR "recall*"))

From the 730 papers identified, 163 were earmarked for full paper screening by at least two independent experienced researchers; 24 of these papers specifically mentioned EFS. At the conclusion of full text screening, 68 papers were included in the scoping review covering PMAPs, including 12 papers specifically related to EFS. More information about the scientific literature review can be found in the Methods section (pages 14-19) of WP1 deliverable 1.1, "Characteristics, gaps, and best practices of pre-market programs", as well as Appendix 2.1 Methods (pages 72-77) and Appendix 2.9 (pages 95-99) of WP2 deliverable 2.1, "EU regulatory framework and international standards". The full discussion of the regulatory context is included in Deliverable 2.1. Deliverable 1.1 also includes a detailed description of the US EFS program.

In addition to the scoping literature review, PMAP-DB and EFS-DB findings informed the WGs, providing details regarding regulatory pathways in various jurisdictions around the world (PMAP-DB), and from the hundreds of EFS gathered in the EFS-DB (see also Deliverable 1.3. Characteristics and state of play of EFS).

9.1.3 Method for Review of Regulatory Background

Based on the established regulatory practice for Clinical Sites 3.1.4. and Clinical Expertise 3.1.5. we found that the MDR and other regulatory guidance do not delineate the requirements for infrastructure from sponsor and clinical competence, however ISO 14155:2020 does describe the roles of investigators in CI. We therefore combined the two. The goal was to evaluate the frameworks to understand how an EU EFS program could be set-up specifically within MDR, with a better understanding of how EFS programs currently are run:

- MDR
- MDCG guidance

- Relevant standards such as ISO 14155 and ISO 14971
- Medical Device Innovation Consortium (MDIC) Blueprint (in progress)
- FDA EFS Program
- Interviews with Consortium CI sites
- Interviews with Patient Advisory Group (PAG)
- Interviews with Consortium Industrial Partners

9.1.3.1 Questionnaire to clinics

The questionnaire comprised 18 main questions, some of which were accompanied by several sub-questions. It primarily consisted of open-ended questions, with one exception: a weighted scoring question.

Interviews were conducted by clinical partners in the consortium interviewing their own key personnel associated with CIs to describe current clinical practice for EFS today.

To prepare this summary, the questions were grouped into six topics, each with its corresponding questions (to see the detailed questionnaire, see Appendix III):

- Clinical Investigation Sites
- Investigators
- Clinical Research Organizations, when applicable
- Independent Ethics Committees / National Competent Authorities
- Budget, resources & timelines
- Additional questions

The task of parsing the responses was shared between two partners. The analysis was “peer-reviewed” to reduce bias.

9.1.3.2 Interview/Questionnaire with Medical Device Developers

The questionnaire comprised 13 questions for 3.1.3., and 4 questions for 3.1.4. and 5 questions for 3.1.5., some of which were accompanied by questions that the participant were asked to rank (a weighted scoring) question themselves. The remainder of the questions were open-ended.

Interviews were conducted by the WP3 leader to describe current clinical practice for EFS today.

To prepare this summary, the questions were grouped according to Task areas and broken down for Clinical Sites to understand what drives the choice of where to conduct a CI, Clinical Competence to try to understand how medical device developers work to reduce learning curves. For Pre-clinical Testing to understand more details around how the testing is performed, the experiences from the FDA EFS program and 'just in time' testing concept.

9.1.4 Methodology for Patient Advisory Group (PAG) focus groups

With the aim of identifying patient perspectives on the developed eligibility criteria, two focus groups involving the HEU-EFS PAG were organized on 5th December 2024 and 20th January 2025. The focus groups were a collaborative effort between EPF, GHH, UB, NIPH, Edwards, and FCRB and were conducted through guided discussions with PAG members to collect their feedback and views. The focus groups helped refine the lists of eligibility criteria as well as the checklist which was developed to help sponsors who analyse the medical conditions and the disease severity level of target patients to be recruited for EFS.

The overall topics addressed in the focus groups were; eligibility criteria for technologies (Task 3.1.1.); eligibility criteria for unmet needs, medical conditions and disease severity of target patient population (Task 3.1.2.); level of evidence required to start an EFS (Task 3.1.3); eligibility criteria for clinical sites (Task 3.1.4.); and eligibility criteria for clinical expertise (Task 1.3.5). The topic of conditions on reimbursing investigational devices (Task 3.1.6.) was not yet addressed due to the extension of the workplan for this specific objective. The topics most relevant from a patient's perspective were selected for the first focus groups in 2024. The second workshop in 2025 complemented the discussion from the previous focus group, introducing new issues and questions as well as further diving into previously addressed aspects.

With the aim of identifying any issues with the proposed criteria and collecting different perspectives, two focus groups involving the HEU-EFS PAG were organized on 5th December 2024 and 20th January 2025. The focus groups were a collaborative effort between EPF, GHH, UB, NIPH, Edwards, and FCRB and aimed at guided discussions with PAG members to collect their feedback and views. The focus groups helped refine the list of criteria as well as the checklist which was developed to help sponsors who analyse the medical conditions and the severity level of target patients to be recruited for EFS.

The overall topics addressed in the focus groups were eligibility criteria for technologies (Task 3.1.1.); eligibility criteria for unmet needs, medical conditions and disease severity of target patient population (Task 3.1.2.); level of evidence required to start an EFS (Task 3.1.3); eligibility criteria for clinical sites (Task 3.1.4.); and eligibility criteria for clinical expertise (Task

3.1.5). The topic of conditions on reimbursing investigational devices (Task 3.1.6.) was not yet addressed due to the extension of work on this specific objective. The topics most relevant from a patient's perspective were selected for the first focus groups in December 2024. The second focus group in January 2025 complemented the discussion from the prior workshop, introducing new topics and questions as well as further diving into previously addressed aspects the relationship between the topics and their associated questions for the PAG.

Appendix III Results

3.1.2. Medical conditions

Table 9 Definitions related to CI in regulatory framework.

	Definition		
Term	**MDR**	**ISO 14155:22020**	**FDA**
'clinical evaluation'	means a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer;	includes an assessment and analysis of clinical data concerning clinical performance, effectiveness or safety of the investigational device or similar devices or therapies.	xxx
'clinical investigation'	any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device;	systematic investigation in one or more human subjects (3.50), undertaken to assess the clinical performance (3.11), effectiveness (3.20) or safety of a medical device (3.34)	any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a

Term	Definition		
	MDR	ISO 14155:22020	FDA
			research or marketing permit.
'sponsor'	means any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the CI;	individual, company, institution or organization taking responsibility and liability for the initiation and management of a *CI* (3.8), and arranging the financial setup	means a person who takes responsibility for and initiates a CI. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. (58.3f)
'subject'	means an individual who participates in a CI; L 117/18 EN Official Journal of the European Union 5.5.2017	individual who is or becomes a participant in a *CI* (3.8), either as a recipient of the investigational device or a *comparator* (3.12) vulnerable subject individuals who are unable to fully understand all aspects of the investigation that are relevant to the	means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

Term	Definition		
	MDR	ISO 14155:22020	FDA
		decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response	
'investigator'	means an individual responsible for the conduct of a CI at a CI site;	individual member of the *investigation site* (3.28) team designated and supervised by the *principal* *investigator* (3.39) at an investigation site to perform CI-related procedures or to make important CI-related and medical treatment decisions **coordinating investigator** *investigator* (3.30) who is appointed by the *sponsor* (3.49) to assist in coordinating the work in a multicentre *CI* (3.8)	means an individual who actually conducts a CI (*i.e.*, under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.
Principle Investigator	Not defined – but described as an 'actor' in Annex XV	qualified person responsible for conducting the *CI* (3.8) at an *investigation site* (3.28)	Means either: (a) The single individual whom an organization that… (others within the group are "co-principal investigators," as defined in this subpart). From the OECD: Principal Investigator

Term	Definition		
	MDR	ISO 14155:22020	FDA
			means an individual who, for a multi-site study, acts on behalf of the Study Director and has defined responsibility for delegated phases of the study. The Study Director's responsibility for the overall conduct of the study cannot be delegated to the Principal Investigator(s); this includes approval of the study plan and its amendments, approval of the final report, and ensuring that all applicable Principles of Good Laboratory Practice are followed
Coordinating Investigator		*investigator* (3.30) who is appointed by the *sponsor* (3.49) to assist in coordinating the work in a multicentre *CI* (3.8)	
Medical Device	means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: — diagnosis,	instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more	an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is— • recognized in the official National Formulary, or the United States Pharmacopeia, or any

Term	Definition		
	MDR	ISO 14155:22020	FDA
	prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, — diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability, — investigation, replacement or modification of the anatomy or of a physiological or pathological process or state, — providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means. The following products shall also be deemed to be medical devices: — devices for the control or support of conception; — products specifically	of the specific purpose(s) of: — diagnosis, prevention, *monitoring* (3.35), treatment or alleviation of disease; — diagnosis, monitoring, treatment, alleviation of or compensation for an injury; — investigation, replacement, modification, or support of the anatomy or of a physiological process; — supporting or sustaining life; — control of conception; — disinfection of medical devices; — providing information by means of *in vitro* examination of specimens derived from the human body; and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means Note 1 to entry: Products which may be considered to be medical devices in some	supplement to them, • intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or • intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes (21 U.S.C. 321(h)).

Term	Definition		
	MDR	ISO 14155:22020	FDA
	intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.	jurisdictions but not in others include: — disinfection substances; — aids for persons with disabilities; — devices incorporating animal and/or human tissues; — devices for *in vitro* fertilization or assisted reproduction technologies. investigational medical device *medical device* (3.34) being assessed for *clinical performance* (3.11), *effectiveness* (3.20), or safety in a *CI* (3.8)	

Table 10 Regulatory framework – mapping of the MDR for roles of sponsors investigators and sites.

Terms	Where in MDR	Details
'clinical investigation' **Number mentioned n=2**	Articles	Art 2.45 (definition) means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device
		Art 23.3 q (label); an indication that the device is a medical device. If the device is intended for clinical investigation only, the words 'exclusively for clinical investigation'
Sponsor n=104	Legislative acts	44 on EUDAMED - function 46 on EUDAMED - on sharing information between competent authorities 63 on Roles as sponsor; being manufacturer or legal person -responsible for the clinical investigation 66 on Harm caused to a subject and civil or criminal liability 68 on Coordinated assessment 69 on adverse events, suspension and termination of ongoing clinical investigations 70 on summary of results
	Definition	Art 2. 49 (definition) `sponsor' means any individual, company, institution or organization which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation;
	Articles	Art 2. 49 (definition) `sponsor' means any individual, company, institution or organization which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation Art 8 harmonized standards Art 33 (EUDAMED) Art 62 obligations of sponsor in clinical investigations on General requirements

		regarding clinical investigations conducted to demonstrate conformity of devices Art 69 Compensation for any damage suffered by a subject Art 70 Application for clinical investigations Art 71 sponsors obligations - Assessment by Member States Art 72 Conduct of a clinical investigation Art 73 Conduct of a clinical investigation Art 74 Clinical investigations regarding devices bearing the CE marking Art 75 Substantial modifications to clinical investigations Art 77 Information from the sponsor at the end of a clinical investigation or in the event of a temporary halt or early termination Art 78 Coordinated assessment procedure for clinical investigations Art 80 Recording and reporting of adverse events that occur during clinical investigations
	Annex XV	Further roles of the sponsor are described chapter iii, of annex xv pt 1-7 CHAPTER III OTHER OBLIGATIONS OF THE SPONSOR 1. The sponsor shall undertake to keep available for the competent national authorities any documentation necessary to provide evidence for the documentation referred to in Chapter II of this Annex. If the sponsor is not the natural or legal person responsible for the manufacture of the investigational device, that obligation may be fulfilled by that person on behalf of the sponsor. 5.5.2017 EN Official Journal of the European Union L 117/171 2. The Sponsor shall have an agreement in place to ensure that any serious adverse events or any other event as

		referred to in Article 80(2) are reported by the investigator or investigators to the sponsor in a timely manner. 3. The documentation mentioned in this Annex shall be kept for a period of at least 10 years after the clinical investigation with the device in question has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market. In the case of implantable devices, the period shall be at least 15 years. Each Member State shall require that this documentation is kept at the disposal of the competent authorities for the period referred to in the first subparagraph in case the sponsor, or its contact person or legal representative as referred to in Article 62(2) established within its territory, goes bankrupt or ceases its activity prior to the end of this period. 4. The Sponsor shall appoint a monitor that is independent from the investigational site to ensure that the investigation is conducted in accordance with the CIP, the principles of good clinical practice and this Regulation. 5. The Sponsor shall complete the follow-up of investigation subjects. 6. The Sponsor shall provide evidence that the investigation is being conducted in line with good clinical practice, for instance, through internal or external inspection. 7. The Sponsor shall prepare a clinical investigation report which includes at least the following: — Cover/introductory page or pages indicating the title of the investigation, the investigational device, the single identification number, the CIP number and the details with signatures of the coordinating investigators and the principal investigators from each investigational site.

		— Details of the author and date of the report. — A summary of the investigation covering the title, purpose of the investigation, description of the investigation, investigational design and methods used, the results of the investigation and conclusion of the investigation. The completion date of the investigation, and in particular details of early termination, temporary halts or suspensions of investigations. — Investigational device description, in particular clearly defined intended purpose. — A summary of the clinical investigation plan covering objectives, design, ethical aspects, monitoring and quality measures, selection criteria, target patient populations, sample size, treatment schedules, follow-up duration, concomitant treatments, statistical plan, including hypothesis, sample size calculation and analysis methods, as well as a justification. — Results of the clinical investigation covering, with rationale and justification, subject demographics, analysis of results related to chosen endpoints, details of subgroup analysis, as well as compliance with the CIP, and covering follow-up of missing data and of patients withdrawing from the clinical investigation, or lost to follow-up. — Summary of serious adverse events, adverse device effects, device deficiencies and any relevant corrective actions. — Discussion and overall conclusions covering safety and performance results, assessment of risks and clinical benefits, discussion of clinical relevance in accordance with clinical state of the art, any specific precautions for specific patient populations, implications for the investigational device, limitations of the investigation.

On changes and modifications during an ongoing clinical study	Legislative acts	68 on Coordinated assessment 84 on Coordinated assessment and vigilance
	Articles	Art 12 Change of authorised representative Art 75 Substantial modifications to clinical investigations Art 78 Coordinated assessment procedure for clinical investigations Art 89 Analysis of serious incidents and field safety corrective actions Art 91 Implementing acts
	Annex XV	3.9. Information about any amendments to the CIP
'investigator' **n=32**	Legislative acts	66 on Harms and civil and criminal liability
	Definition	Art 2. 54: means an individual responsible for the conduct of a clinical investigation at a clinical investigation site;
	Articles	Art 21 Devices for special purposes
		Art 62 General requirements regarding clinical investigations conducted to demonstrate conformity of devices *On : The investigator shall be a person exercising a profession which is recognised in the Member State concerned as qualifying for the role of investigator on account of having the necessary scientific knowledge and experience in patient care. Other personnel involved in conducting a clinical investigation shall be suitably qualified, by education, training or experience in the relevant medical field and in clinical research methodology, to perform their tasks. n* Art 62.4j *A clinical investigation (…) may be conducted if (…).:* *the medical care provided to the subjects is the responsibility of an appropriately qualified medical doctor or, where*

		appropriate, a qualified dental practitioner or any other person entitled by national law to provide the relevant *patient care under clinical investigation conditions;* Art 62.6 *The investigator shall be a person exercising a profession which is recognised in the Member State concerned as* *qualifying for the role of investigator on account of having the necessary scientific knowledge and experience in patient care. Other personnel involved in conducting a clinical investigation shall be suitably qualified, by education, training or experience in the relevant medical field and in clinical research methodology, to perform their tasks.* Art 64 Clinical investigations on incapacitated subjects Art 65 Clinical investigations on minors Art 68 Clinical investigations in emergency situations Art 69 Clinical investigations in emergency situations Art 71 Assessment by Member States Art 72 Conduct of a clinical investigation Art 73 Electronic system on clinical investigations Art 76 Corrective measures to be taken by Member States and information exchange between Member States
	Annex XV	CHAPTER I *2.7 Investigators shall have access to the technical and clinical data regarding the device. Personnel involved in the* *conduct of an investigation shall be adequately instructed and trained in the proper use of the investigational* *device, and as regards the clinical investigation plan and good clinical practice. This training shall be verified and*

		where necessary arranged by the sponsor and documented appropriately. Chapter II, *1.13. evidence from the sponsor that the clinical investigator and the investigational site are capable of conducting the clinical investigation in accordance with the clinical investigation plan;*
Other personnel **Healthcare professionals** **n= 18**	Legislative acts	43 *on transparency and adequate access to information in general* 44 EUDAMED as a source for Information to Healthcare Professionals on devices in general 76 *on awareness among healthcare professionals, users and patients about the importance of reporting incidents.* 78 *on investigation of incidents*
		Art 11 on complaints and reports from healthcare professionals
	Authorized representative	Art 12 Change of authorised representative
Legal person related to clinical investigation. **n=30**	Legislative acts	63 It should be possible both for the manufacturer and for another natural or legal person to be the sponsor taking responsibility for the clinical investigation.
	definition	Art 2.30 *manufacturer' means a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark;* Art 2.32 *'authorised representative' means any natural or legal person established within the Union who has received and accepted a written mandate from a manufacturer, located outside the Union, to act on the manufacturer's behalf in relation to specified tasks with regard to the latter's obligations under this Regulation;*
	Articles	Art 62.2 *Where the sponsor of a clinical investigation is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative. Such*

		legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to this Regulation, and shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication with that legal representative shall be deemed to be a communication with the sponsor.
	Annex XV	IB 4.1 *A signed statement by the natural or legal person responsible for the manufacture of the investigational device that the device in question conforms to the general safety and performance requirements apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subject.* Chapter III *The sponsor shall undertake to keep available for the competent national authorities any documentation necessary to provide evidence for the documentation referred to in Chapter II of this Annex. If the sponsor is not the natural or legal person responsible for the manufacture of the investigational device, that obligation may be fulfilled by that person on behalf of the sponsor.*
Multi sites		Art 76 Corrective measures to be taken by Member States and information exchange between Member States
Feasibility studies under	Articles	Art 82 1. Clinical investigations, not performed pursuant to any of the purposes listed in Article 62(1), shall comply with the provisions of Article 62 (2) and (3), points (b), (c), (d), (f), (h), and (l) of Article 62(4) and Article 62(6). 2. In order to protect the rights, safety, dignity and well-being of subjects and the scientific and ethical integrity of clinical investigations not performed for any of the purposes listed in Article 62(1), each Member State shall define any additional

		requirements for such investigations, as appropriate for each Member State concerned.
Site: **N= 60**	Legislative acts	
		The facilities where the clinical investigation is to be conducted shall be suitable for the clinical investigation and shall be similar to the facilities where the device is intended to be used. 1.13 (CIP)evidence from the sponsor that the clinical investigator and the investigational site are capable of conducting the clinical investigation in accordance with the clinical investigation plan; 3.1.3 (CIP) Available and necessary; Information on the principal investigator at each investigational site, the coordinating investigator for the investigation, the address details for each investigational site and the emergency contact details for the principal investigator at each site. The roles, responsibilities and qualifications of the various kinds of investigators shall be specified in the CIP.
Sites	Manufactory site n=4	Annex 8 ROCEDURE FOR CUSTOM-MADE DEVICETECHNICAL DOCUMENTATION; manufacture sites Annex VII EQUIREMENTS TO BE MET BY NOTIFIED BODIES 4.5.2, Quality management system auditing Annex II - identification of all (Manufacturing sites, including suppliers and sub-contractors, where design and manufacturing activities are performed.
Subjects **n=49**	Definition	Art 2.45 ‘clinical investigation’ means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device

		Art 2.55 informed consent' means a subject's free and voluntary expression of his or her willingness to participate in a particular clinical investigation, after having been informed of all aspects of the clinical investigation that are relevant to the subject's decision to participate or, in the case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical investigation Art 57 adverse event' means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device
	Legislative acts	Scope and on safety of the subjects 64 on O 14155:2011 on good clinical practice for clinical investigations of medical devices for human subjects, 67 on To protect the right to the protection of personal data 69 on report certain adverse event…of the subjects 72 on protecting measures of vulnerable populations Incapacitated subjects, minors, pregnant women and breastfeeding women require specific protection measures. Who are to be excluded from feasibility studies
	Articles	Art 3.6 and 7 *European database on medical devices* Art 33 European database on medical devices, protection of rights of subjects Art 62 General requirements regarding clinical investigations conducted to demonstrate conformity of devices *On safety, dignity and well-being of the subjects participating in a clinical investigation* *On appropriately protection of vulnerable subjects*

		On justification of risks – to benefits in clinical investigations, and design to minimize harm *the medical care provided to the subjects is the responsibility of an appropriately qualified medical doctor or dentist* *on protection of the health and safety of the subjects and their personal data* Art 63 on Informed consent Art 64 Clinical investigations on incapacitated subjects Art 68 Clinical investigations in emergency situations Art 71 Assessment by Member States Art 72 Conduct of a clinical investigation on safety and well-being of subjects are protected Art 73 Electronic system on clinical investigations on «no personal data of subjects shall be publicly available Art 74 Clinical investigations regarding devices bearing the CE marking Art 75 Substantial modifications to clinical investigations Art 82 Requirements regarding other clinical investigations
	Annex 15 CIP	Annex 15, chapter II, 1.11 *"On summary of the clinical investigation plan including the objective or objectives of the clinical investigation, the number and gender of subjects, criteria for subject selection, whether there are subjects under 18 years of age»* 3.6. 3 *Information on subjects, selection criteria, size of investigation population, representativeness of investigation population in relation to target population and, if applicable, information on vulnerable subjects involved such as children, pregnant women, immuno-compromised or, elderly subjects.* 3.15 CIP *Criteria and procedures for follow-up of subjects following the end, temporary halt or early termination of an investigation,*

		for follow-up of subjects who have withdrawn their consent and procedures for subjects lost to *follow-up* 4.3 *roof of insurance cover or indemnification of subjects in case of injury, pursuant to Article 69 and the* *corresponding national law.* 4.5 — *a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects; and*
Pilot, feasibility, first-in-man	n=1	CLINICAL EVALUATION AND POST-MARKET CLINICAL FOLLOW-UP PART A CLINICAL EVALUATION Part Apt 1A on clinical development plan
Training of personnel in clinical investigations **n=25**		Art 32 Summary of safety and clinical performance on suggested profile and training for users
	MDR, Annex XV	Annex XV, *Chapter 1, on manufacturers obligations* *4.c provide information for safety (warnings/precautions/contra-indications) and, where appropriate, training to users.* *5.b give consideration to the technical knowledge, experience, education, training and use environment, where* *applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled* *or other users).* 2.7 *Investigators shall have access to the technical and clinical data regarding the device. Personnel involved in the conduct of an investigation shall be adequately instructed and trained in the proper use of the investigational device, and as regards the clinical investigation plan and good clinical practice. This training shall be verified and where necessary arranged by the sponsor and documented appropriate'*

		Annex XV, Chapter II, 1.13. evidence from the sponsor that the clinical investigator and the investigational site are capable of conducting the clinical investigation in accordance with the clinical investigation plan

Table 11 Ethics committees in the MDR.

Ethics committees	
MDR: **Legislative acts 65**	It should be left to the Member State where a CI is to be conducted to determine the appropriate authority to be involved in the assessment of the application to conduct a CI and to organise the involvement of ethics committees within the timelines for the authorisation of that CI as set out in this Regulation. Such decisions are a matter of internal organisation for each Member State. In that context, Member States should ensure the involvement of laypersons, in particular patients or patients' organisations. They should also ensure that the necessary expertise is available.
Article 62	3. CIs shall be designed and conducted in such a way that the rights, safety, dignity and well-being of the subjects participating in a CI are protected and prevail over all other interests and the clinical data generated are scientifically valid, reliable and robust. CIs shall be subject to scientific and ethical review. The ethical review shall be performed by an ethics committee in accordance with national law. Member States shall ensure that the procedures for review by ethics committees are compatible with the procedures set out in this Regulation for the assessment of the application for authorisation of a clinical investigation.

	At least one lay person shall participate in the ethical review.
Article 82 **(In general, as pilot stage clinical investigations are conducted to gather preliminary safety and/or performance data, the use of Article 62 of the MDR should be foreseen. In cases of doubt, it is recommended to apply under Article 62 of the MDR)**	1. Clinical investigations, not performed pursuant to any of the purposes listed in Article 62(1), shall comply with the provisions of Article 62 (2) and (3), points (b), (c), (d), (f), (h), and (l) of Article 62(4) and Article 62(6). 2. In order to protect the rights, safety, dignity and well-being of subjects and the scientific and ethical integrity of clinical investigations not performed for any of the purposes listed in Article 62(1), each Member State shall define any additional requirements for such investigations, as appropriate for each Member State concerned.

Table 12 MDCG Medical device guidance on CI.

Guidance	Description
MDCG 2021-08.	CI application/notification documents which details the application/notification documents for CIs at various CI pathways. MDCG 2021-6 Regulation (EU) 2017/745 – Questions & Answers regarding CI – December 2023 says that depending on the overall test design, usability testing may or may not fall under the definition of CI in Article 2(45)
MDCG 2020-10/Rev	Says CI may be used for conformity procedure for investigational device cf. article 62 = applicable regulation = MDR art.80. &2-3. Other CI cf. article 82 or other national legislation = applicable regulation is national legislation = no provisions in MDR. Safety reporting may be regulated in national legislations in the country where the investigation is conducted.
MDCG 2024-3	Guidance on content of the CI Plan for CIs of medical devices states "Discuss the type of investigation sites (e.g., specialised clinic, primary health care centre, manufacturer's custom-built facility etc.) and differences in investigation site environments. Elaborate on why the elected sites are deemed appropriate for the conduct of the CI. In multicentre/multinational studies, it might be necessary to consider any expected differences in the standard of care or patient outcomes based upon the geographic distribution of the intended patient or user populations. Discuss the impact and account for any local adaptations."
According to MDCG 2021-6 Regulation (EU) 2017/745 – Questions & Answers	According to MDCG 2021-6 Regulation (EU) 2017/745 – Questions & Answers regarding CI – December 2023, pilot stage CIs are designed to enrol a limited number of subjects to assess a device early in its development phase with respect to the initial clinical safety and/or performance, e.g., device functionality.

9.1.5 Task 3.1.4 Questionnaire template for Clinics

Introduction

Based on the risk assessment, medical devices can undergo three general stages of clinical development. These stages can be dependent on each other and doing a thorough evaluation in one stage can make the next stage much more straightforward.

If a **pilot stage** is necessary, (an) exploratory CI(s) will evaluate the limitations and advantages of the medical device and is commonly used to capture preliminary information on a medical device (at an early stage of product design, development, and validation) to adequately plan further steps of device development, including needs for design modifications or parameters for a pivotal CI. This stage includes first in human, early feasibility studies and traditional feasibility Cis.

Early Feasibility Studies (EFS) are a limited CI of a device early in development, typically before the device design has been finalized, for a specific indication (e.g., innovative device for a new or established intended use, marketed device for a novel clinical application). It can be used to evaluate the device design concept with respect to initial clinical safety and device clinical performance or efficacy (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 CI can guide device modifications. An early feasibility CI does not necessarily involve the first clinical use of a device.

A **First in Human (FIH)** study is a type of study in which a device for a specific indication is evaluated for the first time in human subjects. An EFS is not necessarily a first use of the device in a human. A device may have already been used for a different intended use.

Each EFS requires its own assessment of the type of site and investigator that will fit that each study's specific needs and potential outcomes. Before vetting a site for an EFS, it is important for sponsors to ask and answer the question of "What could possibly go wrong?" and then determine the site features and investigator characteristics needed to attend to these issues.

Questionnaire

This questionnaire belongs to the Harmonised approach to Early Feasibility Studies for Medical Devices in the European Union (HEU-EFS) project. It has been developed according to the results from the literature review in WP2.

The objective of this task (Task 3.1.4) is to develop **eligibility criteria** for clinical sites to get access to the future EU EFS Program.

The objectives of this questionnaire are:

1. To describe the characteristics, organisation and functioning of clinical sites with experience in EFS among the HEU-EFS clinic partners.
2. Understanding the meaning of each of the requirements identified in WP2.
3. To identify a minimum set of mandatory requirements for the clinical sites to start an EFS.
4. To identify how end-user's competencies might reduce the impact of the learning curve with new technology that will be investigated in the EFS stage.

When answering the questionnaire, please think about your experience in your hospital, regarding planning and conducting pre-market CIs for medical devices in the pilot stage of clinical development, as well as the challenges associated.

For familiarity with terminology, we included FIH to the questions along with EFS, since they are both pilot stage CI with similar requirements (according to ISO 14155), and respondents would be more familiar with the term FIH, and because clinical sites are used to encompass them as FIH.

Participation and confidentiality

All information collected in this questionnaire will be kept confidential, in accordance with applicable laws.

1. In which country are you located?
2. How many EFS and/or FIH has your hospital conducted in the past 10 years?
3. Please, describe in the field below how your hospital is organized and conducts an EFS and/or FIH, including the roles of the *roles/personnel that are participating in a typical EFS and/or FIH at your hospital from the Sponsor/developer to the lowest in the hierarchy?* (**i.e. mapping of organizational execution of an EFS and/or FIH**). (For example, do you have a preselected Clinical Research Organizations (CRO) or an Academic Clinical Trial Unit in charge of organizing the EFS with professionals in different roles, such as Study Nurse, Study Coordinator, Data Entry, etc.)

   3.1. *If you have a CRO involved, what **qualifications and/or experience** do you expect for relying on a CRO for conducting an EFS and/or FIH?*

   3.2. *Are there any roles that you would have liked to have that are not available/are missing?*

4. How do you interpret a clinical site having a **proven track record** of efficiently and successfully completing research trials? (You can answer in qualitative and/or quantitative terms)

   4.1. *Please describe the gaps and challenges faced on this aspect when communicating with National Competent Authorities (NCA) in your country*.

5. What do you understand by **clinical site experience** in human subject monitoring and patient protection measures?
   - **5.1.** *Please describe the gaps and challenges faced on this aspect when communicating with NCAs in your country*.
   - **5.2.** *Please describe the gaps and challenges faced on this aspect when communicating with IECs in your country*.
6. What **competences, qualifications and/or experience do you require** (or expect) from **investigators** to deem them suitable for conducting an EFS and/or FIH?
   - **6.1.** *Do you experience gaps and challenges faced on this aspect when communicating with NCAs in your country*?
   - **6.2.** *Do you experience gaps and challenges faced on this aspect when communicating with IECs in your country*?
7. Do you have any strategy in place to help manage the timeline between IEC approval, contract approval, and the enrolment of the first patient in the EFS and/or FIH? Please describe your strategy.
   - **7.1.** *Do you internally use any template for contract signing?*
   - **7.2.** *How are financial arrangements managed? Are they coordinated with the contract, or handled by a department other than Legal? Additionally, could you provide an estimated timeline from IEC approval to contract signing?*
   - **7.3.** *Please describe the gaps and challenges faced on this aspect when communicating with NCAs in your country*.
   - **7.4.** *Please describe how you interact with your Ethics Committees (IECs). Do you contact them before each study? please describe the gaps and challenges faced on this aspect when communicating with Independent Ethics Committees (IECs) in your country*.
8. How do you ensure you have **access to the appropriate patient population** for your EFS and/or FIH?
   - **8.1.** *Please describe the gaps and challenges faced on this aspect when communicating with NCAs in your country*.
9. How do you ensure that the **resources for EFS and/or FIH are used efficiently and remain within the set budget**?
   - **9.1.** *How are the unforeseen costs managed (e.g., extended patient stays, Serious Adverse Events (SAEs) or Device Deficiencies (DDs)?*
   - **9.2.** *How do you manage amendments to the study protocol or device, and how quickly can you implement these changes?*
   - **9.3.** *Do you apply any risk mitigation strategies related to budget management when conducting EFS/FIH studies? If so, could you provide a few examples?*
   - **9.4.** *Please describe the gaps and challenges faced on this aspect when relating with IECs in your country*.

10. Please describe the characteristics, composition, experience and organisation of the IECs responsible for reviewing an EFS and/or FIH for approval in your hospital. Specify whether the IEC is internal to your institution or external.

10.1. *What additional safety measures should be included in an EFS or FIH to increase safeguards for patients according to the IEC point of view (i.e. clinical criteria for early termination, independent DSMB…)?*

11. The MDIC website provides information on clinical site characteristics, including examples of criteria (and scores) for selecting a clinical site for an EFS. In the table below, you will find these criteria along with a corresponding score to represent their importance for a Clinical Site to carry out EFS (extracted from the MDIC website). Could you please indicate the weight you believe should be assigned to each criterion relative to others?

Site Selection Criteria	Definition for criteria's score	Score
Investigator's expertise in the field	1=Poor 3=Fair 9=Strong (Elite)	
Commitment of Investigator/Passion	1= None 3= Dedicated 9=Partner	
Availability of the Investigator	1=Limited 3=Fair 9=Available when needed	
Site's research staff	1=≤2 people 3=3-4 people 9=>5 people	
IEC's experience with EFS	1= None/poor 3= modest 9= multiple reviews/year	
Volume of procedure /month	1= <3/months (low) 3= 8-12/months (medium) 9=> 12/months (high)	
Proximity of the site (travel time) to sponsor	1= F>4 hours (poor) 3= 2-4 hours (fair)	

Site Selection Criteria	Definition for criteria's score	Score
	9=<2 hours	
Notoriety of the site	1=Limited 3=Fair 9=Prestigious (High)	
Record for Site Start-up time	1=>6months 3=4-6months 9=<4months	

12. In your opinion, which areas need improvement in your country (IEC approval, NCA approval, budgeting, contract signing, patient recruitment)? Kindly provide reasons for your selection.

12.1. *What are your suggestions or ideas for improvement in these areas?*

13. What other obstacles to conducting an EFS/FIH have you encountered that haven't been addressed in this questionnaire?

14. Please describe the gaps and challenges the NCAs have in your country to review an EFS and/or FIH.

14.1. *Please describe how you interact with your NCA. Do you contact the NCA before each study?*

15. Please describe the gaps and challenges the IECs have in your country to review an EFS and/or FIH.

15.1. *Please describe how you interact with your IEC. Do you contact the IEC before each study?*

16. In your experience which factors around training and learning curves are key to success in EFS and/or FIH studies?

17. In relation to learning curves, are there any previous studies where your hospital has experienced these to be more challenging than others, are there specific technologies or ways in which the training has been done that have or could have affected this?

18. Do you wish to make any additional comment?

9.1.6 Detailed description of the results from Task 3.1.4 Clinical Sites questionnaires

9.1.6.1 Investigators

Investigators' attributes

In this section no distinction is made between clinical expertise and technical expertise.

- Organizational skills, empathy towards patients, dedicated to innovation, patient safety commitment, and adaptability are valued, as these align with the clinical investigation CI's objectives and ethical considerations.
- Investigators must provide feedback to sponsors on device functionality, underscoring a collaborative approach (D).

Learning curve and training

The learning curve varies based on the complexity of the device, the procedure, and the investigator's experience. Training plays a pivotal role in preparing investigators for initial interventions. Key considerations include:

- **Training methods:** Simulators, procedural videos, hands-on practice, and pre-clinical work (e.g., animal or cadaver models) are valuable tools for building readiness and confidence (A, B, D).
- **Sponsor involvement**: Sponsors often provide tailored training resources to enhance investigator preparedness (B).
- **Experienced clinicians:** Their familiarity with similar devices helps optimize outcomes and facilitates team mentoring, overcoming learning curve challenges. This not only refers to principal or key investigators in the sites. The site must be willing to overcome the training curve before to enter into real evaluation(B).
- **Proctors[2] and clinical specialists:** When talking about the training curves, their guidance is highly beneficial, although selecting proctors with both technical and clinical expertise can be challenging (D).

Some sites prefer investigators with extensive experience who require minimal additional training, particularly for breakthrough devices (D). Others prioritize adaptability and preparation over predefined qualifications (B).

Diverging Views on Investigator Profiles: (D)

a. Key Opinion Leaders (KOLs):

- One site (D) cautions against using KOLs, citing their often lack of hands-on involvement and operational focus.
- Others value KOLs if they are dedicated and operationally engaged.

b. Standardization vs. Flexibility on required qualifications:

Further internal divergence exists within one clinical site (D) concerning standardized qualifications versus situational flexibility.

- Some advocate for specific certifications or predefined criteria.
- Others emphasize overall aptitude, adaptability, and site capabilities.

9.1.6.2 Contract Research Organizations (CROs)

Process for selecting and qualifying Clinical Research Organization (CROs)

A **focus on practical and personal experience** as criteria to select a CRO for conducting a study is observed in two clinical sites (B and D), contrasting with hospital A adopting a **highly structured and formalized approach** based on internal procedures and documented audits. The importance of **experience in research** and **experience in early-stage clinical investigation CIs** is emphasized in most clinical sites too.

Two clinical sites (B and D) stressed the **lack** of CROs' **familiarity with European regulations** for Medical Devices regarding EFS and the importance of **training** of the CROs (e.g., ICH-GCPs, management of clinical investigation CIs, patient monitoring, ISO14155, etc.).

Only one country (A) mentioned the existence of **a minimum set of requirements for CROs**.

Lastly, it is extracted from another clinical site (D) some **factors** that ought to be considered when selecting a CRO:

- **Resource Availability:** CROs based in hospitals with a high volume of clinical investigation CIs tend to have more resources.
- **Regulatory Department:** The presence of an in-house regulatory department is considered advantageous.
- **Site Selection Expertise:** CROs have demonstrated experience in site screening and the ability to provide feedback about site adequacy.

- **Project Volume:** CROs manage a substantial number of projects in the clinical area, showcasing its capacity and expertise.
- **Professional Experience:** CROs have documented evidence of staff training and professional experience.
- **Monitoring Capabilities:** CROs can demonstrate the expertise and resources of the monitoring team.

Importance of specific expertise in the clinical area and/or in EFS

All clinical sites agreed that **experience in the clinical area relevant to the study** is critical for the selection of the CROs.

One clinical site (D) specifies that while direct experience with EFS is not mandatory, expertise in the **relevant clinical field** is essential.

Experience with medical devices in early feasibility studies (EFS) can be **complemented** by exposure to **more advanced stages of clinical investigation CIs**, such as pivotal or post-market clinical investigation CIs **involving medical devices**. Alternatively, relevant experience may also come from **early-phase studies** (phase I or II clinical trials) **with drugs**, provided that it is supported by a strong background in clinical investigation CI with medical devices.

Desired or missing roles in the CROs

The role of the Principal Investigator is to also ensure the sufficient number of investigators to take care of the number of patients requested for the study. Several professional unmet needs in internal CROs in the hospitals are highlighted, although variations on missing profiles exist across clinical sites:

- Clinical site A - **Research Nurses**: Dedicated research nurses exclusively assigned to EFS.
- Clinical site B - **Statistical Services**: Greater accessibility to statistical support services
- Clinical site B - **Project Managers**: A need for project managers with expertise in **medical devices** and **regulatory knowledge**
- Clinical site D - **Specialized Profiles**: Including experts in:
  - Big Data and AI (depending on study demand).
  - Biomedical engineering for clinical trial management.
  - Regulatory matters regarding clinical investigation CI with medical devices.
- Clinical site D - **Medical Expertise**: A stronger presence of medical professionals within CRO teams.

Quality requirements for CROs

Extracted from one of the hospital's procedures as supplementary information, here is a minimum set of requirements that might be presented as a quality criteria applied to evaluate a CRO. These criteria include:

- **General information:** a short description of the company.
- **Quality management system:** to have a description of the role and responsibilities of the Quality Assurance department.
- **Personnel:** organizational chart with the job description of the involved functions on the study (project manager, data manager, biostatistician, quality assurance, technical roles).
- **IT resources:** asking the list of computerized systems used in the clinical investigation CI activities (Clinical Trial Management System, eCRF usability, Statistical packages, IVRS/IWRS, ePRO, others) and/or used in laboratory activities (e.g. LIMs, systems to report results, etc.), and its datasheet.
- **Project management:** how the CRO defines, establishes, and allocates all project related duties and functions, before initiating a project.
- **Biostatistics:** a description of the methodology for developing the Statistical Plan, or Standard Operating Procedures (SOPs) if available.
- **Other information:** e.g. description of documents retention.

9.1.6.3 National References from clinical sites and expertise questionnaire responses

1. Ministerial Decree of November 15, 2011 (Italy) - Definition of the minimum requirements for contract research organizations (CROs) in the context of clinical trials of medicinal products.
2. DECREE 406/2006, of October 24, 2006 (Catalonia, Spain) - Requirements and procedure for the accreditation of clinical research ethics committees.
3. Legislation for medical devices (Denmark) - List of acts, executive orders, regulations and circulars applicable in Denmark.
4. Indagini cliniche con dispositivi non marcati CE (Italy) - Information about CI of non-CE marked medical devices.
5. CI of medical devices (Denmark) - Information about CI of medical devices and how to apply for authorization of a CI.
6. Arrêté du 29 septembre 2010 fixant les conditions d'aménagement, d'équipement, d'entretien et de fonctionnement ainsi que les qualifications nécessaires du personnel intervenant dans les lieux de recherches biomédicales devant faire l'objet d'une autorisation selon l'article L. 1121-13 du code de la santé publique - Légifrance - Conditions that the clinical site and teams involved in medical research must meet. Describe the responsibilities of the research site manager, specifically the principal investigator.
7. Arrêté du 12 mai 2009 fixant les conditions mentionnées à l'article R. 1121-11 devant figurer dans la demande d'autorisation des lieux de recherches biomédicales prévues

à l'article L. 1121-13 du code de la santé publique - Légifrance - List of details that must be included in the application for site authorization.

8. Article L1123-7 - Code de la santé publique - Légifrance - Criteria on which the French IEC (CPP: Committee for the Protection of Persons) bases its opinion.
9. Article R1123-4 - Code de la santé publique - Légifrance - Composition of the French IECs
10. modele-anglais_convention-coordonnateur_version-20220409.docx Template of the sole agreement for contract signing
11. Bonnes Pratiques Cliniques (BPC) • GIRCI IDF Link to the ICH-GCP training provided by GIRCI for the PI to renew their certificate.

9.1.6.4 Overview of PAG workshops questionnaires

Table 13 Overview of questions discussed with the PAG in the focus groups.

Topic	Questions involved
Eligibility criteria for technologies	Focus groups 5/12/2024 Imagine you are considering participating in an EFS. Remember that the device design is not yet final in an EFS because EFS can help finalise the design. • How would the type of device studied in an EFS influence your decision to participate o invasive implanted device vs. non/less invasive digital health device, o Device at a very early stage of development, o risks vs. benefits of device, o possible side effects o unknown risks Focus group **20/1/2025** Areas of Focus: • Anatomical Understanding o Extend learnings from pre-clinical testing/knowledge • New/Expanded Intended Uses o Utilization of a device approved for one patient population on a new population • Unmet need/Breakthrough o Introduction of new technology to a new patient population Questions: • Does the knowledge that the device being evaluated within the EFS is still being finalized, and you would be one of the first

Topic	Questions involved
	patients worldwide to receive the device, influence your willingness to participate in the EFS? • What number of previously treated patients would make you feel more comfortable with being treated with an early-stage device that is still being finalized? • What information regarding the technology (provided by the sponsor via the Patient Information Sheet) would assist in making the decision to participate in an EFS?
Eligibility criteria for unmet needs, medical conditions and disease severity of target patient population	**F**ocus group **5/12/2024** Imagine a sponsor needs to select the population for an EFS of a new, unfinalized device they've developed. To guide patient selection, they're using the checklist we created. From your perspective as a patient: • Are there any additional points not included in the checklist you believe the sponsor may consider to make a more informed, patient-centred decision? How can we improve the checklist? • Are there any criteria that you think are not essential or unclear? • Are there any concerns that you want to share based on your experience?
Level of evidence required to start an EFS	Focus groups **5/12/2024** Different types of evidence will be generated before starting an EFS, with testing of for example: • Device materials • Mechanical functioning of device • Electrical components and software • Biocompatibility • In vivo (animal studies) • In silico (computer simulations) • Shelf-life / Stability • Sterility With the list above in mind: • What kind of evidence should be generated before an EFS is initiated? Is anything missing? • What evidence would help you decide on participating in an EFS? Focus group **20/1/2025** Areas of Focus: • Building on the General Safety and Performance Requirements

Topic	Questions involved
	• Benefit-Risk Analysis must be positive as far as possible Questions: • Manufacturers will test to a more limited extent, if they see for example anatomy or physiology needs to be tested in patient, first in human testing will then answer many questions, how do you feel about this? • Often testing of other devices is leveraged in the USA to allow the EFS to be started, how should this be explained to the patients?
Eligibility criteria for clinical sites	Focus group **5/12/2024** Imagine you are considering participating in an EFS. • What is important to you when thinking about the hospital where the EFS will take place? • infrastructure, • equipment, • procedures, • access, • transport, • available support, • emergency support • etc. Focus group **20/1/2025** Imagine you are considering participating in an EFS. • What characteristics do you consider most important in a clinical site to feel safe participating in a clinical trial with medical devices? • How important is it for you that the clinical site has specific facilities (e.g., comfortable waiting areas, advanced technology)? • What concerns or barriers about the clinical site might make you hesitate to participate in an EFS (e.g., access to emergency care, regular check-ins, mental health support)? • What do you think a clinical site should have to ensure your well-being during a clinical trial? • What practical factors (such as location, consultation hours, availability of transportation) would influence your decision to participate in a clinical trial?
Eligibility criteria for clinical expertise	Focus group **5/12/2024** Imagine you are considering participating in an EFS.

Topic	Questions involved
	• What would you like to know about the investigation team/researchers who conduct the EFS? · their skills, · prior experience, · conflicts of interest, · usability - handling · learning curve of investigator with the device · sponsor checklist · etc. Focus group **20/1/2025** Imagine you are considering participating in an EFS. • What do you expect from the medical and research staff in terms of communication, empathy, and follow-up during a clinical trial (e.g., timely updates, clear explanations of procedures, compassionate interactions)?

The Harmonised approach to Early Feasibility Studies for Medical Devices in the European Union (HEU-EFS) project is supported by the Innovative Health Initiative Joint Undertaking (JU) under grant agreement No 101112185. The JU receives support from the European Union's Horizon Europe research and innovation programme and life science industries represented by MedTech Europe, COCIR, EFPIA, Vaccines Europe and EuropaBio.