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 3.2

HEU-EFS methodological framework

Co-funded by the European Union

Disclaimer:

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ABBREVIATIONS

AI	Artificial Intelligence
ARMS	Administer and/or Remove Medicinal Products
CE	Conformité Européenne
CECP	Clinical Evaluation Consultation Procedure under MDR
CI	Clinical Investigation
CIP	Clinical Investigation Plan
CIPS	Coordinated Assessment for Clinical Investigations and Performance Studies - Coordinated Assessment – MDR
CS	Common Specifications of MDR
DHT	Digital Health Technologies
EC	European Commission
EFS	Early Feasibility Studies
EMA	European Medicines Agency
EPF	European Patients Forum
EU	European Union
EUDAMED	European Database for Medical Devices - MDR
ExP	MDR Expert Panel at EMA
FDA	Food and Drug Administration
FDA EFS Program	FDA Early Feasibility Program
GSPR	General Safety and Perform Requirements, MDR
HEU-EFS	Harmonized Approach to Early Feasibility Studies for Medical Devices in the European Union
HTA	Health Technology Assessment
HTACG	Health Technology Assessment Coordination Group
HTAR	Health Technology Assessment Regulation (EU) 2021/2282
HTD	Health Technology Developer (party who plans to bring a health technology to market)
ICF	Informed Consent Form
IDE	Investigational Device Exemption with the FDA
IEC	Independent Ethics Committees
ISO	International Organization for Standardization
IVDR	In Vitro Diagnostic Regulation (EU) 2017/746

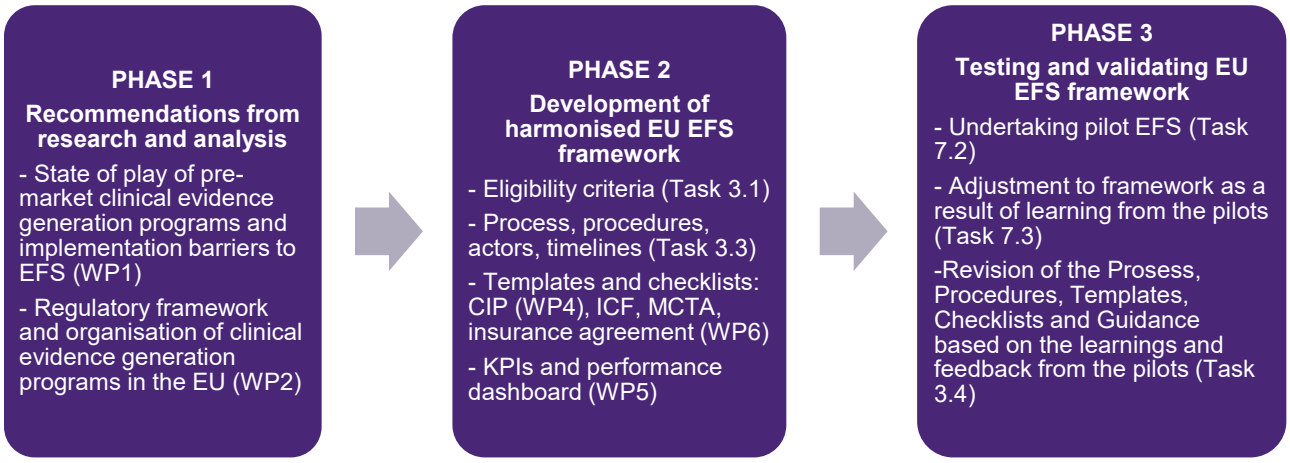
JCA	Joint Clinical Assessments under HTAR (EU) 2021/2282
JSC	Joint Scientific Consultation under HTAR (EU) 2021/2282
KPI	Key Performance Indicator
MCTA	Master Clinical trial Agreement
MD	Medical Device
MDD	Medical Device Directive
MDCG	Medical Device Coordination Group
MDCG guidance	Medical Device Coordination Group (MDCG) guidance (EU) 2017/745
MDR	Medical Device Regulation
NCA	National Competent Authority
NB	Notified Body
PAG	Patient Advisory Group
PECP	Performance Evaluation Consultation Procedure under IVDR
PMCF	Post-Market Clinical Follow-up Studies
SME	Small and Medium Enterprise

EXECUTIVE SUMMARY

The 'Harmonized Approach to Early Feasibility Studies for Medical Devices in the European Union' (HEU-EFS) project aims to develop a robust, widely applicable, and harmonized framework for Early Feasibility Studies (EFS) of medical devices (MDs)—including digital health technologies (DHTs)—within the European Union (EU). This framework is designed to be fully aligned with the Medical Device Regulation (MDR), looking at synergies with processes defined in the Health Technology Assessment Regulation (HTAR), and for DHTs specifically looking at the interplay between the Artificial Intelligence (AI) Act and MDR To update the framework after the pilots.

The HEU-EFS project is structured into three main phases, and this deliverable is part of Phase 2, as shown in Figure 1.

Figure 1: Main phases of the HEU-EFS project



PHASE 1

The first phase sought to **understand the current state of play** and **lay a solid foundation for the recommendations and process proposals for a harmonised EFS in the EU**, built upon a comprehensive understanding of the regulatory framework and international standards applicable to clinical investigations (CIs) of MDs. It also involved an in-depth analysis of the current pre-market CI pathways, examining their strengths, weaknesses, and opportunities.¨, as well as the organisational characteristics of National Competent Authorities (NCAs).

The findings confirmed the major challenge - the absence of a structured pathway dedicated to conducting EFS and un-harmonised evaluation criteria across NCAs. Applications for EFS currently, fall under Article 70 of the MDR, which outlines steps, timelines, and responsibilities for CI applications but treats all CIs uniformly, without distinguishing between study types (e.g., first-in-human, EFS,

pivotal studies). This lack of differentiation results in an unclear and inconsistent regulatory environment across EU Member States (MSs), with no dedicated EFS process and guidance, eligibility criteria, or templates. Consequently, sponsors face increased administrative burdens, lengthy processes, and reduced predictability and transparency in the authorisation process—hampering EFS as a valuable mechanism for early clinical evidence generation within the EU.

The absence of standardised guidance and templates for key EFS documents—such as the Clinical Investigation Plan (CIP), Informed Consent Form (ICF), Investigator's Brochure (IB), and Master Clinical Trial Agreement (MCTA), which further contributes to inefficiencies, ambiguous, and delays especially for start-ups / SMEs. As a result, NCAs often receive incomplete or low-quality applications, which prolong authorisation timelines for innovative MDs. Sponsors are therefore required to navigate a fragmented system where national processes vary significantly, creating unpredictability, confusion and inefficiencies in regulatory and development strategies, which may impact assessment and access strategies further down the line.

The research found that early regulatory dialogue may benefit both sponsors and regulators by ensuring that clinical evidence generation strategies meet expectations and by facilitating discussions on potential challenges. In the EU, regulatory advice mechanisms exist in part—through processes such as Scientific Advice from the EMA Expert Panels under MDR, Early Dialogue with NCAs, Structured Dialogue with Notified Bodies (NB) and Joint Scientific Consultations (JSCs), but there is no unified advisory structure comparable to the U.S. FDA's Q-Submission program or US EFS Program. That program provides a structured pre-submission pathway enabling sponsors to seek feedback on key development aspects (e.g., biocompatibility, bench testing, cybersecurity) before conducting an EFS.

In contrast, the EU lacks a centralised advisory system offering guidance at key stages of the CI process. While some NCAs provide pre-submission or innovation meetings, their format and consistency vary widely, ranging from informal exchanges via email to formal paid 'scientific advice' sessions requiring specific applications. However, these are not integrated into a coherent or structured framework.

Establishing Early Dialogue between sponsors and NCAs both prior to and during EFS is crucial to enhance study design, improve the quality of clinical evidence, prevent delays, shorten time to place on the market, and reduce unnecessary testing costs. It also fosters trust, transparency, and alignment between sponsors and regulators, ultimately accelerating EFS timelines and improving the quality of clinical evidence.

The involvement of patient advisory groups, patient associations, Expert Panels, and HTA bodies in MD development remains limited, despite their potential to enhance usability, accessibility, and

alignment with patient and societal needs. The systematic engagement of patients could improve study design, clinical relevance, and the potential for market uptake and reimbursement, yet such integration is still rare across Europe's pre-market CI pathways.

In summary, four key recommendations emerged to strengthen the EU EFS framework:

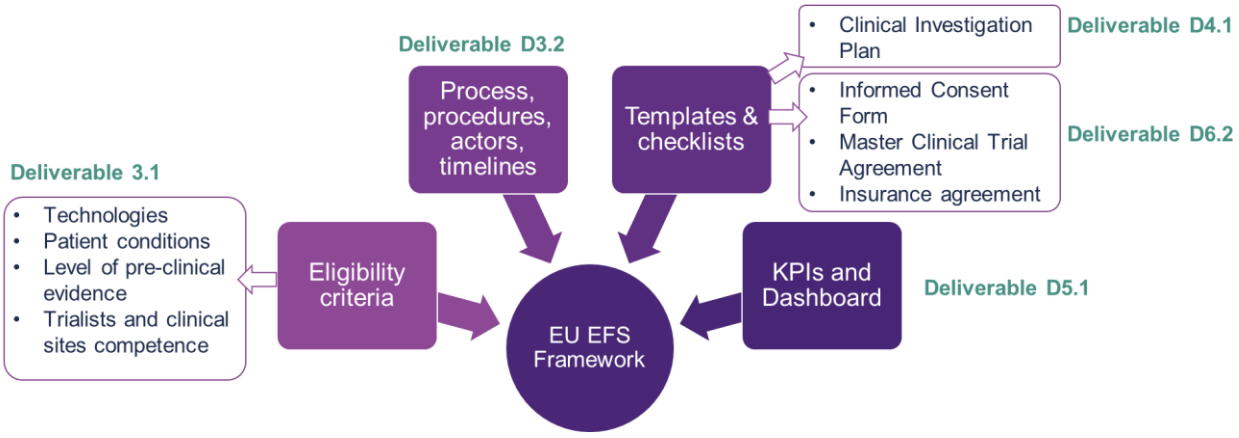
1. **Harmonise application and assessment procedures** for pre-market CIs across Member States to ensure consistency, timing efficiency, transparency, and predictability.
2. **Establish a structured and continuous regulatory dialogue** between sponsors and NCAs to enable early and iterative interactions throughout the EFS lifecycle.
3. **Promote systematic stakeholder involvement**, particularly of patients, Expert Panels, and HTA bodies, to enhance study relevance and real-world alignment.
4. **Integrate DHT-specific considerations** within the EU EFS programme.

PHASE 2

Building on these recommendations, Phase 2 focused on developing a harmonised framework for EFS, consisting of four key components (Figure 2):

1. **Eligibility criteria** defining the characteristics of the MDs (including DHTs) proposed to undergo an EFS, medical conditions and populations to be included in an EFS, the level of pre-clinical evidence necessary to start an EFS, and the requirements for clinical sites and clinical expertise needed to conduct an EFS. **Processes, procedures, actors, and timelines** governing EFS submissions—outlining the steps for submission to NCAs, the roles of stakeholders, and defined timeframes for each phase with the objective to accelerate evaluations, taking inspiration from the mapping of the current pathways available that can aide in the EFS CI process.
2. **Harmonized templates and checklists** for key documents (CIP, ICF, MCTA, Insurance Agreement) to streamline EFS submissions and facilitate the preparation of high-quality applications, thus improving process efficiency.
3. **An European EFS Dashboard** collecting data and key performance indicators (KPIs) for all EFS conducted in the EU/EEA, to monitor performance, evaluate impact, and provide feedback to regulators and policymakers—enhancing EU competitiveness and attractiveness for clinical research investment, particularly for SMEs, spin-offs, and start-ups.

Figure 2 The EU EFS framework components



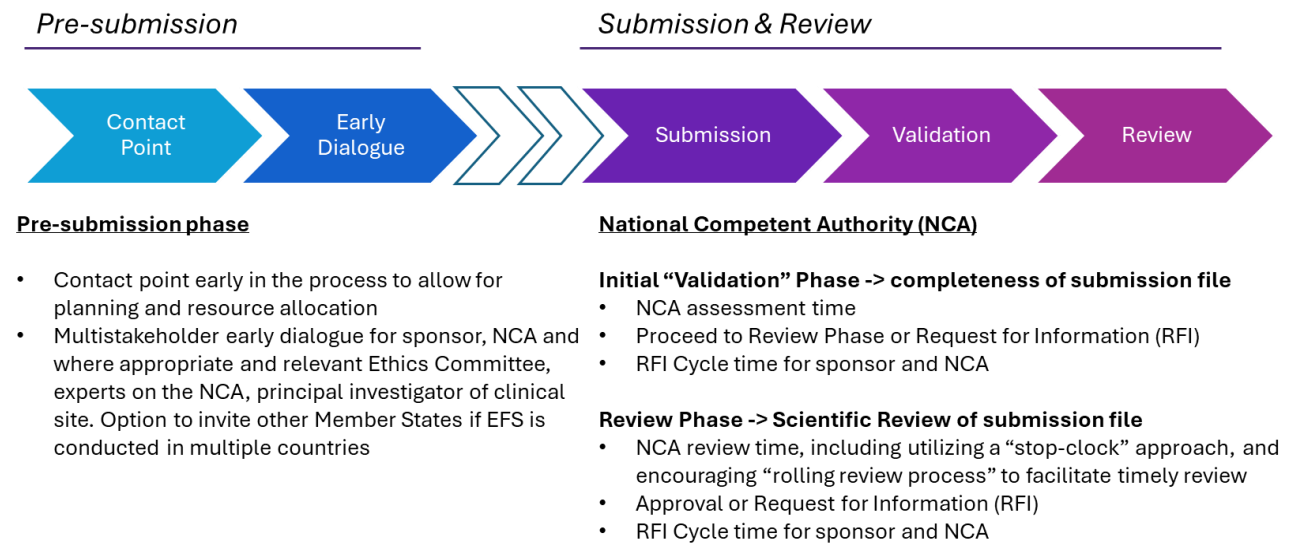
This deliverable outlines the proposed process for EFS in the Europe. Where the proposal aims to:

- Enhance readiness and efficiency among all key actors—both NCAs, ethics committees and EFS sponsors.
- Improve resource allocation, timing, and planning while clarifying EFS objectives and potential challenges.
- Facilitate EFS involving investigational sites across multiple Member States.
- Strengthen early clinical evidence generation in the EU, expanding patient access to innovative solutions while upholding safety principles.

The proposed process is built on three key principles: **early dialogue**, **strengthened coordination**, and **timing efficiency**. Figure 13 illustrates the proposed EU-EFS process, which will be tested in the pilot use-cases. The process comprises three sequential steps:

1. Notification of a Contact Point and Early dialogue during the pre-submission phase;
2. Validation - Completeness check of the Submission
3. Review of the submission.

Figure 3: Overview of the proposed EU EFS process (to be tested in pilots)



PHASE 3

The final phase of the HEU-EFS project, is the testing and validating of the proposed framework in the pilots, from which feedback will be gathered (WP7). Insights and outcomes from the pilots will then be consolidated into all work packages to develop a comprehensive final guidance, revised process, templates, checklists for a harmonized EU EFS Program representing the ultimate deliverable of the project D3.4.

1. Introduction

Within the 'Harmonized Approach to Early Feasibility Studies for Medical Devices in the European Union' (HEU-EFS) project, Work Package 3 (WP3) *Methodology Development: Rationale, Processes, and Procedures* aims to develop a robust, widely applicable, harmonised framework for Early Feasibility Studies (EFS) for medical devices (MDs), including digital health technologies (DHTs) in the EU, fully aligned with the Medical Device Regulations (MDR), and identifying the synergies with Health Technology Assessment (HTAR)the Artificial Intelligence (AI) Act.

WP3 has been informed by findings from research and analysis on state of play of pre-market clinical investigations (CIs) approval pathways and implementation barriers to EFS (WP1) and regulatory framework and institutional and organizational characteristics of EU competent authorities (WP2*)*.[1]

In its initial phase, WP3 identified eligibility criteria in terms of characteristics of the MDs (including DHTs) proposed to undergo an EFS, medical conditions and populations to be included in an EFS, the level of pre-clinical evidence necessary to start an EFS, and requirements for clinical sites and clinical expertise needed to conduct an EFS.[2]

As a next step, Task 3.3 described in the present deliverable, has developed the process, procedures, actors, and timelines of EFS submission. Specifically, this includes outlining the steps required for submission to national competent authorities (NCAs), identifying the stakeholders involved and their respective roles, and establishing the timelines for each phase of the process.

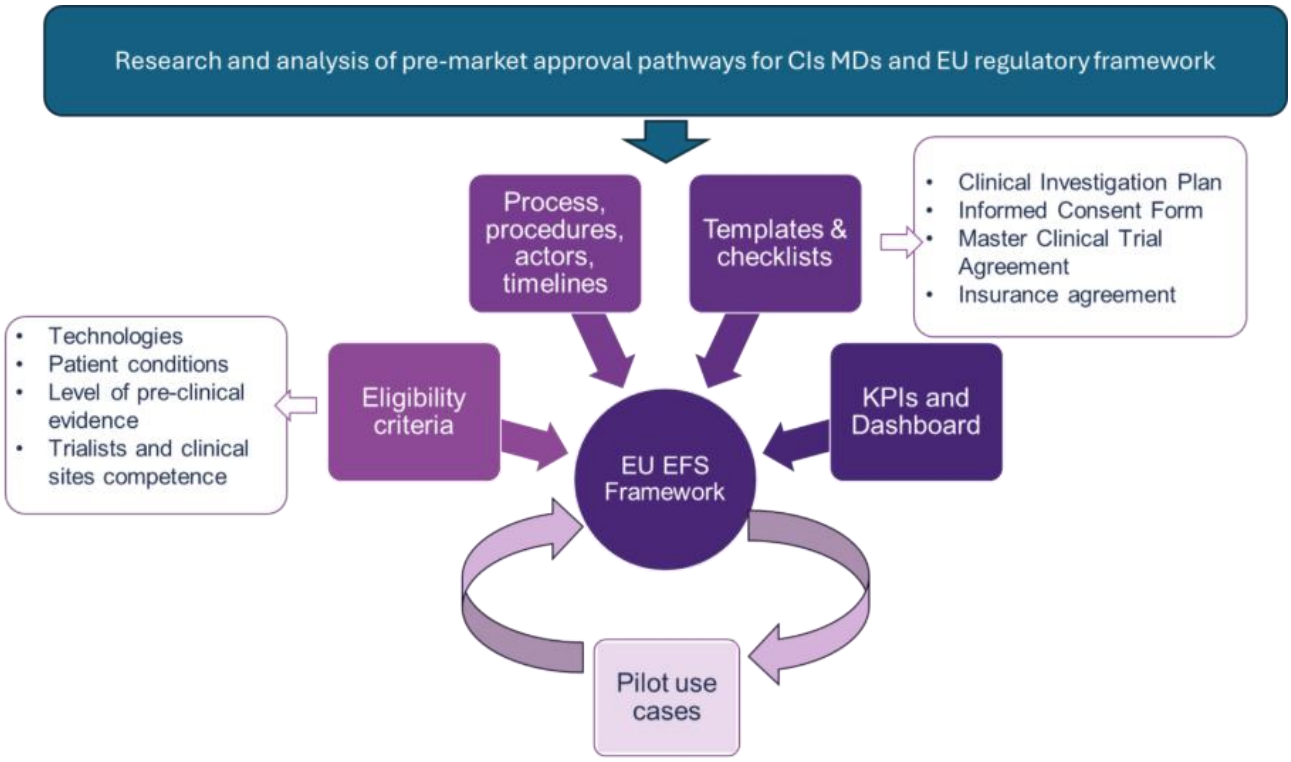
The task builds upon the recommendations from WP1 and WP2, which called for harmonising applications and assessments for EFS, establishing a standardised EU regulatory dialogue and collaborative engagement process, implementing a structured stakeholder involvement, and will in the next phase also include a structured EFS process for DHTs.

The process, procedures, and timelines, along with the eligibility criteria, are key elements of the EU EFS framework (Figure 4). This framework also includes harmonised templates and checklists for the Clinical Investigation Plan (CIP), Informed Consent Form (ICF), Master Clinical Trial Agreement (MCTA), Insurance Agreement, and key performance indicators (KPIs) to monitor the performance of EFS developed in the other WPs. The next stage of the HEU-EFS project is the testing and validating of the proposed framework in the pilots (WP7). feedback will be gathered from the pilot use cases for the implementation of the methodology (WP7). This will help validate the framework and provide recommendations for adjustments. Where the insights and outcomes will be consolidated into all work

[1] The deliverables of WP1 and WP2 are available from https://heuefs.eu/reports/
[2] Deliverable D3.1 Eligibility criteria and patient contribution to EFS https://heuefs.eu/reports/.

packages to develop a comprehensive final guidance, revised process, templates, checklists for a harmonized EU EFS Program, the final deliverable of the project D3.4.

Figure 4: The EU EFS framework components



WP3 is distinguished by its inclusive approach, involving all the stakeholders of the consortium, including HTA bodies, patient associations, clinical sites, clinicians, academic institutions, health technology developers (large to SMEs, including also digital developers), and CROs, as well as members of the external Advisory Board (e.g., NCAs, national ethics committees) and the Patient Advisory Group (PAG). Their active contributions have been essential to ensure the methodology's broad applicability.

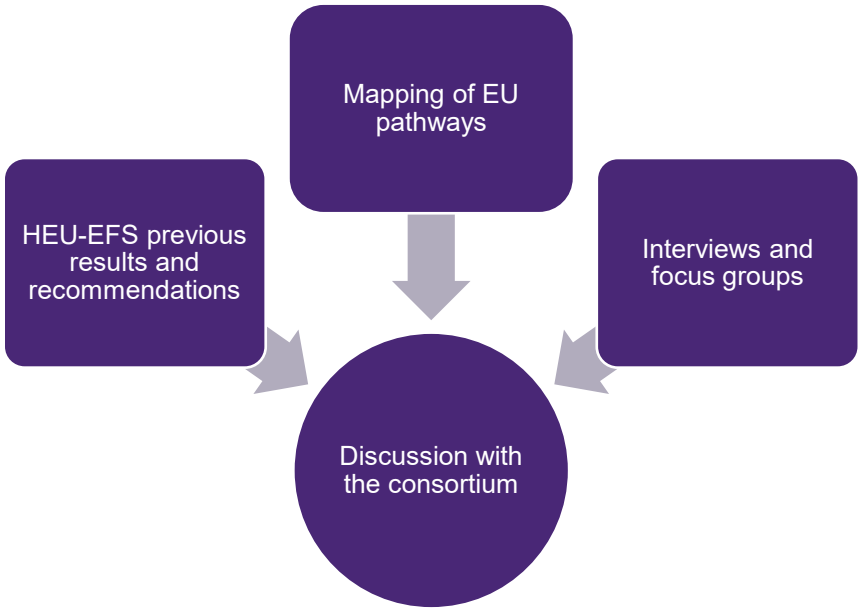
This report presents the proposed process for EFS, which will be tested and validated through pilot-use cases and subsequently refined based on the feedback collected during their implementation. Section 2 describes the methodology applied. The subsequent sections the results are presented in detail: Section 3 summarises the scope and characteristics of existing regulatory pathways in the EU investigated to identify areas of alignment and potential synergies with the proposed framework; Section 4 presents the outcomes of interviews and focus groups conducted with key stakeholders; and Section 5 provides a synopsis of the proposed EFS process in the EU. Finally, Section 6 outlines the future development and optimisation of the EU EFS framework, including its alignment with evolving EU regulatory initiatives, its adaptation to DHTs, and the preparation of the final Guidance document (D3.3).

2. Methods

To support the development of a sound, widely applicable, and harmonised framework for EFS in the EU, a structured approach, based on three key components was adopted (Figure 5):

1. Consideration of the recommendations resulting from the research and analysis activities conducted on the current state of play of pre-market programs, including EFS, barriers to the conduction of pre-market CIs, regulatory framework, and institutional and organizational characteristics of EU competent authorities,[3] and eligibility criteria for EFS in the EU regarding technologies, medical conditions and populations, preclinical evidence, requirements for clinical sites and clinical expertise developed during the initial phases of the project.[4]
2. Analysis of existing key regulatory pathways for medical devices in Europe (e.g., scientific advice from Expert Panels, early dialogue, pilot coordinated assessment), to identify areas of alignment and synergies to inspire the development of the proposed framework.
3. Engagement with both consortium partners (i.e., health technology developers—including SMEs—and clinical sites), NCAs, and PAG representatives through interviews and focus groups.

Figure 5: Key components of the method adopted to develop the framework for EU EFS



[3] The recommendations derived from the research and analysis activities are presented in Deliverable D2.3 *Recommendations for HEU-EFS on the current state of play of pre-market programs and EFS, of the regulatory framework, and of the institutional and organizational characteristics of EU competent authorities* (LINK).
[4] Eligibility criteria for EFS are described in Deliverable 3.1 *Eligibility criteria for EFS* (LINK).

Building on the outcomes of these methodological steps, a proposed process was formulated. The proposal was subsequently discussed extensively among the co-authors of this deliverable, as well as with the entire consortium, the AB and the PAG during dedicated online meetings and the second-year consortium meeting.

2.1. Recommendations from the HEU-EFS Project

The research and analysis phase yielded three main recommendations, detailed in Deliverable 2.3[5], that served as the foundation for the development of the framework:

(i) **Develop a harmonised process for EFS applications across EU countries** to enhance the efficiency and predictability of EFS, reduce administrative burden, and minimise delays arising from procedural variabilities.

(ii) **Establish the foundation for a harmonised and standardised EU-level dialogue and collaborative engagement process**, including a clear procedure for seeking regulatory guidance. This should outline the various regulatory interactions required before and during an EFS—such as preliminary guidance on regulatory pathways, protocol design guidance, pre-submission advice, and ongoing dialogue throughout the EFS to discuss any necessary amendments.

(iii) **Implement a structured stakeholder engagement approach**, involving NCAs, patients and their associations, Expert Panels, and HTA bodies, starting from the early stages of development.

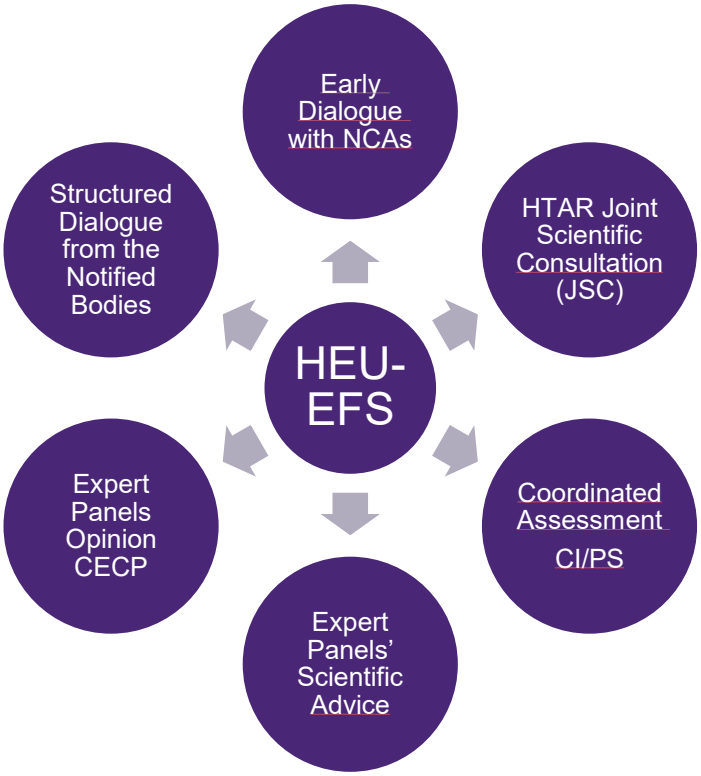
In addition, a key general recommendation was to **ensure that the EU EFS program adequately incorporates DHT-specific needs**. Since the framework is expected to be tested only in“traditional” MDs pilots, the version developed so far does not include spcifics for DHT. Deliverable D3.3 *EU EFS Program Final Guidance*, which contains the final guidance on the program rationale, process, procedures, actors, timelines, and templates, will be updated to also incorporate DHT-related aspects.

[5] Recommendations for HEU-EFS on state of play of regulatory framework and institutional and organizational characteristics of EU competent authorities

2.2. Analysis of Existing Regulatory Pathways in the European Union

To map existing regulatory pathways for medical devices in the EU which may serve as a valuable source of inspiration, we leveraged findings from the scoping literature and regulatory mapping undertaken in WP1 and WP2, complemented by an in-depth review of the MDR and HTAR, and the Medical Device Coordination Group (MDCG) guidance, the HTAR guidance and other area-specific sources. Figure 6 shows the pathways analysed.

Figure 6: Pathways currently available within the European regulatory landscape for advice and clinical evidence generation



2.3. Focus groups and interviews with stakeholders

Engagement activities targeted a range of stakeholder categories, including NCAs, small and large Health Technology Developers, clinical sites, and PAG members.

2.3.1. Interviews with NCAs

The research team developed a questionnaire — approved by the Bocconi University Ethics Committee (EA000947) — designed to explore NCAs' experience with EFS-like studies[6] and gather their perspectives on the characteristics of a harmonised EFS approval process in the EU. Topics discussed included:

(1) Experiences with EFS-like studies;
(2) Dialogue between NCAs and sponsors for EFS;
(3) Challenges to and opportunities for harmonisation;
(4) Efficiency of EFS applications evaluation; and
(5) Ethical approval.

The full interview protocol containing the interview questions can be found in the Appendix 9.1. To ensure transparency, the questions were shared with interviewees ahead of the interviews.

Subsequently, 21 EU NCAs and one EEA NCA with experience in EFS-like studies were identified through queries of the EFS Database developed under Deliverable 1.3 *Characteristics and State of Play of EFS*. The identified NCAs where contacted with the support of the Chairs of the Clinical Investigation and Evaluation Working Group and invited to participate in the interviews. To maximise participation, non-responding NCAs were followed up with reminders and, where possible, approached through personal contacts of consortium members.

In total, eight NCAs (i.e., Austria, Belgium, Czech Republic, France, Ireland, Italy, Norway, Portugal) were interviewed. Two NCAs (i.e., Italy, Norway) participated in a pilot phase, which was used to test and refine the interview protocol. This phase included an online focus group with five representatives from one NCA and an in-person focus group with two representatives from another NCA. Insights from the pilot did not lead to significant changes in the interview guide. This guide was then applied in five subsequent online focus groups and one individual interview with representatives from six different NCAs (two participants per focus group session, and one participant in the individual

[6] EFS-like was defined as a study having the terms «early feasibility» or «EFS» in the title or summary of the study or a study being a pre-market clinical investigation (e.g., early feasibility, proof of concept, first in human) of medical devices or drug-device combinations and having the following features: 1) Study type: Interventional; 2) Estimated sample size: <= 30; 3) Interventional mode: single group assignment; 4) Masking: None (Open label). Please see *D1.3 Characteristics and state of play of EFS* for additional details (LINK).

interview; n=11). Each country participated in a separate session. Focus groups and the interview lasted approximately 90 minutes and were recorded and transcribed using Microsoft Teams, with the consent of the interviewees. Thematic analysis was conducted using deductive coding based on the interview topics and questions.

In addition, NCAs practices that were described during the interviews and that we believed could be potential “best practices” for EFS were identified, drawn, and reported.

2.3.2. Focus Groups with Consortium Health Technology Developers

Two focus groups were conducted with HTDs, members of the consortium: one with large companies (n=5 companies) and one with SMEs (Small to Medium Enterprises) (n=3 companies). The topics discussed in both focus groups included:

(1) Interactions with NCAs and Experiences with EFS-like studies;
(2) Timelines;
(3) Iterative Approach and modifications during EFS;
    (3a) Interactions Around Amendments to EFS,
(4) Harmonisation of a Future EU EFS;
(5) Interactions with Ethics Committees; and
(6) Interactions with other EU Bodies and Specialised Validation Teams, Pilot Coordinated Assessment, European Medicines Agency (EMA) Expert Panel.

Focus groups lasted approximately 90 minutes and were recorded and transcribed via Microsoft Teams, with the consent of the interviewees. The information collected was analysed using thematic analysis with deductive coding based on interview topics and questions.

In addition, private consortium partners, including those proposing pilot use-cases (n=3) were regularly consulted throughout the development phase of the proposed process, Section 5.

2.3.3. Focus Groups with Consortium Hospital Partners

A focus group was conducted with the Consortium Hospital Partners (n=4 Hospitals). The topics discussed included:

(1) Experiences with EFS-like studies;
(2) Sponsors of EFS;
(3) Training provided by Sponsors for Sites Undertaking EFS;
(4) Phased enrolment to EFS;
(5) Iterative Approach and modifications during EFS;
(6) Harmonisation of a Future EU EFS;

(7) Interactions with NCAs and Ethics Committees; and
(8) Interactions with other EU Bodies and Specialised Validation Teams.

Focus groups lasted approximately 90 minutes and were recorded and transcribed via Microsoft Teams with the consent of the interviewees. The information collected was analysed using thematic analysis using deductive coding based on interview topics and questions.

2.3.4. Focus Groups with PAG members

During the annual meeting, immediately after the plenary discussions, a Focus group was conducted with the PAG. The PAG members discussed the proposed process with Task 3.3 leaders and co-leaders and one of the Health Technology Developers partner of the project also showed an example of the type of device that has previously undergone an EFS; they also had the benefit of having had the whole framework presented from all the WPs and especially the panel discussions on the proposed process. Their feedback and understanding of the process was collected, and informed some of the adjustments made in the process.

2.4. Proposal of the new process

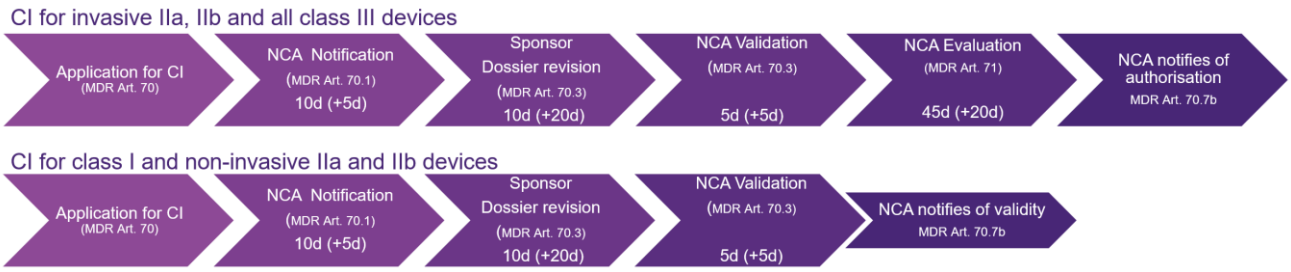
Based on analysis, recommendations from other WPs and the Focus Groups, dedicated Task 3.3 meetings and discussions with Consortium partners, and interviews with NCAs, a newly structured approach for engaging with NCAs and EFS submission process was developed. Consortium members collaborated by sharing best practices to the proposed methodology. During the annual meeting two panel discussions were held; the first to gather input from the NCAs on the AB, and the second with the entire Consortium, the PAG, and the AB.

3. Results of Mapping Existing Regulatory Pathways

3.1. Process for approval of Clinical Investigations including EFS under the MDR

Under the MDR clinical investigations have three distinct stages; firstly exploratory investigations, such as first-in-man studies, feasibility and pilot studies, secondly confirmatory investigations, such as pivotal clinical investigations, and finally post-market studies such as post-market clinical follow-up (PMCF) studies once the device has been placed on the market, CE marked. EFS fall under the exploratory investigations. Clinical investigations of MDs that fall under the MDR are notified or submitted, validated and evaluated in accordance with Art. 70 of the MDR. Within with Art. 70 there are two routes; one for class I and IIa and IIb non-invasive devices, where there is a minimum timeline to start the CI of 15 days, if there are no requests by the MS NCA to the sponsor to revise the dossier, if there are requests then the maximum days will be 55 days. For invasive class IIa, IIb and all class III devices there is an additional evaluation of 45 days (+ 20 days), leading to a minimal timeline of 60 days with a maximum timeline of 120 days, as shown in Figure 7. CIs involving devices that already bear a CE-mark and are conducted within the intended use are outside the scope of the HEU-EFS process.

Figure 7: Application for CIs under Art. 70 of the MDR, the top line showing the procedure for invasive class IIa, class IIb or all class III devices, the lower line for class I, non-invasive class IIa or non-invasive class IIb medical devices.



3.2. Regulatory Map and Guidance and types of regulatory interaction

To develop recommendations for the EU-EFS framework, including accompanying procedures and templates, we conducted a mapping of existing key regulatory processes relevant to medical technologies. The objective of the mapping was to identify potential areas of alignment and synergy of new and well established EU process, specifically in view of the eligibility criteria with the coordinated assessment and the 2025 pilot, Expert Panel opinion, and HTA Joint scientific consultation (JSC). Insights from national experiences, particularly direct advice from NCAs and Structured Dialogue by the Notified Bodies (NBs), were also considered (Table 1). Of note, the direct advice from the NCAs is described in more detail in Section 4.1.2 while the remainder are described in the sections below.

Additionally, the Consortium is aware that the MDCG is currently developing a guidance for Breakthrough Technologies, aiming to define a streamlined and centralised designation process for technologies to ensure timely access to innovative devices that introduce a high degree of novelty with respect to the device technology or the related clinical procedure, that are expected to provide a significant positive clinical impact on patient or public health, for a life-threatening or irreversibly debilitating disease or condition, by either offering a significant positive clinical or health impact compared to available alternatives and the state of the art, or by fulfilling an unmet medical need where there is an absence or insufficient alternatives available for that purpose. In view of this scope, it is believed that these devices are also the type of devices that may require an EFS.

As part of this mapping specific details of the regulatory pathways which could be of relevance to the future EU-EFS framework were identified. An overview of the mapping is shown chronologically, to show what could be relevant before a clinical investigation, during and after, in Table 1 and Table 2. Subsequently a detailed description of the regulatory processes is provided in the following sections.

Table 1: Brief overview of mechanisms currently available for medical device HTDs to obtain early advice on the clinical development strategy for CI.

	Advice prior to Clinical Investigation		
	EMA MDR Expert Panel Scientific Advice	**Joint Scientific Consultation**	**Notified Body Structured Dialogue**
Eligibility for pathway / program	Class IIb active devices (ARMS) Class III devices	• Class III Implantable Devices • Class IIb active devices (ARMS)	• All device classes
Aim	Advice on intended clinical development strategy	• HTDs to obtain scientific consultation during the planning of the clinical investigations for a MD based on the clinical information and evidence that may be needed for a Joint Clinical Assessment (JCA) in the context of the EU HTA Regulation. • The focus of the JSC is for health technology assessments, not clinical evidence needed for conformity assessment.	• For the NB to provide information on the conformity assessment procedure – preapplication and application processes • high-level aspects of manufacturer's evidence for the conformity assessment including: • clinical, technical, and regulatory conformity approaches
Actors	Manufacturer (EU or EU authorized representative) EMA Expert Panel	• HTD submits request • EU Commission transmits • HTA Bodies • EMA Expert Panels • HTD	• HTD should have a contract in place with the Notified Body • Notified Body
Timelines	60 days	• Approx 75 days	• Pre-application • During application • Post-certification
Legal basis	MDR Art. 61.2 MDR	• HTAR Art.16 • HTAR Art. 17	• MDR Annex VII 1.2.9
Fees	No fees in 2025	• No fees	• Not clear, may be included in fees paid as client of Notified Body

	Advice prior to Clinical Investigation		
	EMA MDR Expert Panel Scientific Advice	**Joint Scientific Consultation**	**Notified Body Structured Dialogue**
Process	Voluntary Manufacturer (EU or Authorized Rep) submits request Exploratory meeting – briefing document to EMA – scientific advice (including questions, meeting where needed)	• Voluntary • Option to be in parallel with ExP Sci. Advice and invite NB as observer. • EC facilitates	• Voluntary • Manufacturers request the advice NBs can discuss (non-exhaustive examples): − Project plans − Submission requirements − Requirements for reporting change − Use of guidance, standards and common specifications − Costs and timelines NBs cannot (non-exhaustive examples): − Complete gap analyses − Check for MDR/IVDR readiness − Review mock files for MDR/IVDR conformity − Review clinical development strategy − Provide technical solutions − Explain how the manufacturer should meet specific regulatory requirements
References	EMA Guide to manufacturers on the procedure for requesting advice from Expert Panels on clinical investigations and/or clinical development strategies for high-risk medical devices (2025)	EU Commission HTAR JSC Overview	MDCG 2022-14 BSI Group Structured Dialogue TUV Sud Structured Dialogue Team NB Code of Conduct

Table 2: Brief overview of clinical investigation regulatory pathways currently available to HTDs of medical devices in the EU.

	Application Process for Clinical Investigations			Evaluation during CE Process
	MDR Clinical Investigation in one MS under Art. 70	**Coordinated Assessment (pilot, 2025)**	**Coordinated Assessment (MDR, 2027)**	**Expert Panel Opinion (CECP)**
Eligibility for pathway / program	• All HTDs wanting to conduct a CI	• Investigational Devices Class III, or invasive Class IIa or Class IIb	• Details of the Coordinated Assessment will be finalized after the pilot	• Class III Implantable Devices • Class IIb active devices (ARMS)
Aim	• Applications for all CIs	• Harmonisation, predictability • Reduced administrative burden • CA transparency and consistency	As for the pilot	Independent scientific opinions, based on the manufactures clinical evidence, to help NBs assess the clinical performance and risk-benefit determinations
Actors	• NCAs • HTDs	• Administered by EU Commission CIRCABC (until EUDAMED is available) • Coordinating Member State with min 2 MS • (Ethics Committee opinion according to national process)	• Administered by EU Commission • EUDAMED (EU Commission) • Coordinating Member State with min 2 MS • The EC will evaluate the CI/PS by May 2026 according to Art. 79	• Notified body triggers • EU Commission transmits • EMA Expert Panels • Manufactures (informed)
Timelines	• Invasive – 120d (70d) • Non-invasive 55d (25d) •	• Pilot Coordinated Assessment: 133 or 163 days • NCA national approval: approx. 10-20 days • EC approval per national rules	• Best case approx. 62d, worst case 112d • EC approval per national rules (may change after pilots)	• Approx 75 days
Legal basis	• MDR Article 70	• Pilot is a 'Regulatory sandbox'	• MDR Art. 78.14 • MDR Art. 79	• MDR Art. 54.1 • MDR Annex IX 5.1

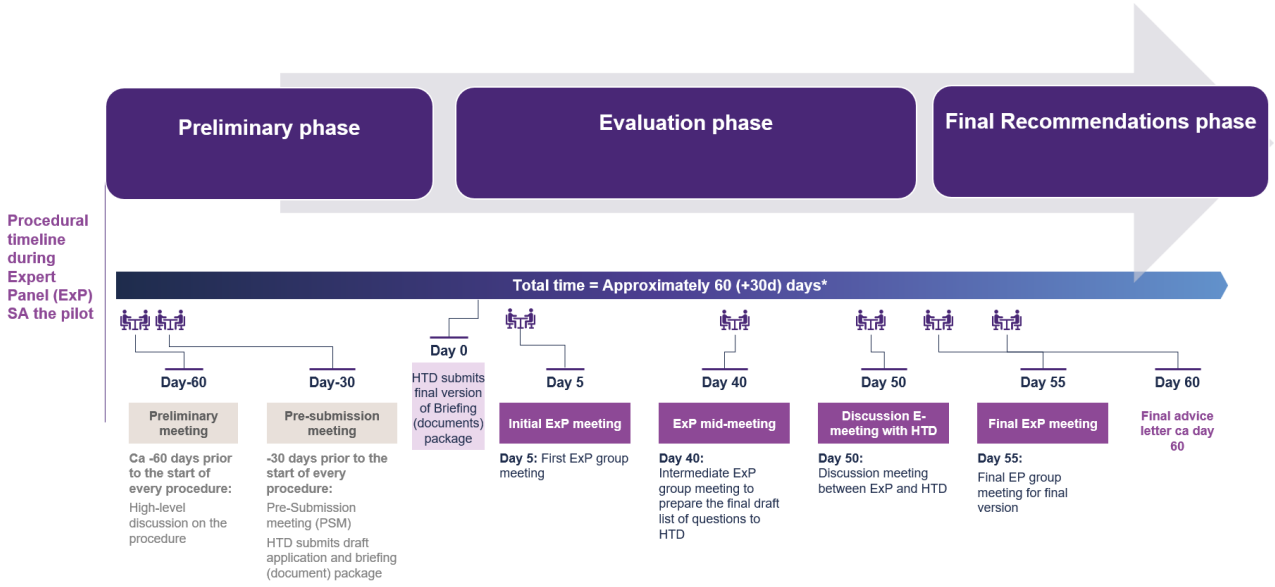
	Application Process for Clinical Investigations			Evaluation during CE Process
	MDR Clinical Investigation in one MS under Art. 70	**Coordinated Assessment (pilot, 2025)**	**Coordinated Assessment (MDR, 2027)**	**Expert Panel Opinion (CECP)**
Fees	• MS dependent	• Each MS can set its fees	• Not known yet	• No fee to date (option available MDR Art. 106(14)
Process	• Sponsor submits CI application to MS NCA. • Notification by NCA • Validation by NCA • Dependent on risk class the Sponsor will receive a notification of validity or: • For invasive CI the NCA performs an evaluation • If positive the NCA notifies of authorisation	• Sponsor submits request to EC • If part of the pilot, submission of application through CIRCA-BC • Assessment follows MDR process as described in SOP for pilot • Positive Assessment • National submission to formally follow MDR	• Sponsor submits application to EUDAMED, indicating which MS should be the coordinating MS • Coordinating MS will be confirmed within the concerned MS • Assessment follows MDR process and timelines • Conclusion and approval of NCA (or refusal)	• Part of conformity assessment • NB triggers process (manufacturer is informed) • EC facilitates • EMA EP provides opinion
References	• MDR Art. 70 • MDCG-2024-3	• EU Commission publication (2025)		• EU Commission CECP overview (2025)

3.2.1. Scientific advice from the MDR Expert Panels at the European Medicines Agency

As described in Article 61(2) of the MDR, the medical device Expert Panels may provide advice on a manufacturer's intended clinical development strategy and proposals for clinical investigation, for class III implantable devices and class IIb active devices intended to administer and/or remove a medicinal product from the human body.

This program allows sponsors / manufacturers / HTDs of high-risk devices established in the EU or through their authorised representatives to apply for advice to the Expert Panels on clinical investigations and / or clinical development strategies[7]. The scientific advice programme is implemented by the European Medicines Agency (EMA) In Figure 8 a schematic of the process is shown.

Figure 8: Diagram showing the process of Scientific Advice with the EMA MDR Expert Panels



The Expert Panels' advice is provided upon a voluntary request from the applicant. Article 61(2) of the MDR states that "*the manufacturer shall give due consideration to the views expressed by the expert panel*". This means that additional actions may be needed from the manufacturer after the provision of the advice. Such considerations are expected to be documented in the clinical evaluation

[7] EMA Guide to manufacturers on the procedure for requesting advice from Expert Panels on clinical investigations and/or clinical development strategies for high-risk medical devices

report (CER) and taken into consideration by the Notified Body at the time of the conformity assessment.

To be eligible, the applicants must meet all the following criteria:

- The device is a **class III device or a class IIb** active device intended to administer and/or remove a medicinal product (ARMS) from the human body.
- The questions asked by the manufacturer pertain to **clinical aspects only**.
- Questions related to clinical investigations pertain solely to **clinical investigations not yet started** (pre-market or post-market).

The prioritisation criteria used in the pilot for the development of this procedure: unmet medical needs or novelty with a possible major clinical or health impact were only used for prioritisation if the number of submissions for a given timeslot exceeded the capacity of the expert panels. The advice from the Expert Panels is prospective by nature and is not an assessment of the clinical data that has already been generated, though preclinical is taken into account.

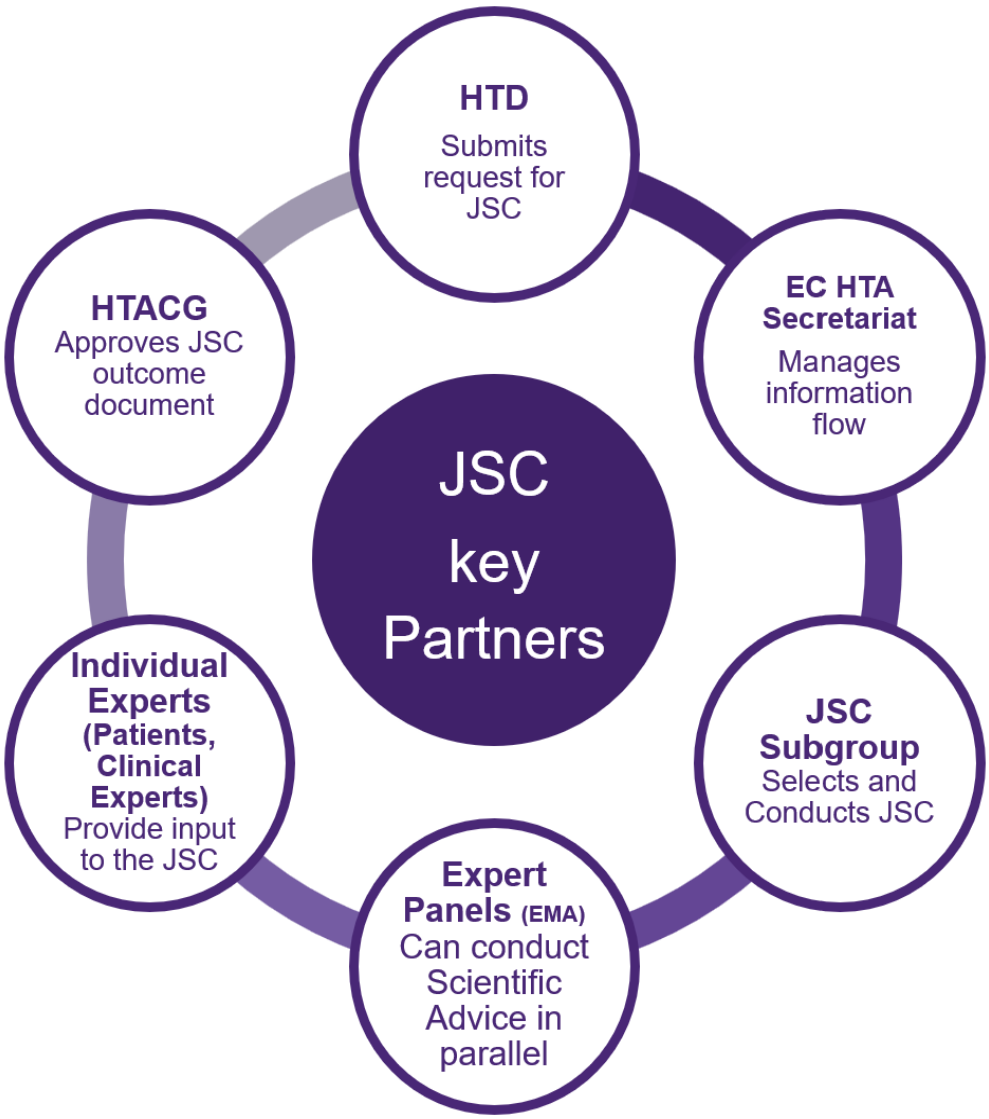
Applicants developing orphan devices are encouraged to consider the separate pilot programme published on EMA website.[8] Aggregated information on advice will be published on a yearly basis and may be presented at specific meetings with interested parties organised by the Agency. Though the advice itself will not be published.

3.2.2. HTAR Joint scientific consultation

A Joint Scientific Consultation (JSC) represents the advice procedure of the Health Technology Assessment Regulation (EU) 2021/2028 (HTAR)[9] for Health Technology Developers (HTDs), which facilitates the discussion of the clinical development plan at an early stage of a medical device/ IVD device (and medicinal product) clinical investigations pushing towards a lifecycle approach to clinical evidence generation key partners in the process are shown in Figure 9.[10]

[8] MDCG 2024-10 Clinical Evaluation of orphan medical devices
[9] Health Technology Assessment Regulation (EU) 2021/2028 (HTAR)
[10] HTAR Joint Scientific Consultations

Figure 9: HTAR Joint Scientific Consultation key partners in the process



The JSC enables HTDs to exchange confidential information on their clinical development plans for a medical device (MD/IVD) (or medicinal product) to obtain guidance on all relevant clinical investigation design aspects, including comparators, interventions, health outcomes and patient populations which would be relevant for a Joint Clinical Assessment (JCA) of those devices, and during a further national health technology assessment (HTA) , such as health economic parameters[11]. However, this is also an opportunity to have advice on the clinical evidence generation from EFS to pivotal to post-market clinical follow-up. This advice can be given in parallel with the Expert Panels (ExP) of the EMA and allows the HTD to invite their Notified Body to join as an observer.

[11] Implementing act on joint scientific consultations on medical devices and in vitro diagnostic medical devices

The Health Technology Assessment Coordination Group (HTACG)[12], appoints an assessor and co-assessor from different Member States to undertake the JSC. The Guidance for the selection of Medical Devices (MD) and In Vitro Diagnostic Medical Devices (IVD) for Joint Scientific Consultations (JSC)[13] details the selection criteria, but a brief description is shown below.

In summary MD and IVD eligible for JSC are devices that will receive a ExP Opinion or View through the CECP/PECP (Performance Evaluation Consultation Procedure):

- Class III Implantable MD
- Class IIb active MD ARMS
- Class D IVD

These devices are therefore likely to be the subject of JCA pursuant to Article 7.1. of the HTAR, and clinical studies and clinical investigations are still in the planning stage (both pre-market and post-market studies).

The potential devices for JSC are selected based on one or more of the following criteria (HTAR Art. 17.3):

(a) unmet medical needs;

(b) first in class;

(c) potential impact on patients, public health, or healthcare systems;

(d) significant cross-border dimension;

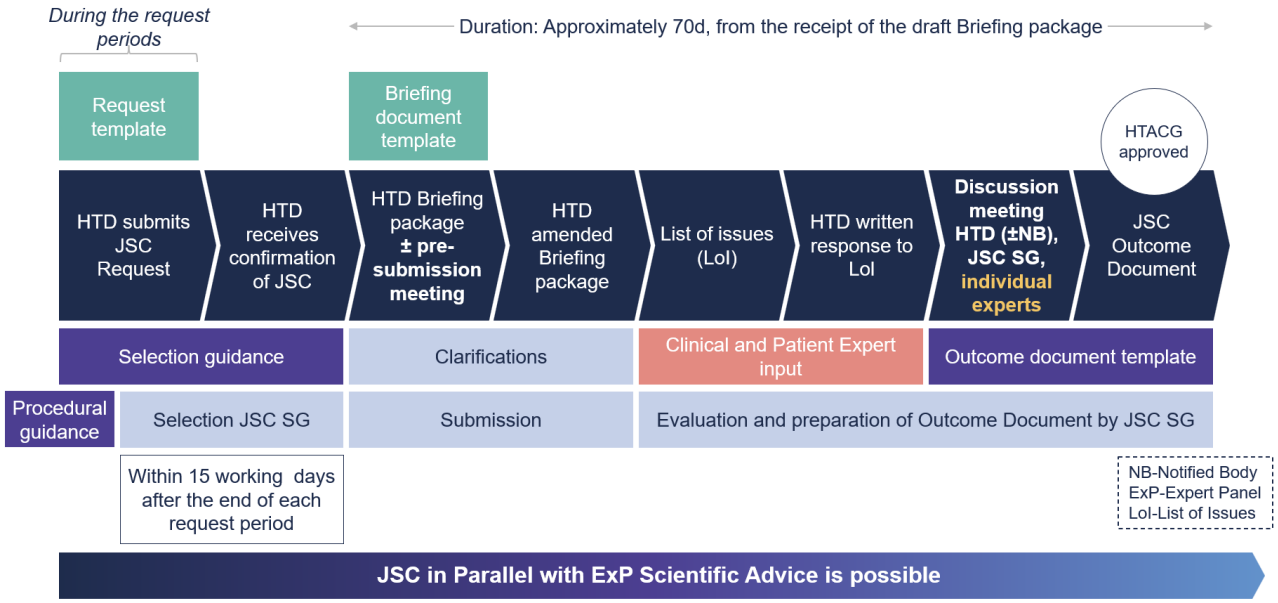
(e) major Union-wide added value; or

(f) Union clinical research priorities.

The JSC can also be conducted in parallel with Scientific Advice from the MDR Expert Panels as described above in Section 3.2.3, the process is shown schematically in Figure 10.[14]

[12] Health Technology Assessment Coordination Group
[13] Guidance for the selection of Medical Devices (MD) and In Vitro Diagnostic Medical Devices (IVD) for Joint Scientific Consultations (JSC)
[14] Procedural Guidance for Joint Scientific Consultations (JSC) on Medical Devices (MD) and In Vitro Diagnostic Medical Devices (IVD)

Figure 10: Schematic overview of the JSC process and parallel JSC with ExP Scientific Advice



3.2.3. Early Dialogue between the Sponsor and the NCA

Many NCAs offer optional opportunities for Early Dialogue to request clarifications around CI objectives and needs, and identification key 'challenges'.

Prior to submitting an application for approval of a CI, sponsors may engage in Early Dialogue with the NCAs involved at the pre-submission stage.[15],[16],[17],[18],[19] The exact requirements for such early engagement vary from NCA to NCA but most are open for the opportunity to request a meeting well in advance of the intended submission of a CI application. The goal of these meetings can be for 'start-ups' to understand the role of the NCA and what the regulatory requirements in the pre-market phase of device development are, to more content related meetings where the sponsor is in the planning phase of a CI application and has concrete questions around the process the clinical strategy. Often there may be a request for the CI to be outlined and details of questions provided in advance of a meeting, while other NCAs have a 'Ask us' web-portal where questions relating to the CI can be sent and answered by email. The goal and timing should be that there is sufficient time to adapt the CI application dossier in line with the regulatory guidance received. In addition, this service provides HTDs/Sponsors and researchers access to expertise on various application processes for

[15] Clinical investigation of medical devices - Norwegian Medical Products Agency
[16] Guidance and regulations - Norwegian Medical Products Agency
[17] Guidance for Medical Devices – Federal Agency for Medicines and Health Products, Belgium
[18] Guidance for the application procedure – Bfarm
[19] HPRA Guide to Clinical Investigations Carried Out in Ireland

CIs, to ask questions around PICO (population, intervention, comparator and outcomes) and study design.

Some of the NCAs, for example those consulted for this deliverable, see Section 4.1, all offer an advisory and guidance service which they encourage the HTDs/Sponsors to take advantage of.

From the dialogue meeting the NCA will gain a more thorough understanding of new innovations, applications to come and can prepare the teams for efficient handling of the applications after submission.

3.2.4. Structured Dialogue between the Notified Body and the HTD

According to MDCG 2022-14,[20] the '*MDCG encourages notified bodies (NB) and manufacturers to organise structured dialogues before and during the conformity assessment process*'. The Structured Dialogue should be aimed at regulatory procedures to enhance the efficiency and predictability of the conformity assessment process for the HTD, while respecting the independence and impartiality of the notified body. The exchanges are encouraged to focus on "what needs to be fulfilled" rather than "how to fulfil".[21]

From this perspective there are limits to what falls under structured dialogue for example providing solutions to the HTD on how to comply with a specific regulatory requirement(s) is not allowed, however the goal is to enhance the efficiency and predictability of the conformity assessment, allowing project plans to be discussed[22],[23]. Due to this limitation other routes for gathering information as early dialogue with NCAs (section 4.1), Scientific Advice from the ExP (section 3.2.1), HTA JSC or JSC in parallel with ExP Scientific Advice (section 3.2.2) may be better routes to pursue in this context. The JSC also opens for the possibility for the HTD to have their Notified Body present as an observer.

3.2.5. Pilot Coordinated Assessment of Clinical Investigations and Performance Studies (CI/PS)

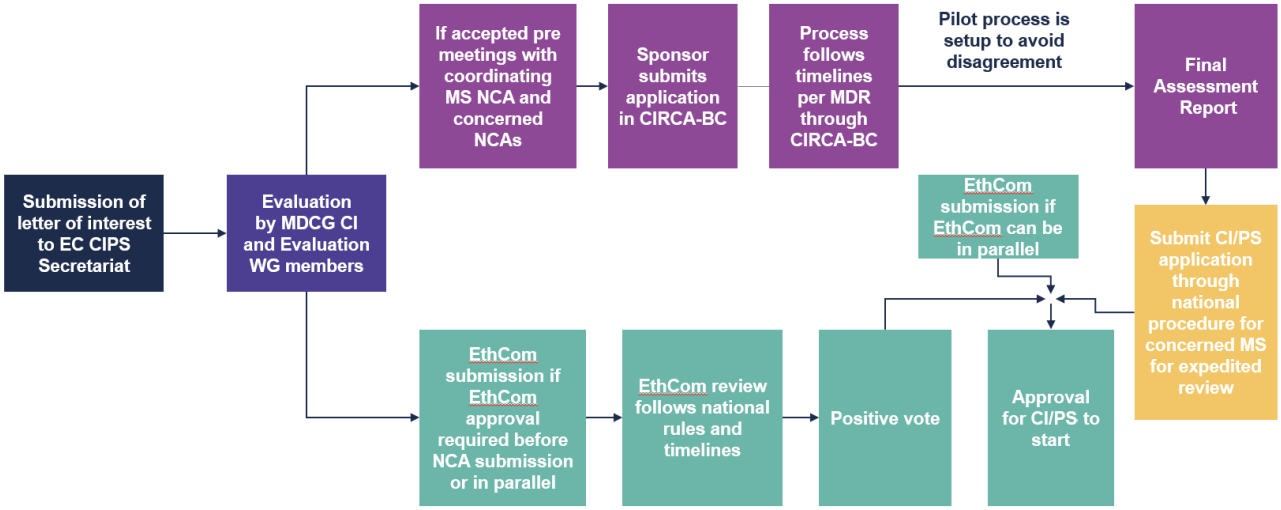
The European Commission (EC), in collaboration with the Member States, have launched a pilot Coordinated Assessment for CI for the coordinated assessment as described in Articles 78 of MDR and 74 of the IVDR[24].

This pilot will allow sponsors to submit a single application for pilot coordinated assessments. The goal is to implement a harmonised, predictable process across Member States, reducing

[20] MDCG 2022-14 - Transition to the MDR and IVDR Notified body capacity and availability of medical devices and IVDs
[21] MDCG 2019-6-Rev.5 - Questions and answers: Requirements relating to notified bodies
[22] TeamNB Code of Conduct for Notified Bodies under Regulations (EU) 2017/745 and (EU) 2017/746
[23] Structured Dialogue from BSI
[24] Pilot coordinated assessment for CI/PS

administrative burden for sponsors and ensuring high transparency and consistency in the coordinated assessment. The Ethics Committee opinion requirements are different across the MS participating in the CI/PS Pilot, and when the process to obtain their opinion should start and when in the CI application process it is required for the national submission may also differ, but these are detailed in the Ethics Committee Opinion[25] document. The pilot CI/PS process is shown in Figure 11.

Figure 11: Overview of Pilot Coordinated Assessment Process



Aim

By participating in the pilot for coordinated assessment, sponsors can benefit from the from the Coordinated Assessment Process which aims to harmonise the process by:

- **Unified engagement**: engage with all the EU countries involved, thus making communication more efficient and clearer while reducing delays.
- **More transparency and harmonisation**: the pilot will enhance transparency, giving sponsors better visibility of the evaluation process across EU countries by access to the operational procedures. Member States NCAs will work together becoming familiar with each other's practices and particularities, thus increasing harmonisation.
- **Simplified requests for information**: experience a more efficient request for information (RFI) process, reducing potential complexities compared to non-coordinated assessments.
- **Consistency across Member States**: reduce discrepancies in assessment due to different national interpretations.
- **Document management efficiency**: a lower number of submissions is expected during the assessment process.

[25] CI/PS Pilot Ethics Committee opinion

- **Simplified management of substantial modifications**: substantial modifications are also planned to be coordinated, ensuring a smooth and coherent process.
- **Faster overall process**: coordinated assessment procedures will enable faster decisions at the national level.

Applications from sponsors will be reviewed based on eligibility criteria and the potential impact on public health of both the clinical investigation or the performance study and will have to meet the following criteria:

1. The clinical investigation or performance study must require authorisation under Article 62(1) of MDR or Article 58(1)-(2) of IVDR.
2. The study must be multinational and involve at least two participating Member States agreeing to join the coordinated assessment pilot, where one Member State NCA accepts to take on the coordination of the assessment.

The investigational device will have to fall under:[26]

- **Medical Devices Regulation (MDR):**
  - investigational devices in class III
  - invasive investigational devices in class IIa
  - invasive investigational devices in class IIb
- **In Vitro Medical Devices Regulation (IVDR):**
  - performance studies carried out under Article 58(1)(b)
  - performance studies carried out under Article 58(1)(c)
  - performance studies carried out under Article 58(2) involving companion diagnostics.

The Member States confirmed to participation in the initial pilot coordinated assessment are:[27] Austria*, Belgium*, Czech Republic, Estonia, Finland, France*, Germany, Greece, Ireland*, Latvia, Luxembourg, Netherlands, Poland*, Portugal, Romania, Slovenia, Spain, Sweden* and Norway. However, this is subject to change so please see the updated list[28] .

3.2.6. Clinical evaluation consultation procedure (CECP)

A notified body (NB) shall follow a clinical evaluation consultation procedure (CECP) (MDR Art. 54) [29]:, when performing a conformity assessment of certain high-risk devices. This is only relevant for class III implantable devices and class IIb ARMS.

[26] Eligibility conditions for CI/PS
[27] National requirements for MDR/IVDR coordinated assessment applications
[28] MS coordinating and participating in the pilot the CI/PS
[29] Work of the Expert Panels

Aim

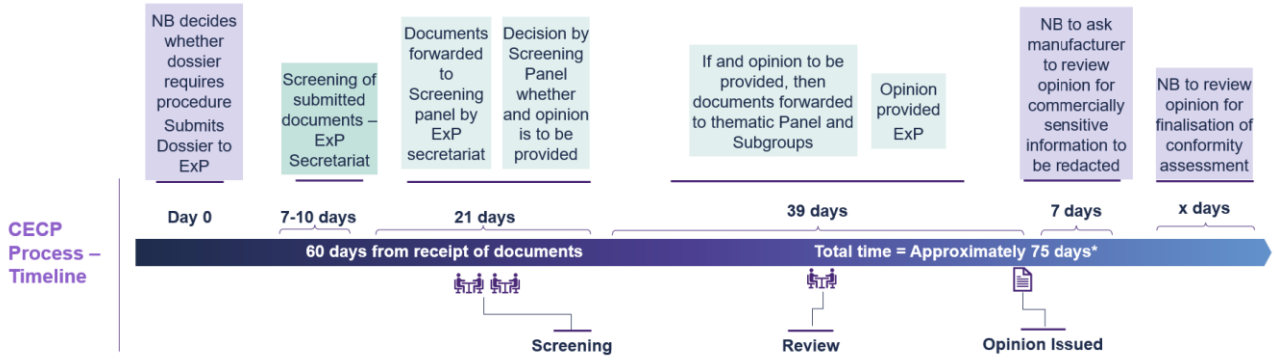
The purpose of the CECP procedure is for the appointed experts from the EMA MDR ExP to provide an independent scientific opinion[30] on the NB's clinical evaluation based on the HTD's clinical evidence.

The expert panel shall decide to provide an opinion in response to a consultation based of all of the following three criteria[31]:

- (i) the novelty of the device or of the related clinical procedure involved, and the possible major clinical or health impact thereof
- (ii) a significantly adverse change in the benefit-risk profile of a specific category or group of devices due to scientifically valid health concerns in respect of components or source material or in respect of the impact on health in the case of failure of the device
- (iii) a significantly increased rate of serious incidents reported in accordance with Article 87 in respect of a specific category or group of devices

For each device falling within the scope of the CECP, it is the NB for the device under conformity assessment who should inform the competent authorities, the authority responsible for NB and the Commission with a justification whether or not the CECP applies to the respective device[32]. Figure 12 shows the CECP process.

Figure 12: Schematic overview of the CECP process and its timeline



[30] Clinical Evaluation Consultation Procedure list of opinion
[31] Work of the Expert Panels
[32] List of opinions provided under the CECP

A NB is required to duly consider the opinion and where necessary take appropriate actions according to MDR Annex IX Section 5.1, after receiving the opinion from the expert panels[33][34],

The Commission will draw up an annual overview of devices which have been subject to the CECP, including.

- for all devices in scope of the CECP, a listing of notifications by NBs on whether or not the CECP applies.
- for all devices not exempted from the CECP, a listing of those for which the expert panels decided to provide an opinion.
- for all devices subject to an opinion from the expert panels, a listing of the cases where the NB did not follow the advice from the expert panel.

It is important to note that there are three exemptions from the obligation for the NBs to follow a CECP (MDR Art. 54) and not all CECP applications will necessarily result in a scientific opinion. If the CECP does not apply, the NB is asked to indicate the reason corresponding to the respective exemption listed under paragraph (2) of the same Article, such as:

- a) a renewal of a certificate issued under the MDR without modification of the device.
- b) the device has been designed by modifying a device already marketed by the same manufacturer for the same intended purpose and the modifications do not adversely affect the benefit-risk ratio of the device.
- c) the principles of the clinical evaluation of the device type or category have been addressed in a Common Specification (CS) referred to in Article 9 of the MDR and the clinical evaluation of the manufacturer for this device is in compliance with the relevant CS for clinical evaluation of that kind of device.

[33] High-risk medical devices: consultation procedures and advice
[34] Expert panels Overview - European Commission

4. Results of Discussion with Stakeholders

4.1. Current Practices of NCAs

Five main themes emerged from the focus groups with the NCAs. These themes were grouped under the topics explored in the Focus Groups: (1) Experiences with EFS-like studies, (2) Dialogue between NCAs and sponsors for EFS, (3) Harmonization, (4) Efficiency of EFS applications evaluation, and (5) Ethical approval. Each theme is reported with a heading, a description, and selection of supporting quotes from NCAs. A complete list of quotes is available in Appendix 7.3. In addition, NCAs practices that were reported during the interviews and that were identified as potential "best practices" for EFS is included.

4.1.1. Experiences with EFS-like studies

Theme #1: Lack of formal EFS definition and homogeneous assessments across NCAs.

NCAs reported the absence of a formal EFS definition under the MDR, this contributes to disparate assessment approach for EFS across NCAs. Four NCAs reported that they do not assess EFS differently from other pre-market CIs. One NCA reported approaching EFS with a higher level of vigilance, particularly in evaluating benefit-risk analysis, preclinical data, and patient monitoring. Four NCAs reported preclinical evidence and the novelty of the device as key elements in assessing EFS. One NCA also mentioned calculation of a 'risk score' to guide the level of assessment. NCAs also mentioned that their assessment of EFS may result in EFS-specific recommendations due to perceived higher risk of such studies, due to lack of previous clinical evidence to build on. The disparate approaches to assess EFS reveal a fragmented regulatory landscape, where the lack of a shared definition creates ambiguity and inconsistency in practice. NCAs mentioned:

"It wouldn't make any difference to us with regard to whether or not they would fit the definition of early feasibility studies under ISO because that doesn't stand in the European regulation like that. That's an ISO [definition] and it's in the FDA, but the MDR doesn't use the term Early Feasibility Studies."

"The [assessment] approach until now—or until recently—was essentially all studies were treated the same, whether the sponsor had qualified them as a first-in-human, early feasibility, or a pivotal study."

"Our scientists or engineers would treat all that [bench and preclinical work] the same, sort of agnostic of whether it's early feasibility or not."

"The [EFS] assessment is different in the way we assess the data and also in monitoring the patient. […] We follow that kind of study [EFS] with the higher grade of vigilance."
"[During EFS assessment] we can have specific recommendations regarding the design of the study, the Data Safety Monitoring Board […]"."
"What's the most important thing for us with all these studies is to see whether there is really a completely novel technology, let's say, or whether it is well-established technology which is now used for an out-of-scope indication or another anatomical site."

Theme #2: Poor EFS documentation quality and limited evidence on novel technologies challenge NCAs' validation and evaluation of EFS.

NCAs reported that EFS application documentation that is poorly organised or does not follow MDCG guidance and therefore poses challenges during EFS validation and evaluation. NCAs believed that sponsors' experience contributes to the quality of EFS application, with less experienced sponsors more likely to submit incomplete or poorly organised materials. These documentation issues may not only reflect individual sponsor performance, but also structural factors, such as a lack of regulatory capacity especially among small or academic spin-off sponsors, which leads to applications that are not adequate for the requirements of CI under the MDR. Poor documentation quality can make the validation and evaluation process cumbersome for NCAs, sometimes resulting in increased time required for assessing EFS. This may contribute to reviewer fatigue, inconsistent evaluations across countries, or cautious rejection of unclear applications. The novelty of the device technology further complicates assessments, as new devices or new device designs may have unclear mechanisms of action or lack established standards for reference, making it difficult for reviewers to fully understand the device or evaluate its' safety. Two NCAs also believed that either the limited availability of clinical data or the absence of relevant guidelines on preclinical tests needed present additional challenges, especially for innovative or first-in-human studies. The NCAs stated:

"Challenges during the validation and evaluation [of an EFS] could be the organisation and the composition of the submissions […] because for a sponsor with not a lot of experience, it could be very difficult to have a submission [that is] well prepared."
"Some applications are very cumbersome and not organized. […] the investigator's brochure [that] is not redacted according to the MDCG guidelines […] So it's a big problem and it takes a long time."
"If you have an experienced sponsor, even if they're doing an early feasibility study, they know what to include in the documentation. While a small academic spin-off [...] you might have more issues with quality of documentation."

"Another [challenge] is if it's a completely new design or new way of introducing a device or something, you also need to really well understand the mode of action. And that is sometimes hard to completely understand from the sometimes limited information that is included in an investigator's brochure."

"If you have a completely new design, there are often no ISO standards, no guidance, nothing... About fatigue testing, bench testing, there's no ISO standard that says these tests have to be performed in order to say the design is safe to go to clinical testing."

"For us [NCA], the worst situation is if [when] there are no human [clinical] data. And that's the most critical issue for us."

Theme #3: Device and protocol modifications during EFS studies are common and managed on a case-by-case basis, posing challenges for NCAs in ensuring data integrity, study validity, and risk management.

NCAs reported that modifications to devices or protocols during EFS are frequent and expected as part of the iterative development process. However, the handling of these changes varies across NCAs and is typically managed on an ad-hoc basis rather than through standardised, planned or pre-authorised scenarios. Substantial device modifications often require closing the current investigation and initiating a new one to ensure valid measurement of patient outcomes and to maintain patient safety. This approach helps maintain scientific integrity when devices evolve significantly during the clinical investigation.

NCAs highlighted possible challenges related to tracking which device version was used for each patient, particularly when sponsors make frequent or incremental modifications. What was particularly challenging and concerning for NCAs was that some sponsors pool data related to different versions of the devices, whether in the same or from different clinical investigations. The blurred distinction between minor and major changes complicates the decision on whether a new study is needed. Transparency and cooperation with sponsors greatly influence the NCAs' ability to monitor and evaluate modifications effectively. Phased or stepwise enrolment strategies were mentioned as a risk management approach to handle uncertainties associated with evolving devices, although such strategies are not always formalised in protocols. NCAs balance supporting innovation with ensuring patient safety and reliable data collection. An extract of what the NCAs stated:

"We sometime have discussion with them [sponsors] because if the design of the device changes a lot, we could discuss with them to close the study and to start a new study. If the difference[s] are too huge, sometimes it's not scientifically correct to measure the result[s] [outcomes] of patients [who have] been treated with different devices."

"You have a device, the device is modified, and from us [our perspective], [we ask ourselves] 'is it [study being conducted] with a modified device? Is it a completely new study? or is it still the same study?' and that's a difficult question [to answer]."

"It's very difficult even for us, who really, deeply traced all the development. [And] this [change] could be small steps in the development, some not substantial, some a little bit more substantial. It's a scale, it's not black and white. [And] at the end of the day, they [sponsors] have the final device, but the data that they have are not all [related to] the final version of the device."

"It's very difficult to distinguish what device was used in each patient."

"We sometimes want to manage risk by phasing the study [and] to have first 3, 4, or 5 patients just to manage risk."

"[There] was a clinical trial that originally planned approximately 50 patients, but it was first-in-human. So, they [the sponsor] submitted these 50 patients. They wanted to submit, but we agreed with them that they might submit as step-by-step process first [with] six patients […] They wanted to apply then evaluation and then if we agree, they could continue."

4.1.2. Dialogue between NCAs and sponsors for EFS

Theme #4: Dialogue improves EFS assessment efficiency and speed through NCA adaptability and sponsor cooperation.

NCAs believed that dialogue with sponsors improves the efficiency and speed of EFS assessment. The benefits are a result of the interplay between NCAs' furthering their own understanding of the device and procedures around it, and the sponsors understanding of the process. The benefits resulting from dialogue are shared among NCAs, regardless of dialogue structure —formal or informal—which varies across authorities. Some NCAs reported a more informal structure to dialogue, where sponsors receive quick advice through conversation (e.g., teleconference) or in written form (e.g., email), and where dialogue could happen pre-submission, pre-assessment, during assessment or during the study. Other NCAs reported less formality to dialogue structures, where they adapt the dialogue process to the sponsors' needs, type of study design, and outcomes. As reported by one NCA, regardless of the dialogue structure, true efficiency depends on the sponsors' readiness to collaborate and implement NCA advice. NCAs acknowledged that the benefits of dialogue may be hampered by policy limitations (e.g., not allowing pre-reviews) and sponsor types,

with larger sponsors often perceived as less flexible in adapting to NCA advice. *NCAs mentioned:*

"We encourage manufacturer[s] to come early during their development to have a discussion with us, and we always experienced that when there was a scientific advice previously, the solution and the assessment is [was] quicker [and] easier for both sides because we have already discussed the project, we have already understand [understood] what are [were] the aim and what they [sponsors] wanted to demonstrate."

The smart ones [sponsors] are cooperative because they feel rightfully that [dialogue] might speed up the approval process. […] If they [sponsors] are cooperative, they basically speed up our evaluation process."

"For all of our scientific advice, there is a specific submission [required for sponsor] with a wishing book, which is prepared by the sponsor, and we work based on this guidance in the wishing book. […] [Dialogue] could happen generally after their [sponsors'] request of information, [which happens] when we send them a list of question […] and just before taking our decision we could have another dialogue with the sponsor to solve the issue[s]."

"There's different types of scientific advice. We have scientific advice regarding the qualification, we have classification, we also have pre-assessment, pre-submission scientific advice... Type 1 is just for a simple question... if you go up to Type 3 then you can have a meeting and then it's more people involved and more questions."

"We don't have a detailed pathway to prior to submission, but we are open to what sponsors want because the needs of sponsors can be very different in terms of if you're an SME [or not]. [For example] if you're a small and medium enterprise with a non-invasive device wishing to do a small study it's very different to a large enterprise with a Class III device. So, we're not massively [or] hugely structured in what our process is."

"We found out that [pre-submission discussion] is extremely useful tool, [especially when] the manufacturer [sponsor] is willing to cooperate and is willing to kind of adjust the protocol. But it's difficult for us because we are not allowed to pre-review the documentation."

4.1.4. Challenges to and opportunities for harmonisation

Theme #5: Coordinated Assessment Pilot help NCAs share learning and collaborate with each other, paving the way for a unified EFS assessment approach in the EU.

NCAs reported that they have different practices to assess EFS, which may result in different assessment outcomes, which can lead to a study being approved in one country, but not in another. NCAs believed that developing a harmonised guidance to be used by all NCAs can help them assess EFS across all phases of the study, including application guidance for sponsors, preclinical testing requirements, study design considerations, and minimum data required before enrolling the first patient, with the goal of this ultimately being endorsed and included in an MDCG guidance. NCAs showed enthusiasm for the Coordinated Assessment Pilot and perceived it as an initial approach to foster shared learning and collaboration among NCAs, allowing authorities to share practices, experiences, and perspectives, and creating an environment where mutual understanding can grow. Two NCAs suggested that informal discussions among member states beyond the Coordinated Assessment Pilot could be an opportunity for a more pragmatic shared learning such as the 'Assessor forum of the MDCG CIE'. The shared learning and collaboration happening during Coordinated Assessment and other informal discussions could lay the foundation for developing harmonised guidance, with synergies drawn for the EFS to follow a consistent and unified approach. NCAs mentioned:

"There are differences [in the assessment] because sometimes we don't authorize some [clinical] trial, which will be authorised in [by] other competent authorities. So, there we are sure that there are differences in our assessments."

"[It] could be interesting to have a guidance and a shared vision between competent authorities regarding what is needed to start [an EFS]."

"It already starts there [beginning of the application] — we need harmonisation, we need to talk to each other and need more guidance or best practices on that."

"If there was [were] more standards available and guidance on the preclinical testing, that would alleviate a lot of the big challenges."

"[it] could be interesting also to harmonize our work practice with other competent authorities to have a guidance particularly regarding the design […], the preclinical data and preclinical requirements, the minimal data that are needed for this type of study before the first patient [is enrolled]."

"[…] developing slightly more prescriptive guidance might be needed [...] but it's a way of how does that get taken on board into ultimately an MDCG-endorsed guidance."

"Currently we are in the way of Coordinated Assessment. We [will be] start[ing] the pilot phase soon and we are very happy to start this pilot phase. We also have an assessor forum, in which we can share our experience and our assessments. And I think all these tools are very important to learn of each other."

"Big help is the assessor's forum […] where we can just talk with each other and that is a big help for harmonization […..] just presenting to each other such cases and applications; and talking about our decision [making] is already harmonizing things. So, the assessors forum is really a big help from the CIE between Member States."

"[The Coordinated Assessment] will be a way for sponsor[s] to have more harmonised view of their trial in Europe, and I think it's really important [for them]. And it's also important for us to learn the practices of our colleagues and to share [our practices] with them."

4.1.5. Efficiency of EFS applications evaluation

Theme #6: Following up with sponsors for additional data and providing standardised templates help address inadequacies in EFS applications.

NCAs reported that insufficient or incomplete data in EFS applications — including safety data, animal studies of adequate duration, biocompatibility testing, and well-defined inclusion criteria — are common issues that hinder timely EFS approvals. Specific examples included missing sections in the investigator's brochure, gaps in preclinical testing, or a lack of supporting documentation. One NCA stated that following up with sponsors to request additional data, such as more detailed histological reports, justification for standard of treatment, or biocompatibility data, especially for implantable or high-risk devices would facilitate a more efficient evaluation. NCAs also mentioned that providing standardised templates and checklists would be a way to guide sponsors through the application process, improve consistency across submissions, and ensure that all essential components are addressed upfront. NCAs mentioned:

"Yes, the most [common] issue for that kind of study [EFS] is the insufficiency of safety data. For example, sometimes we have no animal study or [we have] animal study, but with a time [that is] not enough [in terms of] length."

"For the validation... sections missing in the Clinical Investigation Protocol or Investigation Brochure, documents missing, documents not properly signed. These are the types of things that we usually encounter during validation. And like I said, they happen for all applications, not necessarily EFS-specific."

"The biggest issue we see is that documents are missing, and especially the preclinical part. [...] If you have just a very short summary of the testing that has been performed

without any details and referring to test reports which are not included, then you have a problem."

"We have a guidance document which clearly states that essential test reports should be included in the submission, but applicants apparently don't read it or forget it, they lose time with it."

"And for me, it's always excellent sign if I ask for the data […] [and] I see that the manufacturer [sponsor] really solved that problem based on the data."

"We required some things which we usually do not require at such kind of depth with other trials, [for example] a very precise description of the standard of treatment."

"We ask for complete data for biocompatibility, which is usually a huge file […] because for some devices it's crucial."

"[Templates] would help with all required sections and information to be there. If they fill out a template and they see this section, then they would know they need to fill it out."

4.1.6. Ethical approval

Theme #7: Diverse ethical approval models—whether centralised, decentralised, parallel, or sequential— across Member States generate operational struggles for NCAs and underscore the need for a harmonized model.

NCAs reflected critically on the ethics approval systems in which they operate, highlighting how different structural models present distinct challenges in the context of EFS. One NCA observed that requiring ethics approval before initiating the EFS assessment may help streamline their review process. While parallel processes were perceived as beneficial for sponsors — reducing waiting times and enabling simultaneous review. Though simultaneous review was by some NCAs described to increase their workload, who must validate ethics documents, coordinate with multiple committees, and consolidate divergent assessments before issuing a final decision. In some cases, this required internal negotiation to resolve disagreements prior to communicating outcomes to sponsors. In decentralised or sequential models, the absence of coordination and parallelism was reported to lead to fragmentation, delays, and burdensome repetition—especially when changes to the application were needed after submission. Some NCAs noted that ethics committees are embedded within healthcare institutions, often with its own procedures and timelines, which complicates centralised oversight or pre-submission dialogue. Beyond structural differences, a shared concern emerged around the lack of consistency among ethics committees, even within the same country. Some committees were described as requiring extensive additional information, while others approved the same applications without conditions. This intra-national variability was seen as a major barrier to predictability and procedural alignment—sometimes even more pressing than cross-country

harmonisation. These accounts suggest that, regardless of the system in place, NCAs are required to navigate trade-offs between speed, control, coordination, and consistency. Ethics approval structures not only influence timelines but also shape the nature of the interaction between regulatory and ethical bodies, the clarity of outcomes for sponsors, and the internal coherence of decision-making across studies. NCAs mentioned:

"Ethics approval is one thing, though, that is an issue on a European basis, and there are different approaches to ethics [approvals], and that is a problem.

"if you're trying to do a multinational study and you have a parallel ethics NCA submission option in one Member State, and you have it sequentially in the other, I think a challenge, up until recently, [is that] individual Member States have no visibility to [of] each other's assessments."

"We have one ethics committee, and we have a very good relationship with them and we meet with them frequently, and I think that very much helps everybody; it helps sponsors as well, even if they may not know it, because issues come up that are solved before they reach kind of an official query problem."

"We need to consolidate the assessment report of the ethics committee with our own assessment report and then sometimes discussions may arise. It kind of adds an additional step to the whole procedure."

"We do notice a lot of differences, even in [our country], between the ethics committees... certain committees would ask a lot of additional information, while another would approve without conditions."

"On European level, harmonisation would be nice, but I think that's really far away... for us, if we have a national harmonisation on that level, that would already help."

"So, a more harmonised approach to ethics [approval] would be something that I would feel would be very helpful."

4.1.7. Potential "best practices" drawn from NCA interviews

Dialogue in the form of written exchanges and/or meetings with the NCAs interviewed:

- The French NCA has an "innovation desk" to provide scientific advice to sponsors, where dialogue may begin with written exchanges and continues with discussions.
- The Irish NCA offers a pre-submission dialogue that is adapted to each sponsor's needs and are proactively engaging specifically EFS.

- The Belgian NCA offers a structured Scientific Technical Advice (STA) service, handled by a dedicated department separate from the R&D unit for CIs; STA operates on a tiered system based on the complexity of sponsors' requests and may involve written responses and/or expert meetings; aside from STA. Sponsors may submit brief informal inquiries for free if responses take under 15 minutes and require no expert consultation.
- The Portuguese NCA, dialogue is available through a separate department that offers scientific and regulatory advice, which sponsors can consult voluntarily. However, the NCA often lacks visibility into whether this channel was used or influenced final submissions.
- The Austrian NCA offers dialogue to provide information or regulatory classifications, and, occasionally, guidance regarding the need to comply with relevant standards. Sponsors can approach the NCA by sending questions via email and receive responses to their inquiries.

Parallel ethics committee review:

From the interviews the following were identified, as the regulatory mapping of the Coordinated Assessment had shown clear differences in MS ethical committee processes, as shown in Section 3.2.5.

- In France, ethical approvals run in parallel with the NCA assessment; the French NCA coordinates both its own and the ethics committee's reviews, but after validation, each body independently conducts its assessment and issues its decision.
- In Belgium, ethical approvals run in parallel with the NCA assessment, resulting in a single, consolidated approval letter issued to the sponsor. The NCA manages the full administrative flow toward the Ethics Committees, including validation of ethics-related documents and coordination of opinions—tasks that demand careful internal coordination, partly delegated to the CT College, which serves as a bridge to the 14 Belgian Ethics Committees.
- Portugal allows for parallel submissions with the ethics committees and the NCA, where the two bodies are aligned in their evaluations and maintain regular internal exchanges, which supports consistency.
- The Austrian NCA reported that, although ethics committee approval is currently required before NCA assessment in their country for practical reasons, parallel review is considered the ideal model. They note that several Member States allow for parallel application submission to both the NCA and ethics committee and can do so because their ethics and competent authorities are more aligned in their processes.

4.2. Focus groups with small to large Health Technology Developers (HTDs)

Interactions with NCAs and Experiences with EFS-like studies

The HTDs described that any interaction or dialogue with the NCAs prior to this submission was beneficial. However, they referred to experiences of written dialogue, their experiences of interaction were mostly post-submission and rarely before submission and rarely face to face dialogue meetings. For those HTDs less experienced with EFS the lack of detailed guidance or standards for EFS was highlighted, where the sponsor responsibility is described or the process of assessment by the NCAs. This was also mirrored by larger HTDs who stated that the process may be influenced and prolonged due to uncertainty around the interpretation of MDR and EFS, and limited compliance, for example to preclinical testing requirements of GSPR can be expected compared to more advanced confirmatory CIs, at the start of an EFS.

Dialogue around this aspect would be very important for the application process.

"Apply to 10 different countries, and you get 10 answers"

The smaller HTDs emphasised the variability in consistency and quality between different NCAs. They described that some NCAs welcome applications and conduct assessments with a high degree of professionality, some are clearly burdened with lack of employees and resources, some seem to lack knowledge and experience in both medical field and regulatory aspects. Their impression was that some NCAs would not take on an application for a premarket CI due to lack of experience in the field, and/or lack of availability of experts. Where one HTD was advised not to perform a premarket CIs in the EU due to the hurdles and difficulties within the regulatory field.

The larger HTDs identified that dialogue was essential when planning EFS for novel and innovative devices to discuss details around the new technology such as:

- what the device is,
- what makes it new,
- what makes it novel.
- the need to understand if the NCAs has the resources or expertise within the country to be able to make an appropriate assessment of the technology.
- issues concerning patient population
- inclusion and exclusion criteria identified as appropriate.
- the bench testing plan that that may be included, what level of evidence is appropriate and why
- balancing the need for testing preclinically with patient protection

The smaller HTDs found the idea of an initial meeting to determine whether their potential device falls within the definition of a medical device, the class of the device, and the timings to be a very useful approach for those who are less experienced.

They also emphasised that a major factor when applying for a CI in Europe is the reputation of the PI (Principal Investigator). If the PI is known to the NCA where the application is submitted, the process would be more likely to proceed. His or her respect among professionals in the medical field and the NCAs, reputation and experience with previous CI is the main key for a positive experience, a lean application process and interaction with the NCAs.

Timelines

Though the MDR timelines are defined as shown in 3.2great variability on approval time was described and this was also shown in the NCA mapping done in Deliverable 2.2.[35] The HTDs commented on the estimated timelines of 120 days from MDR Art. 70, which often ran over and some NCAs do not follow. Throughout the focus groups suggestions were given for an optimal duration of each phase and how to contribute to achieve these timelines. In addition, critical areas were identified "where we want to propose something new and something different."

"With FDA and IDE, whether it's EFS or a major study, it's a 30-day review and they almost always hit that with rare exception. That predictability in Europe is probably a big ask, but that certainly would be the goal."

The smaller HTDs said they had the impression that some NCAs were reluctant to accept premarket studies for novel devices due to time needed for validation and assessment.

Some HTDs found a timeline of 106 days for EFS approval acceptable, while others found that the 30-day timeline for evaluation after the pre-dialogue process as known from FDA desirable. The process under FDA often results in a conditional approval for a staged enrolment of patients. Under the MDR, some HTDs described that the NCAs tend to accept all or nothing in compliance before approving an EFS. HTDs described that conditional approvals could be beneficial in terms of an iterative approach, timelines, and the risk evaluation for patients under MDR.

For advanced and innovative devices, the NCA may use external clinical specialists, which can prolong the evaluation period. The list of questions from the experts to the sponsors can be long. A suggestion was made to ask for a prioritised and shortened list of questions from the experts involved.

[35] Deliverable 2.2; Research and analysis on regulatory framework, and institutional and organizational characteristics of EU competent authorities

Iterative Approach and modifications during EFS

Currently the communication with the NCA is during the application and evaluation period. Communication often consists of questions which are sent from the NCA to the sponsor, and this process was described as exhausting and led to longer timelines, with several rounds back and forth. Several factors were mentioned as rationale behind this. This process may be necessary for the NCAs to understand the CI and the details of the intervention so as to become sufficiently informed to assess an application.

"Super helpful if we could all agree that there will be changes that will come and let's just agree to keep it in one study and go from there."

The challenges are mostly related to applications and evaluations process of the main study and not to the interaction with the NCA and ethic committee for modifications during a CI. However, the opportunity to discuss possible changes in an EFS at an earlier stage and establish a constructive dialogue was seen as positive. Early dialogue to discuss possible changes that may be necessary in an EFS, to increase understanding of an innovative device, and risks associated with it, was believed may contribute to a smoother application process.

The HTDs agreed that early interaction with the NCAs would be beneficial and expressed the wish for expertise in the different medical fields, although it was felt that this may not be realistic in the short term. A proposal of regional NCA collaborations with allocated expertise from learned societies, such as medical specialities like orthopaedic and cardiovascular, was discussed drawing parallels to the EMA for medicines.

Interactions Around Amendments to EFS

Experience reported was limited on issues concerning dialogue around possible design changes, and planning for these changes together with the NCA before the EFS is initiated, but it was seen to have the potential to avoid application delays during the EFS. In their experience the smaller HTDs have found that to apply for modifications to the device during a CI is not seen as a hurdle, changes are under normal circumstances accepted within 1-3 months. In some situations, pauses are made to conduct amendments and resubmissions.

From experience, staged enrolment with an initial five patients which may show the need for modifications to the device, once these changes are made then the EFS continues with the new version in five more patients. This has been an accepted approach for EFS from some NCAs.

Harmonisation of a Future EU EFS

In the future, the HTDs proposed that dedicated assessment teams in the NCAs for innovative high-risk devices would be beneficial, and for consistency during notifications and assessment of design changes, the same evaluation team would receive any documentation on amendments. The HTDs suggested that one way forward would be to identify those NCAs with experience in the field and with innovative devices as this would lead to more streamlined interactions and predictability from all sides. However, they stated that dedicated assessment teams may not be realistic as all NCAs would have to have this approach, meaning that these dedicated teams would need to have authority across member states. A similar suggestion also came from smaller HTDs, in line with the European Patent Office -system, where a centralised decision is made at the EU-level with national adaptations, this is also based on the experience that resources for the NCAs at a national level can be challenging for some countries.

Interactions with Other National Authorities including Ethics Committees

Ethics was identified as both challenging and unpredictable depending on which MS the EFS is planned to be conducted in. The smaller HTDs said they would also like pre-submission meetings with ethics committees.

The larger HTDs also stated that other national authorities can be involved, for example in the case of radiation approval. In some MS, additional approval from the ministry of health in addition to the NCA and ethics committees may be needed. All these additional approvals were described as taking time and varying from one MS to another. Coordination between NCAs and other national bodies would lead to more predictability and streamline the process.

Interaction with other EU Bodies and Specialised Assessment Teams

As mentioned, the HTDs are positive to specialised assessment teams, especially if they are more experienced in high-risk fields and innovative devices, thereby leading to more predictability.

Pilot Coordinated Assessment (CI/PS)

The pilot for the MDR's Coordinated Assessment (MDR Art. 78) started in February 2025 and the HTDs were positive to this initiative, the actual Pilot Coordinated Assessment is described in more detail in Section 3.2.5. One concern raised was however, that the CIPS (Pilot coordinated assessment for clinical investigations and performance studies) may lead to prolonged timelines due to the coordination between the NCAs.

> *As long as it [the Coordinated Assessment] helps the speed [of approval] - … some competent authorities may give up a little bit of their control…but an increase [in] the predictability and that is really what is important for the sponsors."*

Some HTDs expressed that Coordinated Assessments are valued and would be a benefit if timelines for evaluation can be reduced. Others expressed that an overall benefit with smooth processes also through amendment process during the EFS would balance the excess use of days during the approval phase of a Coordinated Assessment. It was highlighted that an issue for the NCAs may be a reduction in national control from the participating NCAs compared to the coordinating NCA. Coordinated Assessments are envisaged to increase the harmonisation and predictability during the application process, which is important for the sponsors, and beneficial for the NCAs. In this process the NCAs are restricted to 60 days during the validation/evaluation period, however, it was reported that the use of this limited time is currently exceeded in most countries in Europe. For the HEU-EFS pilots a multi-centre study which involves more than two countries is less likely, but if it was it could qualify for the pilot Coordinated Assessments.

MDR Expert Panels at European Medicines Agency (EMA)

The Scientific Advice of the EMA Expert Panels (ExP) may lead to a more harmonized and efficient NCA evaluation in the process for EFS. However, the degree of delegated authority given ExP scientific advice is not, as yet, established, but the expertise and the expert panel opinion could be a vital key to success. More details on the process are described in Section 5. The interaction with the ExP may reduce the timeline during the NCA application validation, if the interaction can reduce the number of individual national experts needed. However, the higher number of experts in the panels and the presumable variability of opinions may impact predictability and may have a negative impact if opinions are heterogeneous. It was also highlighted that the experts in the ExP may not be experienced with clinical investigations, as the conflict-of-interest process removes those who have collaborated with device developers, and those who collaborate and sit on the boards of HTDs. This may limit their ability to provide relevant advice for innovative, high-risk devices. The HTDs stated that the experience with EFS in Europe is limited and felt that the NCA experience is mirrored by the excess use of NCAs external experts when evaluating EFS applications. The partners mentioned that travel, language and cultural differences could lead to disadvantages in performing an EFS or other studies in Europe.

The HTARs Joint Clinical Assessment and Joint Scientific Consultation may be beneficial because of reduction in the need for national experts, as they leverage the ExP clinical experts. For orphaned devices these expert panels might play an absolute role, as there may be few national experts.

4.3. Focus group with Clinical sites who run EFS

Experiences with EFS-like studies

Most of the clinical sites had experience with EFS initiated by external sponsors rather than in-house innovations. These studies were not explicitly described as EFS. The EFS conducted were often high-risk invasive devices, particularly in the areas of cardiology, nephrology, and oncology.

Sponsors of EFS

The clinical stated that sites are most often selected by the sponsor, key to selection is often the Principle Investigator (PI). Clinical sites noted that their willingness to take on a study is often dependent on the sponsor's prior experience with EFS and their understanding of both European regulatory requirements and national frameworks. Familiarity with the ethics committee application process for clinical investigations is also considered important. However, some MS have had a national initiative for tender processes, where the clinical sites have applied to take on a study, supported from the regulatory and economic perspective.

Principal Investigator

The Principal Investigator (PI) is typically responsible for overseeing the clinical investigation. Their input is essential from the early phases, particularly during the drafting of clinical and regulatory documents such as the Clinical Investigation Plan (CIP), to ensure accurate and comprehensive coverage of clinical aspects. They are involved in the study design alongside the sponsor, but do not directly take part in the submission process of clinical investigations to the NCA and ethics committee. If the involvement of the PI helps to expedite the process by clarifying clinical issues or addressing requests from Ethics Committees and NCAs, the PIs at the clinical sites welcomed this. However, this involvement should remain strictly within the scope of their clinical expertise and be sought only for matters of that nature. Without encroaching on the sponsor's responsibilities, the PI's role must be limited to urgent and relevant issues pertaining to clinical questions.

It is important to note that the physician involved can either be the Lead Principal Investigator (Lead PI) of the study or, alternatively, an independent Medical Advisor or Key Opinion Leader (KOL) designated by the sponsor. The clinical sites emphasised that the specific choice here is less critical than ensuring qualified medical oversight is present.

The final version of the CIP submitted to the NCA must be the final version approved by the Coordinating Investigator, PI for several sites. If there are clinical questions about the EFS study raised by the NCA or ethics committee, it is often the PI / Coordinating Investigator's responsibility to provide a response. The PI is involved in the process, in the background, but are not directly involved in exchanges and discussions with the NCA and ethics committee.

Some clinical sites are familiar with their NCA and initiate an informal dialogue when planning CI, that their PI is well known to the NCA is a great advantage in the process.

Some differences also emerged during discussions. In certain countries, there is a dual-level national responsibility for clinical investigations, where a Coordinating Investigator is responsible at the national level, and Principal Investigators are responsible at each individual clinical site. Nevertheless, the Coordinating Investigator often holds a role equivalent to what is internationally referred to as a Principal Investigator.

Additionally, some clinical sites reported initiating informal dialogues with their NCA when planning clinical investigations. In these cases, having a PI who is well known to the NCA was considered a significant advantage in facilitating the process.

Training provided by Sponsors for Sites Undertaking EFS

Both clinical sites and sponsors play a role in training of personnel involved in the EFS, but for new and innovative devices it is seen as key that the sponsors be able to provide training for clinical staff. Sponsors often have their own training programmes, specifically tailored to the device under investigation. Often one-two clinicians are trained by the sponsor and these clinicians then continue the training others internally, the sponsors are also often present during the first implantations.

Phased enrolment to EFS

For pivotal trials the clinical sites described that there is a so called ‘rolling -phase’, to improve the learning curve of clinical staff, where the clinician operates on a few patients, and these are monitored, as the device is new for the clinician. This aids the clinicians reaching plateau, they perform a series of 5-10 cases assisted by a proctor or sponsor. Therefore, based on this experience, the phased enrolment of EFS would not be difficult to integrate into their internal procedure. They also described that a staggered enrolment could be a condition of approval from the NCA.

Iterative Approach and modifications during EFS

As design changes are seen as the aim of EFS, the ability accommodate these are key to from clinical site perspective. The sponsor must be able to achieve approval for amendments quickly from NCA, and NCA must be responsive in their decision. Then, repeating training for the clinical staff involved in the study, if the device changes affect the procedure. Mapping potential scenarios, to anticipate changes, especially related to adverse events or adverse effects is important. Harmonisation of a Future EU EFS

The clinical sites agreed that a more harmonised approach is needed to promote innovation and clinical research, to ease the process and clear pathway for sponsors. They also brought up the idea of dedicated NCA assessment teams, that this would be an advantage to allow more predictability.

Dialogue with NCAs was seen as key, to allow sponsors and sites to describe new devices and procedures and understand if specifics in the applications were unclear.
The new website for Clinical Trials related to the new Clinical Trial Regulation (CTR)[36] in EU for medicines has raised awareness and shown harmonisation is possible. It also shows clinical sites maps where clinical research in EU is performed.

Interactions with NCAs and Ethics Committees

Involving the Lead PI in an Early Dialogue was described as highly beneficial. However, in some previous multi-national site CIs, they have experience where the Lead PI was either not fully committed or had limited availability for meetings over several months. Such limitations have previously caused delays in other types of activities within a Clinical Investigation.
If this issue arises in an Early Dialogue meeting, it would ultimately impact the study approval timelines.

To prevent similar issues, the Early Dialogue process would demonstrate strong commitment and availability. If the Lead PI is unable to consistently participate, it will become apparent and be proactively countered.

Interactions with other EU Bodies and Specialised Validation Teams

NCAs or Ethics Committees may raise questions related to centre-specific details that typically can only be addressed effectively by the centre's investigators. Furthermore, involving each centre's investigators are crucial not only for clinical oversight, but also for administrative reasons. Certain documents require their signature, and any delay in securing their participation can subsequently delay submission and approval timelines.

4.4. Focus group with PAG

During a face-to-face meeting with the PAG immediately after the annual meeting 2025 we introduced them in more detail to the proposed process and provided a case-study for a device that has been through an EFS, including patient engagement activities. These include patient specific material for trial education, patient journey mapping, patient listening sessions, patient preference studies, as well as definition and inclusion of patient centric endpoints and assessments. We then discussed the process in detail. While the workshop was mainly conducted in person, a small number of PAG members and partners joined the focus group online.

[36] Clinical Trial Regulation

In the discussions, PAG members underlined the lack of meaningful patient representation in Ethics Committees, criticising current approaches as insufficiently inclusive and sometimes prescriptive. They called for meaningful engagement of patients throughout the lifecycle of devices not only for inclusiveness purposes, but also to ensure that medical devices meet the real needs of patients, also contributing to more cost-effective research.

To the question whether regulatory oversight is needed, PAG members noted that it generally is to ensure patient safety, but a balance must be found to allow testing and trials of potentially life-saving products. Transparency must be at the core of the EFS process. partners clarified that EFS “best practices” are still emerging due to limited NCA participation in the project, while PAG members valued the diversity of involved NCAs (i.e. both small and large countries); partners added that participating NCAs became more receptive to EFS over time.

On patient engagement and recruitment, PAG members emphasised that unanswered questions create barriers to participation and called for clearer, patient-focused information and endpoints that consider the patient as a whole rather than just the isolated condition. An EFS “support group”, involving neutral parties or patient organisations to support the patient as they go through the EFS process, could be helpful. They highlighted the need for both patient- and clinician-reported data for better outcomes. Partners explained that EFS involves staged, non-randomised recruitment, sometimes excluding co-morbidities, but always requiring comprehensive patient information (as opposed to anonymised patient profile information) due to the small study size. Safeguards discussed included the structured chain of information delivery (from manufacturer to regulator, ethics committee, physician, and finally patient) and the importance of the role of Data Safety Monitoring Boards in ensuring patient protection, including in sham surgery cross-over cases.

5. Methodological Framework: Proposed Process, Procedures, and Timelines

Based on analysis, recommendations from other Work Packages and the Focus Groups, as well as interviews held with NCAs, a newly structured approach for engaging with authorities and ethics committees during EFS process is proposed.

5.1. Eligibility Criteria

The process also builds on the work on eligibility criteria from D3.1. 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.

5.1.1. Technology

Three general device scenarios have been identified as most applicable to conduct EFS under the EU-EFS program:

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.

5.1.2. Medical conditions and populations included in EFS.

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

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.

5.1.3. Level of pre-clinical evidence

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

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’.

5.1.4. Clinical sites and clinical expertise need to conduct an EFS

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.

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.

As a result of the mapping performed of pathways available, focus groups and interviews with NCAs proposed process aims to:

- Ensure readiness and efficiency, including timing, for key actors, both on the side of authorities (NCAs and ethics committees) as well as the initiator (sponsors) of the EFS.

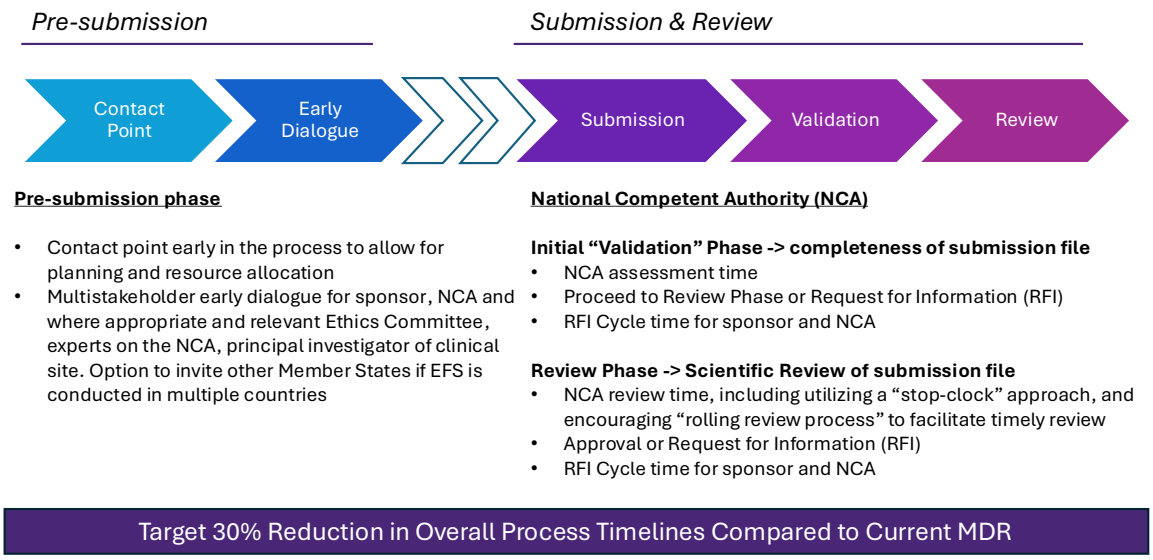
- Improve resources, timing, planning and efficiency, clarify EFS objectives and needs, and identify key potential challenges early on.
- Enhance opportunity to conduct EFS involving investigational sites in more than one MS.
- To strengthen investments into early clinical evidence generation in Europe and provide innovative devices to patients whilst ensuring a high level of patient safety.

For the proposed process the key principles are based on **Early Dialogue, strengthened coordination** and **timing efficiency**. For the benefit of all stakeholders and to provide patients access to the latest technology, while ensuring an appropriate benefit-risk evaluation and a reduction in cycle times (validation and review phases). The goal is a total cycle time reduction of 30% when compared to the timelines presented in Art. 70 of the MDR, shown schematically in Figure 7. Art. 70 defines two phases and provides timelines for each of the phases. The first phase is the described as a validation phase and can conclude in 10 days if the file has been assessed to be complete, however this can extend to 55 days when deficiencies are noted requiring correction of the sponsor. Timelines are articulated for both the NCA and Study Sponsor. The second phase is described as the scientific review phase and can conclude in 45 days if the NCA does not identify any deficiencies, but this can then extend beyond 65 days to accommodate additional information requests of the sponsor by the NCA. These timelines are only articulated for the NCA. Individual cycle times proposed are for consideration and can be used as targets during the pilot phase to assess the suitability of reducing the cycle time by 30%. In addition to reducing timelines previously specified in Art. 70, the sponsor must also demonstrate a commitment to respond to requests from the NCA in a proactive and timely manner.

5.2. The schematic overview of the proposed EU EFS Process to be tested in pilots

The proposed approach shown in Figure 13 will be implemented in a sequence of 3 steps:

Figure 13: Schematic overview of the proposed EU EFS Process to be tested in pilots



5.2.1. Step 1 - Contact Point: Notification

Objectives:

Notify and inform the applicable authorities and ethics committees of an upcoming EFS with the intent to undergo the accelerated process. The notification is intended to be a simple checklist that allows the sponsor to inform the authority of key elements of the planned clinical investigation. This notification shall allow the authority to determine if 1) the technology and clinical investigation are suitable to be characterised as an EFS and 2) if the technology warrants the need to involve additional specialists to support the review of the clinical investigation. 3) Indicate a tentative timing for submission.

Implementation Plan:

This first contact point could take place at any time during sponsor preparation (could be months before actual submission). Written feedback from NCA would be expected in a timely manner (~10 days) and would be anticipated being an acknowledgment of receipt of the information. Could also be a potential confirmation of eligibility for the EFS, such as: "Yes, we believe you are eligible for an EFS accelerated review and your technology is relevant. NCA confirms the need for an expert."

Authorities might request further clarifications or call for a meeting, on which the sponsor would be expected to react within 5 days.

Actions to undertake:

1.0 The sponsor sends an initial email to the NCA with the EFS outline, including:

1.1 Details on the technology:

- Technological eligibility (5.1): unmet needs, breakthrough device, anatomical understanding, new/expanded use
- Risk class confirmation, including DHTs
- Patient population
- Applicable ISO standards

1.2 Plan and timing for Early Dialogue (if relevant) and subsequent submission, plan to submit in more than one Member State.

1.3 Checklist to ensure readiness for EFS, providing early insights to NCAs on the preparedness and experience of the sponsor:

- Quality Management System certificate
- Team / company history and EFS experience
- Declaration that EFS will not solely support Conformity Assessment
- Information on EFS approval / status in other jurisdictions
- Where applicable (and as per future MDCG Guidance when published) technology Breakthrough designation information
- DSMB (Data Safety Monitoring Board) charter or plan
- Patient protection measures (e.g. staggered enrollment, qualified personnel, frequent follow-ups)

In addition to encouraging early interaction with the NCA, engagement with the reviewing/coordinating Ethics Committee should also be prioritised. While some variability in the access to the Ethics Committee is anticipated, attempting to include the reviewing/coordinating Ethics Committee in the Pre-submission phase may allow for future interactive discussions on the CIP, Informed Consent Form (ICF) and other Ethics Committee submission deliverables. Where relevant and if clinical sites are already identified, an email should also be sent to the Ethics Committee about the EFS plan.

When the technology under investigations is determined by the NCA to meet the EFS eligibility criteria and the documentation prepared in support of the 1.3 Checklist validates the sponsor's readiness to conduct the EFS study, accelerating the review of the EFS study as compared to the timelines articulated in Article 70 shall be encouraged.

5.2.2. Step 2 - Early dialogue in pre-submission phase

Objective:

Interact with and give the opportunity for the pre-identified NCA to review and discuss specific aspects raised at the request of the sponsor. Information should be provided by the sponsor that allows the NCA to have sufficient background to provide appropriate feedback.

Implementation Plan:

Sponsor triggers request, meeting to take place within 30-60 days

Actions to undertake

2.0 Sponsor preparations:

2.1 High-level details similar to the contact point

2.2 EFS synopsis, including purpose, endpoints/outcomes, follow-up, and oversight

2.3 Prepared relevant questions with background details for NCA.

2.4 Discuss potential changes during the EFS rollout when anticipated.

2.4 Indicate the timing of submission by the sponsor.

Participants:

- Main participation would be expected to be the sponsor and the (lead) NCA.
- Offer the possibility for NCA experts, Ethics Committee, and clinical site investigators (PI) to join. In case of multiple MS, additional NCA could be offered possibility to join.

5.2.3. STEP 3 – SUBMISSION (validation and review process)

Objective:

Submission and validation by NCA

Implementation Plan:

Sponsor submits application. Validation to take place in a timely manner, aim to achieve overall timing efficiency as noted in decision tree provided below (Table 3).

Actions to undertake:

3.1 **Sponsors Submission to system** (online platform with information repository on CIRCABC if available) – sent to NCA, and Ethics Committee if allowed by national processes, and other MS where appropriate. In cases where an online platform is not available, submission shall proceed according to local requirements.

Submission file includes:

3.1.1 EFS Eligibility criteria: technology as defined in Section 5.1 - anatomical learning, new/expanded intended use, unmet need/breakthrough device. Focus on Class III and Class IIb

3.1.2 Clinical Investigation documentation: Ensure and justify appropriate documentation for the intended use of the device in the stage of development, taking into account the specificity of an EFS. Consider MDR Annex XV, and provisions in MDCG 2024-5 chapter 2.3.2 (and checklist in Appendix A).

3.1.3 EFS qualification for accelerated review.

3.1.4 It is also suggested to review the website for the reviewing/coordinating Ethics Committee to ensure the application and submission deliverables are clear and provided in the initial submission. The deliverables from Work Package 6, will also support the application to the Ethics Committee.

Table 3: Decision tree

NCA(s) Action	Initially proposed timing
Initial "Validation" Phase: completeness of submission file	**7 – 39 days** - *NCA assessment time: 7 days (12 max)* - *Proceed to Review Phase or Request for Information (RFI)* - *Target RFI Cycle time: Sponsor 7 days (17 max), NCA 5 days (10 max)*
Review Phase: Scientific Review of submission file	**30-45 days** - *NCA review time: 30 days (45 max) utilising a "stop-clock" approach and rolling review option to address real time NCA observations* - *Approval or Request for Information (RFI)* - *Target RFI cycle time: Sponsor 20 days (30 max), NCA –utilise time remaining at point of "stop clock".*
TOTAL	Overall, 30% timing efficiency compared to current MDR (Objective for timing could be from 37 to 84 days).

5.2.4. CHANGES During the Conduction of EFS

It is anticipated that during the EFS, learnings from completed procedures may necessitate the modification of the investigational device, the study procedure, CIP and/or the ICF. To allow for continued learnings, changes shall be supported with evidence consistent with the original application with an emphasis on allowing more changes to be categorized as non-significant changes (MDCG 2020-3). Justification for supporting the categorization of the change type shall be maintained by the study sponsor. When the changes have the potential to impact the risks to the patient (or could negatively impact safety and performance), a more conservative approach should be taken when implementing the change. To expedite the implementation of the change, pursuing dialogue with the NCA and/or Ethics Committee should be considered. Ultimately, change management will be conducted in accordance with MDR Art. 75 or existing national policies.

Pre-planned changes known ahead of study initiation should be articulated to the NCA and reviewing Ethics Committee during the Pre-Submission phase either through inclusion in the Contact Point communication or a topic of discussion during an Early Dialogue meeting.

6. Outlook and next steps

As described in the Introduction, the proposed framework builds upon the deliverables from both the earlier and parallel work packages, which have culminated in the proposed process which is to be tested in the pilot use cases. The process will be further optimised based on feedback from the pilots, which will not only use the process proposed but also make use of the WP3-developed guidance WP3, checklists WP4,6,7, and templates from other WPs to form the EU-EFS framework.

In addition, this future framework is intended to be adaptable to digital health technologies (DHTs), recognising their growing role in the healthcare innovation landscape. Though DHTs differ from traditional MDs, there is a clear need for a harmonised approach within the EU-EFS framework. During the optimisation phase both during and after the pilots a dedicated Taskforce has been established for DHTs to ensure that the framework accommodates the unique aspects of these technologies.

The landscape of medical device regulation in Europe is currently in flux, as amongst other developments, the interplay between the AI act and the MDR has only just begun to be interpreted, and the first MDCG guidance https://health.ec.europa.eu/document/download/b78a17d7-e3cd-4943-851d-e02a2f22bbb4_en?filename=mdcg_2025-6_en.pdff was recently released. At the same time, both the MDR and IVDR are undergoing a targeted evaluation. The consequence of this evaluation is expected to be substantial where the key topics that have been mentioned are ‘increased predictability’, ‘proportionality’ and ‘simplification’ amongst others. Additionally, a ‘Breakthrough’ guidance is expected to be released before the end of 2025, the scope of which is believed to fit well with the type of devices that the HEU-EFS project is expecting that the EU-EFS framework will be relevant for. Finally, the HTAR is only just coming in to play for MDs Over the next two years, experience gained through the first Joint Scientific Consultations (JSCs) and Joint Clinical Assessments is likely to inform further adaptations and optimisation of the framework.

Based on the expected regulatory changes, the enactment of the HTAR, the incorporation of DHTs, and the feedback anticipated from the pilots, the EU-EFS framework proposed at the end of this project may differ significantly from the version presented here.

For practical purposes, we are also developing a Guidance document immediately following the submission of this deliverable, which will provide a user-friendly guide of the proposed framework and consolidate the different components of the EU-EFS framework, illustrated in Figure 1, drawing together all the deliverables to date such as the eligibility criteria, process and timelines, templates and checklists, and key performance indicators. This Guidance will subsequently be revised and submitted as the final project deliverable (D3.3).

7. Appendices

7.1 Interview protocol for NCA interviews

Introduction

The present document has been created as part of the **Harmonised Approach to Early Feasibility Studies for Medical Devices in the European Union** (HEU-EFS) project (Grant Agreement no. 101112185). Funded by the Innovative Health Initiative (IHI), HEU-EFS aims to develop a robust, standardized methodology and set recommendations to streamline Early Feasibility Studies (EFS) within the EU. More information can be found in the official project website: https://heuefs.eu/.

The aim of the interview is to explore your **experience with EFS-like studies** and your visions on the desired characteristics of a **potential harmonised approval process** for EFS in the EU.

Experience with EFS-like studies

As part of the project we created a comprehensive **database of EFS-like clinical trials** gathering data from international registries, literature reviews, news sites, and various other sources.

For **EFS-like study** we refer to studies with the following characteristics:

- Description in title or summary of the study as **«early feasibility»** or **«EFS»**

OR

- **Pre-market clinical investigation** (e.g., early feasibility, proof of concept, first in human) of medical devices or drug-device combinations AND
- Study type: **Interventional** AND
- Estimated sample size **<= 30** AND
- Interventional mode: **single group assignment** AND
- Masking: **None** (Open label)

In the excel file attached to the email that we sent you, there is a list of EFS-like studies that have been approved in your country. With reference to those CIs:

1. Do you consider that these studies are Early Feasibility Studies?
2. What were the key considerations that led you to authorise these CIs? Do they differ in comparisons with other pre-market CIs (pivotal, traditional feasibility studies)? If so, how?
3. What specific challenges did you encounter during the validation and evaluation processes?

4. Since the design of the device may not be completely set, how did the sponsor manage any modifications to the protocol and/or product?

Desired characteristics of EFS in the EU

As part of the HEU-EFS project, we are aiming to identify areas of harmonisation for application and evaluation/validation of EFS in the EU, while remaining aligned with the MDR and MDCG guidance documents. In particular, we have identified the following areas:

Harmonisation

5. In your experience, do you feel that evaluations/validations differ among Member States' NCAs?
6. What are the main challenges to develop a harmonized approach to EFS in the EU?

   [Probes: coordinated regulatory interaction, ethical approval, templates]
7. What opportunities would you see to have a more coordinated or harmonised approach to EFS in the EU?

Dialogue between NCAs and sponsors for EFS

8. Do you as a NCA offer a dialogue with sponsors? If so, how is the dialogue process structured?
9. In case a dialogue process is present, would you recommend specific guidance to the sponsor on dialogue in EFS?

   [Probes: dialogue initiation; dialogue modality; discussion of CI design; discussion of pre-clinical testing requirements]

Efficiency of EFS applications evaluation

10. What specific areas of the application can be improved (from the sponsors side) to facilitate the evaluation of EFS applications by NCAs? What are the most common issues in the applications hindering timely approval?
11. Are there areas where the sponsors preparing an EFS application could need support to ensure timely evaluation?

    [Probes: pre-submission guidance; compliance with MDR; expert panels collaboration; coordinated assessment]

Improved ethical approval process for EFS

12. Is there an optimal model for ethical approval - before, after, or in parallel - with submission to NCA?
13. In your experience are your evaluations/validations aligned with the ethics committees?

7.2 Full quotes supporting themes generation from NCA interviews

Theme #1: Lack of formal EFS definition and homogeneous assessments across NCAs

“It wouldn't make any difference to us with regard to whether or not they would fit the definition of early feasibility studies under ISO because that doesn't stand in the European regulation like that. That's an ISO [definition] and it's in the FDA, but the MDR doesn’t use the term Early Feasibility Studies.”

“We do not have a legal or regulatory framework for looking at it differently and I think that's the main point.”

“The [assessment] approach until now—or until recently—was essentially all studies were treated the same, whether the sponsor had qualified them as a first-in-human, early feasibility, or a pivotal study.”

“We do not specifically look at the fact if it's early feasibility or not, we usually make a general risk score to see what type of expert needs to have a look at it."

“Our scientists or engineers would treat all that [bench and preclinical work] the same, sort of agnostic of whether it’s early feasibility or not.”

“It's the same considerations topic wise for early feasibility studies and pivotal studies. So both need to be [compliant with] the state-of-the-art when it comes to biocompatibility sterilization, statistics, and documentation that needs to be provided. Everything regulatory that has to be looked at is the same.”

“The [EFS] assessment is different in the way we assess the data and also in monitoring the patient. […] We follow that kind of study [EFS] with the higher grade of vigilance.”

“[During EFS assessment] we can have specific recommendations regarding the design of the study, the Data Safety Monitoring Board […], and the assessment of vigilance of the study because we have also risk assessment procedure for our assessment of vigilance of clinical trials.”

"What's the most important thing for us with all these studies is to see whether there is really a completely novel technology, let's say, or whether it is well-established technology which is now used for an out-of-scope indication or another anatomical site."

Theme #2: Poor EFS documentation quality and limited evidence on novel technologies challenge NCAs’ validation and evaluation of EFS.

“Challenges during the validation and evaluation [of an EFS] could be the organisation and the composition of the submissions […] because for a sponsor with not a lot of experience, it could be very difficult to have a submission [that is] well prepared.”

“Some applications are very cumbersome and not organized. Sometimes we receive 100 files for the same application, [with] the investigator's brochure [that] is not redacted according to the MDCG guidelines and [without] a summary of the different clinical tests done […] So it's a big problem and it takes a long time.”

"If you have an experienced sponsor, even if they're doing an early feasibility study, they know what to include in the documentation. While a small academic spin-off [...] you might have more issues with quality of documentation."

"In my experience, the quality is the worst for the non-commercial and universities [...] I don't want to say that they're all as bad, but usually we have seen protocols of four or five pages, which is really not sufficient."

“We had the issues of signatures - that are missing very often and asked for the validation - [and] Ethics Committee [which is] very important.”

"Another [challenge] is if it's a completely new design or new way of introducing a device or something, you also need to really well understand the mode of action. And that is sometimes hard to completely understand from the sometimes limited information that is included in an investigator’s brochure."

“Challenges concerning the [EFS] assessment are mainly on the preclinical data, security [safety] data, mechanical data. It takes a lot of time to read all the documents, and it's also very complicated when the medical device is a complicated medical device. Sometimes it's difficult to understand the mechanism of action of the different piece[s] of the medical device.”

"If you have a completely new design, there are often no ISO standards, no guidance, nothing... About fatigue testing, bench testing, there’s no ISO standard that says these tests have to be performed in order to say the design is safe to go to clinical testing."

“For us [NCA], the worst situation is if [when] there are no human [clinical] data. And that's the most critical issue for us.”

Theme #3: Device and protocol modifications during EFS studies are common and managed on a case-by-case basis, posing challenges for NCAs in ensuring data integrity, study validity, and risk management.

“The protocol could be modified after the first patient [is treated], [which] is the aim of the studies [EFS]. So, for us it's not a problem [to allow device modifications] if we have the right documentation and right explanation […] if it is in the way to improve the safety of patient, it's always good for us.”

"We sometime have discussion with them [sponsors] because if the design of the device changes a lot, we could discuss with them to close the study and to start a new study. If the difference[s] are too huge, sometimes it's not scientifically correct to measure the result[s] [outcomes] of patients [who have] been treated with different devices."

"Ad-hoc is better because we will reassess when they [device designs] will change."

"Sometimes modifications need new preclinical testing, but sometimes not. It depends on the modification."

"You have a device, the device is modified, and from us [our perspective], [we ask ourselves] 'is it [study being conducted] with a modified device? Is it a completely new study? or is it still the same study?' and that's a difficult question [to answer]."

"We had a lot of experiences with small companies who try to develop devices, and they change it continually during the clinical trial and [what] happened [was that in the end] they pool all the data."

"It's very difficult even for us, who really, deeply traced all the development. [And] this [change] could be small steps in the development, some not substantial, some a little bit more substantial. It's a scale, it's not black and white. [And] at the end of the day, they [sponsors] have the final device, but the data that they have are not all [related to] the final version of the device."

"It's very difficult to distinguish what device was used in each patient."

"We sometimes want to manage risk by phasing the study [and] to have first 3, 4, or 5 patients just to manage risk."

"[There] was a clinical trial that originally planned approximately 50 patients, but it was first-in-human. So, they [the sponsor] submitted these 50 patients. They wanted to submit, but we agreed with them that they might submit as step-by-step process first [with] six patients […] They wanted to apply then evaluation and then if we agree, they could continue."

"When we receive substantial modification, we make a new assessment to see if the device has substantially changed or not, and if it has substantially changed, then we forward the modification to an expert to have a deeper assessment."

Theme #4: Dialogue improves EFS assessment efficiency and speed through NCA adaptability and sponsor cooperation.

"We encourage manufacturer[s] to come early during their development to have a discussion with us, and we always experienced that when there was a scientific advice previously, the solution and the assessment is [was] quicker [and] easier for both sides because we have already discussed the

project, we have already understand [understood] what are [were] the aim and what they [sponsors] wanted to demonstrate."

"[Sponsors] want to take advantage of the dedicated meetings with the goal of ultimately reducing the actual assessment time during the official submission."

The smart ones [sponsors] are cooperative because they feel rightfully that [dialogue] might speed up the approval process. […] If they [sponsors] are cooperative, they basically speed up our evaluation process."

"For all of our scientific advice, there is a specific submission [required for sponsor] with a wishing book, which is prepared by the sponsor, and we work based on this guidance in the wishing book. […] [Dialogue] could happen generally after their [sponsors'] request of information, [which happens] when we send them a list of question […] and just before taking our decision we could have another dialogue with the sponsor to solve the issue[s]."

"The disadvantage is of course that it's not for free anymore... but we do make a difference between quick, frequently asked questions which we keep providing for free. If we can answer it within 15 minutes, if it doesn't take more than 15 minutes of our time, we respond just by e-mail. […] There's different types of scientific advice. We have scientific advice regarding the qualification, we have classification, we also have pre-assessment, pre-submission scientific advice... Type 1 is just for a simple question... if you go up to Type 3 then you can have a meeting and then it's more people involved and more questions."

"We do have dialogue with sponsors to prior to submission. In terms of the dialogue structure, we have pre-submission meetings and we request sponsors to send in a pro forma prior to the pre-submission meeting and then that will lead to them sending in some information on the study. […] There is some structure to it [dialogue]. We don't have a detailed pathway to prior to submission, but we are open to what sponsors want because the needs of sponsors can be very different in terms of if you're an SME [or not]. [For example] if you're a small and medium enterprise with a non-invasive device wishing to do a small study it's very different to a large enterprise with a Class III device. So, we're not massively [or] hugely structured in what our process is."

"How it works is that we are approached by sponsors. In [our NCA], we are a rather small department, and we have the possibility [for sponsors] of sending us e-mail questions, and we answer all of them."

"The department is quite accessible and you can reach out to them to have a dialogue. We do filter, we do explain what we can do and what we can't do. So the dialogues we had so far were mostly where people really had no clue about how it works with our competent authority, what we offer, what we need."

"We found out that [pre-submission discussion] is extremely useful tool, [especially when] the manufacturer [sponsor] is willing to cooperate and is willing to kind of adjust the protocol. But it's difficult for us because we are not allowed to pre-review the documentation."

"We do have a kind of better experience with pre-submission discussion with smaller companies than with bigger corporates who have their own views and own rules."

Theme #5: Coordinated Assessment Pilot helps NCAs share learning from and collaborate with each other, paving the way for a unified EFS assessment approach in the EU and an MDCG-endorsed guideline.

"There are differences [in the assessment] because sometimes we don't authorize some [clinical] trial, which will be authorised in [by] other competent authorities. So, there we are sure that there are differences in our assessments."

"There is a very big difference [in terms of evaluation/validations of EFS] among member states […] we mainly look at it from the article point of view - Article 82, Article 62, that's our main issue. - And here, yes, I see big differences."

"[Having a harmonised approach] might be difficult because we might think differently than our colleagues in other countries. And also, even if we agree [on] how to do the phasing of clinical trial […] that might be OK for [our NCA], but that might not be so OK for [an]other country."

"Harmonised standards can be very vague sometimes, and it can be difficult for manufacturers [sponsors], especially with these type of novel devices, to justify that they have done preclinical testing to the point to which preclinical testing is no longer acceptable that you need to go to human [clinical] testing."

"The challenges will be to fix what are the minimum data needed to authorise this type of studies [EFS]. I think for implantable device and non-implantable device it [the assessment] is not the same […]."

"[It] could be interesting to have a guidance and a shared vision between competent authorities regarding what is needed to start [an EFS]."

"It already starts there [beginning of the application] — we need harmonisation, we need to talk to each other and need more guidance or best practices on that."

So, there's already a need for harmonisation at the very beginning of the application."

"If there was [were] more standards available and guidance on the preclinical testing, that would alleviate a lot of the big challenges."

"A more harmonised approach to ethics would be something that I feel would be very helpful."

"[it] could be interesting also to harmonize our work practice with other competent authorities to have a guidance particularly regarding the design […], the preclinical data and preclinical requirements, the minimal data that are needed for this type of study before the first patient [is enrolled]."

"[…] developing slightly more prescriptive guidance might be needed [...] but it's a way of how does that get taken on board into ultimately an MDCG-endorsed guidance."

"Currently we are in the way of Coordinated Assessment. We [will be] start[ing] the pilot phase soon and we are very happy to start this pilot phase. We also have an assessor forum, in which we can share our experience and our assessments. And I think all these tools are very important to learn of each other."

"[The Coordinated Assessment] will be a way for sponsor[s] to have more harmonised view of their trial in Europe, and I think it's really important [for them]. And it's also important for us to learn the practices of our colleagues and to share [our practices] with them."

"This coordinated assessment process that is very helpful. and member state[s] [can decide to participate in] it without any legal necessity, without any legal obligation, but really just freely because they want to help. but at the moment it's limited to high-risk multinational commercial studies."

"Big help is the assessor's forum […] where we can just talk with each other and that is a big help for harmonization ….] just presenting to each other such cases and applications; and talking about our decision [making] is already harmonizing things. So, the assessors forum is really a big help from the CIE between Member States."

"I would hope a couple of NCAs […] would collaborate on the assessment. So, I think that's something that could be done realistically without any changes of legislation or amending the MDR, that we could do, you know, within the next 18 months or so."

Theme #6: Following up with sponsors for additional data and providing standardised templates help address and prevent missing information EFS applications.

"Yes, the most [common] issue for that kind of study [EFS] is the insufficiency of safety data. For example, sometimes we have no animal study or [we have] animal study, but with a time [that is] not enough [in terms of] length. For example, for an implant, if the animal study has been done only for six weeks, that is not sufficient. We need a longer animal clinical study to have good information concerning security [safety]. And sometimes we need six months for animal studies. It depends on the medical device."

"Most common issues for these applications of EFS are safety preclinical data. So we need to have - even if it's early feasibility - enough safety aspects for the patients […] because we have applicants who want to go into patients too early."

“Sometimes we [don’t] have the Data Safety Monitoring Board. […] So, it cannot be acceptable.”

"For the validation... sections missing in the Clinical Investigation Protocol or Investigation Brochure, documents missing, documents not properly signed. These are the types of things that we usually encounter during validation. And like I said, they happen for all applications, not necessarily EFS-specific."

"The biggest issue we see is that documents are missing, and especially the preclinical part. [...] If you have just a very short summary of the testing that has been performed without any details and referring to test reports which are not included, then you have a problem."

"We have a guidance document which clearly states that essential test reports should be included in the submission, but applicants apparently don't read it or forget it, they lose time with it."

“And for me, it's always excellent sign if I ask for the data […] [and] I see that the manufacturer [sponsor] really solved that problem based on the data.”

“We required some things which we usually do not require at such kind of depth with other trials, [for example] a very precise description of the standard of treatment. In other words, what would happen with the patients if they were not treated by the investigational device. Rarely, it's as detailed and as precise as I would like to have it and see it and that's very frequently the reason why we are asking manufacturer to rework on that because that's where the risk analysis comes from.”

“We ask for investigational plan of the device just to prevent that in several countries they are running parallel early feasibility trials which is not ethical.”

“We ask for complete data for biocompatibility, which is usually a huge file […] because for some devices it's crucial.”

“What is absolutely crucial for me, for implantable devices, [is to have] data from labs with good lab practice, and we ask for very detailed histological data and protocols.”

"[Templates] would help with all required sections and information to be there. If they fill out a template and they see this section, then they would know they need to fill it out.”

Theme #7: Diverse ethics approval models—whether centralised, decentralised, parallel, or sequential— across Member States generate operational struggles for NCAs and underscore the need for a harmonized model.

“Ethical approval is a little bit pain in [our country] comparing to [other] countries. And this is why: we do not have one or few ethical committees, but [we have] ethical committees [that] are let's say organisational [organisations] which [that] are established by [consist of] the healthcare providers. And so, every centre has Its own ethical committee, and the review of ethical committee needs to be

part of the submission to the regulatory authority, which might be difficult for manufacturers because the evaluation is not going in parallel. And issue[s] might come from that, especially if we want to ask for changes. Which is quite probable if we do not discuss before submission […] so they [sponsors] have to go again with that change to these ethical committees."

"Ethics approval is one thing, though, that is an issue on a European basis, and there are different approaches to ethics [approvals], and that is a problem.

"I believe in Europe [has] discrepancy for member states if they need the Ethics Committee before, during or after approval."

"if you're trying to do a multinational study and you have a parallel ethics NCA submission option in one Member State, and you have it sequentially in the other, I think a challenge, up until recently, [is that] individual Member States have no visibility to [of] each other's assessments."

"We have one ethics committee, and we have a very good relationship with them and we meet with them frequently, and I think that very much helps everybody; it helps sponsors as well, even if they may not know it, because issues come up that are solved before they reach kind of an official query problem."

"We need to consolidate the assessment report of the ethics committee with our own assessment report and then sometimes discussions may arise. It kind of adds an additional step to the whole procedure."

"The way we work I think the sponsor really likes it. For us it's more work because we do need to validate also the ethics documents, we need to provide all the information to the ethics committee through the CT College, which is a department within another governmental structure in [our country] who selects the independent Ethics Committee and forwards the documentation to the Ethics Committee"

"The positive part is that we can issue only one approval letter for the sponsor. If there are differences in opinion between the ethics committee and the agency, we need to clarify them internally and reach a common decision before the final approval, refusal, or any outcome is communicated. It is good that this discussion happens beforehand — it makes the process easier for the sponsor."

"We do notice a lot of differences, even in [our country], between the ethics committees... certain committees would ask a lot of additional information, while another would approve without conditions."

"On European level, harmonisation would be nice, but I think that's really far away... for us, if we have a national harmonisation on that level, that would already help."

"So, a more harmonised approach to ethics [approval] would be something that I would feel would be very helpful."

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