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

WP4 Methodology development: evidence requirements, data, and statistical tools

DELIVERABLE 4.1 (1/3)

EU EFS Clinical Investigational Plan

Co-funded by the European Union

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Project Acronym	HEU-EFS
Project Title	Harmonised approach to Early Feasibility Studies for Medical Devices in the European Union
Project Coordinator	Giuditta Callea giuditta.callea@unibocconi.it
Grant Agreement Number	101112185
Project Duration	October 2023 – October 2027 (48 months)
Deliverable Number	4.1
Work Package	4
Task	4.1 and 4.2
Lead Beneficiary	Meditrial
Status	Completed
Dissemination Level	Public
Type	R – Document, report
Due Date of Deliverable	30-09-2025
Actual Submission Date	17-10-2025
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File History				
Version	**Date**	**Status**	**Author**	**Review**
1.0	15-07-2025	V1.0	Dr Monica Tocchi, E.Russo (Meditrial)	Giuditta Callea (UB)
2.0	30-09-2025	V2.0	Dr Monica Tocchi, E.Russo (Meditrial), Alessandra Denaro, Karine Miquel (Abbott)	Giuditta Callea, Francesca Pissarello, Helen Banks, Federico Facciolo (UB)

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ABBREVIATIONS

CI	Clinical Investigation
CIP	Clinical Investigation Plan
DHT	Digital Health Technology
EFS	Early Feasibility Studies
EU	European Union
HEU-EFS	Harmonized Approach to Early Feasibility Studies for Medical Devices in the European Union
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISO	International Organization for Standardization
MD	Medical Device
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation
NB	Notified Body
PAG	Patient Advisory Group
UB	Bocconi University
WP	Work Package

EXECUTIVE SUMMARY

This document, titled **Deliverable (D)4.1 *EU EFS Clinical Investigational Plan*,** is a detailed report prepared under **Work Package 4 (WP4)** of the **HEU-EFS (Harmonised approach to Early Feasibility Studies for Medical Devices in the EU)** project.

◇ **Purpose of the Deliverable**

To develop a **standard Clinical Investigation Plan (CIP) template** specifically tailored for **Early Feasibility Studies (EFS)** of medical devices (MDs) within the European Union (EU) regulatory framework.

◇ **Background and Objectives**

- **EFS** are early-stage clinical studies critical for evaluating novel MDs before full-scale trials.
- Although recognized internationally (e.g., ISO 14155:2020), the EU lacks a **dedicated EFS protocol template**.
- **WP4's main objective** is to fill this gap by creating a **standardized, regulation-compliant CIP template**.

◇ **_Work Plan Overview**

WP4 is divided into two tasks:

1. **Task 4.1 – Gap Analysis**
    a. Led by **Meditrial** with multiple partners (Abbott, Bocconi University).
    b. Reviewed existing regulatory templates (e.g., ISO 14155, MDR Annex XV, MDCG, ICH M11).
    c. Identified **gaps and limitations** in current templates, especially regarding small-scale, flexible, adaptive study designs needed for EFS.
2. **Task 4.2 – CIP Template Development**
    a. Based on findings from Task 4.1, Meditrial drafted the initial EFS CIP template. The draft underwent two rounds of consortium-wide review, incorporating over 320 comments from partners and experts.
    b. As part of this process, **input was also gathered from the Patient Advisory Group (PAG)** to strengthen the patient-centered aspects of the template. PAG members provided insights on how to improve the clarity and accessibility of patient-facing sections, particularly regarding the proposed lay summary accompanying the CIP. Their recommendations included the use of simple language, concise formats, and

alternative communication methods (e.g., audio or visual formats) to accommodate different levels of health literacy.

c. These suggestions were considered in the refinement of the lay summary structure and content, helping to ensure that the final CIP template is not only regulatory-compliant but also mindful of patient communication needs.

d. An important addition to this deliverable is the EFS CIP Checklist, developed in response to stakeholder feedback indicating that some organizations would encounter hardship in using a different CIP format than their internal one. The checklist functions as a cross-referencing and alignment tool, enabling sponsors to ensure that their existing CIPs fully meet the EFS-specific requirements and quality standards established by HEU-EFS.

◇ Key Results

- A **comparison table** of existing templates and standards showing lack of EFS-specific guidance.
- A **first-of-its-kind, structured CIP template and related checklist** designed for:
  - Iterative design
  - Small sample sizes
  - Limited-site studies
  - Risk/benefit assessment
  - Statistical planning
  - Regulatory documentation
- Template integrates stakeholder feedback and will be validated through pilot studies in **WP7**.

◇ Conclusion

This deliverable contributes a **critical, standardized tool** for advancing high-quality, early-stage medical device investigations in the EU. It supports regulatory alignment, practical implementation, and may influence global standards.

1. Introduction

Early Feasibility Studies (EFS) represent an essential stage in the clinical development of innovative medical devices (MDs), allowing early evaluation of a device's functionality and safety before committing to full-scale clinical investigations (CIs). Although recognized in international standards such as ISO 14155:2020, EFS remain underrepresented in terms of formalized guidance and documentation specific to the European regulatory environment. In particular, there is no dedicated protocol template that systematically addresses the distinctive features and needs of EFS—such as small-scale implementation, iterative device adaptation, and flexible study designs.

Work Package 4 (WP4), as part of the HEU-EFS project, was established to fill this gap by creating a standardized Clinical Investigation Protocol (CIP) template specifically adapted to EFS within the EU context. The goal of this deliverable (D4.1) is to provide a clear and practical tool for investigators and sponsors, supporting the preparation of high-quality, regulation-compliant protocols tailored to early-stage clinical evaluation of medical devices.

The work was structured in two core tasks. The first, Task 4.1, focused on analysing the regulatory and methodological landscape relevant to EFS. This included reviewing applicable EU and international standards—such as MDR Annex XV, ISO 14155:2020, MDCG guidance, and frameworks for digital health technologies—and identifying areas where current resources fall short of EFS-specific requirements. In this phase, WP4 also built upon knowledge generated by earlier WPs (WP1, WP2, and WP3), ensuring alignment with prior assessments on regulatory processes, stakeholder roles, and patient engagement.

While the CIP is primarily intended for regulatory and clinical users, feedback from the Patient Advisory Group (PAG) was also considered to improve the clarity and usability of sections aimed at patient or public communication. PAG members emphasized the importance of concise, clear summaries and supported the use of lay-language explanations to facilitate understanding among diverse audiences.

This engagement contributed to the structure of the lay summary section within the CIP template, aligning with broader efforts across the HEU-EFS project to enhance patient involvement in early-stage clinical research.

Task 4.2 involved drafting, refining, and validating the EFS CIP template by defining the structure and content required to guide users through critical aspects of EFS protocol development—ranging from study objectives and design considerations to risk management, statistical planning, and regulatory

documentation. The following sections outline the methodology and results related to both deliverables.

By delivering this tailored EFS protocol template, WP4 contributes a foundational component to the broader HEU-EFS initiative, supporting early, high-quality clinical investigation of medical devices across the EU through a common, structured, and regulation-aligned approach.

2. Methodology

To develop a robust and fit-for-purpose CIP template for EFS, WP4 adopted a two-phase methodological approach. The first phase focused on identifying regulatory and structural gaps through a comparative analysis of existing templates and guidelines. The second phase involved the drafting, multi-stakeholder review, and iterative refinement of the EFS CIP template, ensuring alignment with regulatory requirements and practical needs. In the course of the second development phase, a need was identified for an industry-friendly EFS CIP Checklist, which was included in the Deliverable D4.2.

2.1. Gap Analysis of existing regulations

The first phase of the work under WP4 focused on identifying the limitations in existing protocol templates and determining the requirements for a CIP specifically tailored to EFS. A structured gap analysis was conducted to assess the adequacy of currently available templates and standards across the medical device and pharmaceutical sectors.

This evaluation was based on an in-depth review of applicable EU and international regulatory standards and guidance:

- **ISO 14155:2020 - Clinical investigation of medical devices for human subjects — Good clinical practice**, particularly Annex A, which outlines general CIP content for medical device investigations;
- **MDCG 2024-3 - Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices**, which provides guidance on CIP structure but lacks EFS-specific considerations;
- **ICH M11 (CeSHarP) - guideline, clinical study protocol template and technical specifications - Scientific guideline**, representing structured approaches in the pharmaceutical domain;
- Relevant sections of **EU Regulation 2017/745 (MDR)**, including Annex XV;
- Additional procedural and regulatory sources related to digital health technologies (DHTs).

The comparison aimed to identify structural gaps, missing methodological guidance, and areas lacking alignment with EFS needs (e.g., small sample sizes, iterative design, limited site involvement). Key findings were discussed in dedicated WP4 meetings, enabling expert input from all partners. These collaborative discussions informed the drafting of the first version of the EFS CIP template.

2.2. CIP Template

The initial draft of the EFS CIP template was prepared by WP4 Leader, Meditrial, based on the analysis and conclusions developed under the gap analysis. This first version aimed to provide a structured and complete format aligned with applicable EU regulations and the unique methodological features of EFS.

Following its completion, the draft was circulated to all WP4 partners for review. A structured feedback process was implemented:

- Over 320 comments and suggestions from WP4 members were documented in a consolidated Table of Changes.
- These comments addressed content clarity, regulatory alignment, usability, and the relevance of specific sections to EFS scenarios.

The WP4 Leader then conducted a detailed revision of the draft, addressing all feedback received. The revised version was subsequently shared with WP4 partners for a second round of review, maintaining a transparent and traceable revision history.

This process was facilitated through regular coordination meetings, targeted working sessions, and active collaboration among WP4 partners. In parallel, feedback was also gathered from the Patient Advisory Group (PAG) to ensure that the template reflected not only regulatory and scientific expectations but also patient-centric perspectives. Contributions from patients and PAG representatives were integrated where appropriate, particularly in relation to transparency, informed consent, and communication with lay participants.

This iterative, stakeholder-informed methodology ensured that the resulting CIP template is robust, adaptable, and aligned with both regulatory requirements and real-world feasibility.

2.3. CIP Checklist

The initial version of the EFS CIP checklist was developed by the WP4 Co-Leader, Abbott, using the CIP template as a foundation. This first draft aimed to offer a structured and comprehensive format aligned with the template's framework.

Once completed, the draft was shared with all WP4 partners for review. A structured feedback process was put in place:

- Comments and suggestions from WP4 members were incorporated using track changes.

- Feedback focused primarily on improving content clarity and usability.

Following this, the WP4 Co-Leader carried out a thorough revision, addressing all received input. The updated version was then redistributed to WP4 partners for a second round of review.

This iterative process was supported by regular coordination meetings and active collaboration among WP4 partners. Thanks to this stakeholder-driven approach, the final CIP checklist template is robust, flexible, and well-aligned with both regulatory expectations and practical implementation needs.

3. Results

3.1. Gap Analysis of existing regulations/Templates

The initial outcome of WP4 was a comprehensive **comparison table** compiling and analysing the most relevant international and European guidelines applicable to clinical investigation protocols, with a focus on their suitability for EFS (Table 1). This table systematically assessed regulatory documents.

The comparison table identified substantial gaps and limitations across all reviewed documents, most notably the absence of guidance specifically addressing the design constraints, adaptive nature, and regulatory needs of EFS. This analysis served as the critical foundation for designing a CIP template that would fill this global void and align with EU-specific expectations under the Medical Device Regulation (MDR).

Table 1 Gap Analysis of Existing Regulations

Source	Purpose	Analysis	Nr of Pages
ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice	Good clinical practice for clinical investigations of medical devices (global standard)	Harmonized with MDR. Specific to medical devices. More flexibility in requirements. Non-specific considerations for EFS.	7
MDCG 2024-3: Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices	EU MDCG guidance describing content of the Clinical Investigation Plan for medical devices under MDR	This document is not a CIP template. The guidance refers to Annex XV, Chapter II, Section 3 of the MDR. A protocol synopsis template is provided.	2
ICH M11: guideline, clinical study protocol template and technical specifications - Scientific guideline,	Harmonised clinical protocol template and technical specs primarily developed for pharmaceutical interventional clinical trials.	Establishes a common Table of Contents. Highlights basic requirements for protocols. Impact similar to CTD/eCTD. Foundational step toward a “digitized protocol”.	100
EU Regulation 2017/745 (MDR) — Annex XV (Chapter II, Sect. 3)	Regulatory requirements for clinical investigations of medical devices in the EU	MDR/Annex XV is a regulatory framework—not a practical template for EFS. It doesn’t define how to justify very small sample sizes or exploratory objectives typical of EFS. It doesn’t define how to manage iterative device changes or justify flexible adaptive methods.	175

Source	Purpose	Analysis	Nr of Pages
Digital Health Technologies for Remote Data Acquisition in Clinical Investigations	Guidance on using digital health technologies (DHTs) to acquire remote data	DHT guidance addresses device-adjacent technologies rather than the investigational medical device lifecycle. It focuses on validating measurement devices and remote data flow, not on EFS needs.	35
National Guidelines/Templates	NA	Analysed National Guidelines and Templates for EFS relevance. None specific to EFS: (SWITZERLAND Template for CIP for clinical investigations involving Medical Devices (MD)); BELGIUM "Clinicalinvestigations –Guidance on Dossier Content" under MDR; SWEDEN Template - Clinical Investigation Plan (CIP) - under MDR; SPAIN Instruction of the Spanish Agency of Medicines and Medical Devices for conducting clinical trials in Spain; ISRAEL Guideline on Submission of a new application for a clinical study on humans; UK University College London CIP for Medical Device Studies	NA

Highlights of Current CIP templates

ISO 14155:2020
Annex A (Normative) specifies the content of a Clinical Investigation Protocol (CIP).

- Harmonized with MDR.
- Specific to medical devices.
- More flexibility in requirements.
- Non-specific considerations for EFS.

7 Pages

MDCG 2024-3:
Guidance on content of the CIP for clinical investigations of medical devices

- This document is not a CIP template.
- The guidance refers to Annex XV, Chapter II, Section 3 of the MDR.
- A protocol synopsis template is provided.

21 PAGES

ICH M11:
Clinical electronic Structured Harmonized Protocol (CeSHarP)

- Establishes a common Table of Contents.
- Highlights basic requirements for protocols.
- Impact similar to CTD/eCTD.
- Foundational step toward a "digitized protocol".

100 PAGES

3.2. CIP Template

The final output of the second phase is a first-of-its-kind CIP template, available in Annex I, that addresses a longstanding gap in international regulatory documentation. Unlike existing templates and guidance documents, which are either too general or focused on full-scale clinical trials, this EFS-specific template is tailored to early-phase, high-risk, and innovative medical device development pathways. It is designed to be clear, structured, and directly implementable by investigators and sponsors, while aligning with EU regulatory expectations.

By producing a standardized, yet flexible tool for EFS protocol development, WP4 has contributed a critical deliverable not only to the HEU-EFS project but also to the broader medical device regulatory landscape. This template lays the groundwork for more consistent, high-quality early clinical investigations across Europe and may serve as a model for global adoption, particularly in jurisdictions seeking to strengthen their early-stage innovation frameworks.

3.3. EFS CIP Checklist

During the development of the CIP template, it became evident that some companies have their own established CIP templates and are unable to deviate from them. As a result, a decision was made to create a CIP Checklist. This checklist was designed to mirror the HEU-EFS CIP template and serves to verify that all required elements are included in the sponsor's version of the CIP.

The CIP Checklist was attached to the CIP template, and both documents were shared together during the second consultation period of WP4.

4. References

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13. International Conference on Harmonization (ICH) Guideline for Good Clinical Practice E6(R2). (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf)

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