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

WP6 - Methodology development: ethical and legal aspects

DELIVERABLE 6.2

Set of templates for the EU EFS Programs - Methodological document

Co-funded by the European Union

Disclaimer:

The Harmonised approach to Early Feasibility Studies for Medical Devices in the European Union (HEU-EFS) project is funded by the European Union, the private members, and those contributing partners of the IHI JU. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the aforementioned parties. Neither of the parties can be held responsible for them.

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 – September 2027 (48 months)
Deliverable Number	D6.2
Work Package	6
Task	6.1
Lead Beneficiary	UB
Status	
Dissemination Level	PU
Type	Other – Template, report
Due Date of Deliverable	30-09-2025
Actual Submission Date	
Author(s) & Organization(s)	Niccolò Palminteri Matteucci, Francesco Malandrini, Diana Panzica, Giuditta Callea (UB), Irene Gonzalez (Edwards Lifesciences).
Reviewer(s) & Organization(s)	Yasemin Zeisl (EPF), Marta Bragagnolo (GHH), Fanny van der Loo, Karin Fricke (Edwards Lifesciences), Alexandra Poulsson, Marit Erna Austeng (NIPH), Manon Gielkens, Sebastiaan de Jongh (MEDTRONIC), Alessandra Denaro, Heiko Zerlik (Abbott), Nicolas Martelli, Ornella Tangila Kayembe (APHP), Laura Sampietro-Colom (HCB), Adrián Valledor (FCRB), Carlo Maria Petrini (ISS), Lise Kvistgaard Jensen, Kristan Kidholm (CIMT), Tom Melvin, Majella Geraghty, Ali McDonnell (TCD), Ilja Michaelis, Marlen Peseke, Sebastian Kuhn (UMR), Marta Kerstan (J&J), Majella Geraghty (TCD), Cinzia Santin (Gore), Carlo Federici (UB).
Contact	francesco.malandrini@sdabocconi.it, niccolo.palminteri@sdabocconi.it

File History				
Version	**Date**	**Status**	**Author**	**Review**
1.0	09-06-2025	V1.0	Niccolò Palminteri Matteucci, Francesco Malandrini (UB)	Giuditta Callea (UB)
2.0	20-06-2025	V2.0	Niccolò Palminteri Matteucci, Francesco Malandrini, Diana Panzica (UB)	Giuditta Callea (UB)
3.0	14/07/2025	V3.0	Niccolò Palminteri Matteucci, Francesco Malandrini, Diana Panzica (UB)	Giuditta Callea (UB), Irene Gonzalez (Edwards Lifesciences), Nicolas Martelli, Ornella Tangila Kayembe (APHP), Dirk Roks, Manon Gielkens, Sebastiaan de Jongh (Medtronic), Sebastian Kuhn, Marlen Peseke (UMR), Alexandra Poulsson, Marit Erna Austeng (NIPH), Tom Melvin, Ali McDonnell (TCD), Adrian Valledor, (FCRB), Marta Bragagnolo (GHH), Yasemin Zeisl (EPF), Carmen Furno, Benedetta Brancadoro (Gemelli), Marta Kerstan (J&J), Arianna Salvatori, Gabriella Di Santo, Antonio Balsamo (AGENAS), Alexandra Poulsson, Marit Erna Austeng (NIPH), Laura Sampietro-Colom (HCB),

File History				
Version	**Date**	**Status**	**Author**	**Review**
				Adrián Valledor (FCRB), Yasemin Zeisl (EPF), Karin Fricke (Edwards.), Marta Kerstan (J&J), Majella Geraghty (TCD), Sebastiaan de Jongh, Manon Gielkens, Dirk Roks (Medtronic), Ilja Michaelis (UMR), Helen Banks (UB), Claudia Louati (EPF).

TABLE OF CONTENTS

ABBREVIATIONS

CI	Clinical investigation
EC	Ethics Committee
EEA	European Economic Area
EFS	Early Feasibility Studies
EU	European Union
HEU-EFS	Harmonised Approach to Early Feasibility Studies for Medical Devices in the European Union
DHT	Digital Health Technologies
IA	Insurance Agreement
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonisation Good Clinical Practice
ISO	International Organization for Standardization
MCTA	Master Clinical Trial Agreement
MDR	Medical Device Regulation
NCA	National Competent Authority
SMEs	Small and medium enterprises
WP	Work Package

EXECUTIVE SUMMARY

In **Deliverable (D)6.2** *Set of templates for the EU EFS Programs* within Work Package (WP) 6 *Methodology development: ethical and legal aspects* - a systematic approach was undertaken to collect and analyse Informed Consent Forms (ICF), Master Clinical Trial Agreements (MCTA) and Insurance Agreements (IA) from various stakeholders, including consortium members (e.g., hospitals and industry), the Advisory Board (AB) (e.g., professional associations), and publicly available sources. This process ensures alignment with regulatory and ethical requirements while facilitating consistency across jurisdictions. The work was facilitated by D1.2 *Pre-Market Approval Pathways - Database* within WP1 *Research and analysis on state of play of pre-market programs and implementation barriers to EFS* findings, such as documentation required for the submission of pre-market clinical investigation applications for medical devices in the EU and other relevant jurisdictions. It also drew on D2.4 (LINK) *Research report summarizing the current EU regulatory framework for clinical evidence generation for MDs and DHTs and relations with the future EU EFS Program* developed under WP2 *Research and analysis on regulatory framework, and institutional and organizational characteristics of EU competent authorities*, which highlighted the need for harmonized templates and tools to streamline documentation and reporting.

D6.2 consists of a set of checklists and templates designed to standardize documentation for patient ICF, MCTA, and IA, promoting clarity, efficiency, and regulatory compliance within the EU Early Feasibility Studies (EFS) framework. The D6.2 received continuous feedback and consultation with the Patient Advisory Group (PAG). This consisted of a survey and two meetings: kick-off meeting and a focus groups. Additional feedback emerged from WP6 Partners and the Advisory Board. Despite that the initial Deliverable consisted of a set of templates, the feedback collected suggested that ICF and MCTA checklists and an IA guidance document represent a more appropriate format to support companies that wish to utilise their own templates. An ICF template was instead delivered as deemed useful to support small and medium enterprises (SMEs).

The following material was thus identified as the target output for the Deliverable. All instruments were conceived to systematically outline the requisite sections for inclusion in application documents and to ensure conformity with applicable regulatory standards, including the Medical Device Regulation (MDR), ISO 14155:2025, the ICH-GCP guidance, and the Declaration of Helsinki. This structured

approach promotes a patient-centred perspective and facilitates compliance with ethical and regulatory requirements:

- **ICF - Checklist and Template**. An ICF checklist serves as a tool for organizations during the clinical approval process. This structured approach promotes a patient-centred approach and facilitates compliance with ethical and regulatory requirements. The accompanying template provides a standardised format for sponsors—particularly SMEs —that may lack internal documentation resources.
- **MCTA – Checklist**. A checklist stands as a flexible support document that ensures all relevant and EFS-specific contractual elements are included. Creating a template for the MCTA was considered potentially burdensome for larger companies that already operate under binding and customised agreements. Additionally, with specific jurisdictions requiring mandatory templates and clinical sites expecting to employ their own forms, a checklist appears to be a more fitting form.
- **IA - Guidance document**. A guidance document is deemed by the Consortium as the most appropriate format to support the interest of hospitals, companies and patients when entering an insurance agreement in an EFS setting. As the insurance agreement is typically non-negotiable, a standardised template appeared to be an impractical solution in most cases.

This report is a complementary methodological document that integrates Deliverable 6.2, classified as ‘Other – Template, report’, by providing a clearer and more consolidated presentation of its outputs (ICF and MCTA checklists, ICF template, and IA guidance document).

Background

Heterogeneity of documentation across EU jurisdictions

Early-stage pre-market clinical investigations (CIs) face challenges arising primarily from the lack of a harmonised EU-level framework specifically tailored to the design, approval, and oversight of early-phase studies—particularly those akin to Early Feasibility Studies (EFS) as recognised in other regulatory settings. As highlighted in Deliverable 2.4 (LINK) *Research report summarizing the current EU regulatory framework for clinical evidence generation for MDs and DHTs and relations with the future EU EFS Program* developed under Work Package (WP) 2 *Research and analysis on regulatory framework, and institutional and organizational characteristics of EU competent authorities*, a key recommendation was that “harmonized templates and tools are needed to streamline documentation and reporting”. From the same deliverable, it emerged that, “companies called for clear guidance on documentation requirements through standardized templates to reduce administrative complexity and ensure consistency across member states. Reliable communication processes were seen as critical for building trust and enabling effective collaboration between innovators and regulators”. In parallel, Deliverable 1.2 *Pre-Market Approval Pathways - Database* within WP1 *Research and analysis on state of play of pre-market programs and implementation barriers to EFS findings* facilitated this work by compiling documentation required for the submission of pre-market CI applications for medical devices in the European Union (EU), showing that different versions of Informed Consent Forms (ICF) and other documents are often used across EU countries.

Key finding of the abovementioned deliverables and comparative analysis within this WP6 *Methodology development: ethical and legal aspects* highlighted of a lack of harmonised documentation. ICF and Insurance Agreements (IA) are required for submission to both National Competent Authorities (NCAs) and Ethics Committees (ECs), Master Clinical Trial Agreements (MCTA) for the undertaking of a CI. Despite a common legal framework for CIs in Europe such as the Medical Device Regulation (MDR), these documents exhibit considerable variation across EU countries and hospitals, potentially resulting in drawbacks among which insufficient information to participants depending on where they are located. Differences in structure, content requirements, and legal provisions often necessitate country-specific adaptations, contributing to delays to both ethical and regulatory assessments. Together, these two levels of fragmentation—documents and processes—constitute a significant obstacle to a coordinated EU approach for early-stage device investigations.

Scope and aims of WP6

The HEU-EFS project aims to overcome these barriers by harmonising procedures and templates, promoting innovation while ensuring patient safety and data integrity. In this context, the present report constitutes D6.2 *Set of templates for the EU EFS Programs* within WP6 address these challenges through the creation of targeted tools tackling major sources of fragmentation: checklists for ICF and MCTA, a standardized ICF template, and guidance for IA.

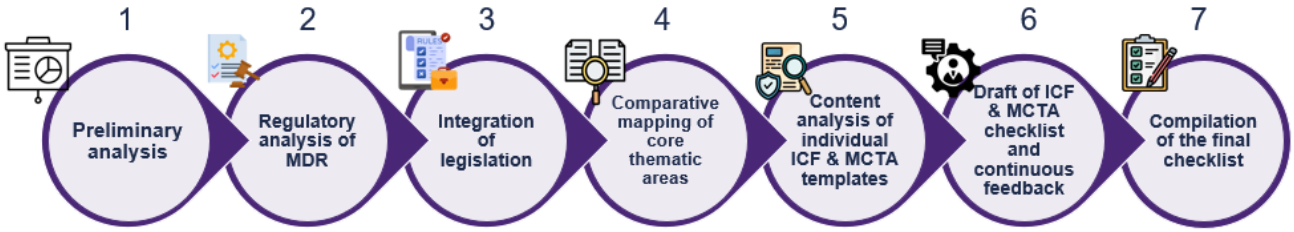
Next Steps

The next steps will focus on the validation and refinement of these tools during the WP7 pilot phase, in close collaboration with NCAs, ECs, and patient associations. In this context, particular attention will be devoted to adapting the checklists to emerging contexts such as Digital Health Technologies (DHTs). As these technologies become increasingly embedded in device development and early-phase studies, they raise new ethical and regulatory questions—including data protection, cybersecurity, interoperability, and the validation of digital endpoints—that will need to be systematically reflected in the documentation framework. Building on the harmonised approach established in D6.2, future iterations will integrate these aspects to ensure that the tools remain relevant, comprehensive, and capable of supporting innovation in a rapidly evolving landscape.

Methods

To address these barriers, WP6 was established with the aim of laying the ethical and legal foundations for a future EU-wide EFS program. The implementation of the checklists followed a structured legal methodology consisting of seven main steps (Figure 1):

Figure 1 Methodological steps for checklist development



1. **Preliminary analysis** – Regulatory analyses conducted under WP1 and WP2 examined EU regulations, member state national laws and pre-market program requirements both generally and within the specific context of EFS. This enabled the collection of essential documents and reference material, providing insight into country-specific regulatory pathways and informing progress within the work package. To ensure a patient-centred ICF, Patient Advisory Group (PAG) members were invited to identify sections most relevant to patients. They also contributed additional recommendations to help shape a more intuitive and user-focused document that aligns with ethical and regulatory standards.
2. **Regulatory analysis of MDR** - The first step involved a comprehensive legal review of the European Regulation 2017/745 (MDR) to identify the mandatory components required for ICF and MCTA. Specifically, for the ICF, ARTs. 62, 63, 64, 65, 66, 69 were the main reference points. For the MCTA, reference was made to: ART. 2, para. 49, 54; ART. 61, 62; ART. 72-80; ART. 109, 110, as well as Annex XV.
3. **Integration of legislation** – Following discussion with the WP6 partners, it was deemed appropriate to supplement the regulatory analysis, and checklists were integrated with **ISO 14155:2025 - Clinical investigation of medical devices for human subjects**, the **International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidance** (ICH E6(R3) effective since July 23, 2025) and the **Declaration of Helsinki**. It should be noted that, for the purposes of writing the checklists, certain a portion of the regulation under scrutiny was clear and imposed specific obligations on the parties, which were directly reflected in the checklists. EFS, due to the nature of the CI, require greater protection for all parties involved.

The nascent stage of these devices means less is known about their risks, necessitating rigorous protection measures to ensure safety. This includes stronger safeguards for human subjects participating in the investigation (e.g. closer monitoring of patients, immediate suspension of the study in case of an incident, multiple interviews with different healthcare professionals before ICF signature), as well as clearer obligations among the stakeholders conducting the study (e.g. more transparency in staff recruitment criteria and indications of individual major responsibilities). These safeguards are implemented through the drafting of detailed contracts and patient disclosures that are clear, simple, yet comprehensive. An extensive approach was adopted: even in situations where the applicable regulations did not impose explicit obligations, the rules were interpreted in a way that ensured both the success of the investigation and the protection of the individuals involved. Particular attention was given to the ICF, especially regarding vulnerable populations. Legal compliance and participant protection were ensured for minors, individuals lacking capacity, and pregnant or lactating women. By defining fundamental requirements, this analysis established a framework designed to uphold participants' rights while minimizing the risk of disputes with investigators, sponsors, and other stakeholders.

4. **Comparative mapping of core thematic areas** – Consortium members from hospitals, industry, clinical research organizations (CRO) and patient associations were consulted to gather examples of relevant documentation. These documents, collected through project partners, were reviewed to identify common sections. Specifically, for ICFs, eleven documents provided by partners were inspected. For the MCTA, nine documents were scrutinised. A colour-coded mapping method was used to highlight critical areas, such as study information, data protection provisions, risk disclosure, and available alternative treatments. This comparative analysis laid the groundwork for a harmonised approach, ensuring consistency across documents while allowing for jurisdiction-specific adaptations.
5. **Content analysis of individual ICF & MCTA templates** – A thorough review of partner-provided ICFs and MCTAs was performed to terminology, formatting, and overall structure. This evaluation ensured alignment with both public and private sector standards, enhancing legal clarity and practical usability. The resulting checklist strikes a balance between regulatory compliance, transparency, and ethical integrity, providing a standardised yet flexible framework for CI documentation.
6. **Draft of ICF & MCTA checklist and continuous feedback –** Preliminary documents were prepared and circulated among WP6 partners to solicit feedback and comments. To support this process, several plenary meetings were held to present key findings and incorporate

stakeholder perspectives aimed at enhancing the checklist content. The feedback received was thoroughly reviewed and integrated into a revised version of the documents

7. **Compilation of the final checklist** - The final phase focused on structuring and drafting the checklist, ensuring the inclusion of all relevant sections identified through previous regulatory analysis and content review. Each section was accompanied by the required information, and applicable compliance standards, ensuring clarity and usability for all stakeholders involved in CIs. In addition, at this stage, it was deemed appropriate to indicate for each section the normative reference on the main documents analysed. These references were incorporated in a way that facilitates the identification of the legal basis without overburdening the text.

To facilitate the preparation of EFS applications, especially to the benefit of SMEs, WP6 team focused on three key areas:

- **ICF:** the final checklist is designed to help practitioners clearly identify the required content for ICF in EFS. A template based on this checklist will also be developed, which can be used directly, especially by SMEs, to serve as a benchmark for comparison when other templates are employed.
- **MCTA**: a final checklist has been developed to assist stakeholders in identifying their respective obligations as defined by industry regulations. Despite the objective stated in the Grant Agreement, it was decided not to develop a template for the MCTA, primarily to respect the negotiating autonomy of the parties involved. The checklist does not aim to interfere with the economic and contractual freedom of the parties but rather clarify roles and responsibilities in EFS. It supports compliance with applicable regulations, with particular attention to third-party protections and clearly defined liabilities. By ensuring clarity of roles and well-regulated contractual obligations, the checklist contributes to safeguarding both stakeholders and contracting parties.
- **Guidelines for finalizing the insurance contract**: following a detailed regulatory analysis, it is evident that insurance coverage is mandatory to protect all parties involved. However, a key challenge lies in the limited bargaining capacity of the insured, who often must accept standard terms unilaterally drafted by insurers. These guidelines aim to assist in identifying the types of risks that should be covered, with particular focus on protections needed during EFS.

The output of this activity includes harmonised checklists and templates that address both ethical (e.g., participant information and consent requirements) and administrative (e.g., sponsor-site contracting, insurance coverage) processes. These instruments are intended to support the WP7 pilot phase and inform broader recommendations for the future implementation of EFS in the EU context.

References

European Commission. (2006). *Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use*. Brussels: European Commission.

European Parliament and Council of the European Union. Regulation (EU) 2017/745 of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002, and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA relevance). Official Journal of the European Union. 2017 May 5; L117:1-175.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline: Integrated Addendum to ICH E6(R3) – Guideline for Good Clinical Practice. Geneva: ICH; 2023.

International Organization for Standardization. ISO 14155:2025 – Clinical investigation of medical devices for human subjects — Good clinical practice. Geneva: ISO; 2025.

World Medical Association. *Declaration of Helsinki: Ethical principles for medical research involving human subjects.* Fortaleza: WMA; 2013.

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