innovative health initiative

HEU EFS
HARMONISED APPROACH TO EARLY FEASIBILITY STUDIES FOR MEDICAL DEVICES IN THE EUROPEAN UNION

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

WP4 Development and Validation of a Standard EFS CIP Template

DELIVERABLE 4.1 (2/3)

Template for a Clinical Investigation Plan for EFS clinical investigations involving Medical Devices

COCIR efpia EuropaBio MedTech Europe from diagnosis to cure Vaccines Europe

Co-funded by the European Union

Disclaimer:

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General Information and Instructions

This document is the Clinical Investigation Plan (CIP) template for Early Feasibility Clinical Investigations (EFS) of medical devices (MD). An EFS is used to evaluate the device design concept with respect to initial clinical safety and device clinical performance or effectiveness (if appropriate) as per intended use in a small number of subjects when this information cannot practically be provided through additional nonclinical assessment or appropriate nonclinical tests are unavailable.

The template is based on the regulations and guidelines referenced in the Bibliography, including but not limited to:

- EU Medical Devices Regulation 2017/745 (MDR)
- European Harmonized Standards
- MDCG Guidelines
- EU HTA Regulation
- ISO 14155:2020

Important: This template provides a general framework that is also applicable to EFS investigations with MD.

Instructions are indicated in *blue italics*. Throughout multiple chapters, these instructions also highlight specific characteristics relevant to EFS: once the individual sections are completed, these should be deleted.

Chapters and sections headings and template text formatted in regular type (black) should be included in the CIP as provided in the template.

Header and footer should contain the following information (on all pages): [Investigation ID], [CIP version number, CIP version date [DD/MM/YYYY], [Page x of xx], other not mandatory information (e.g., Sponsor Logo).

In places where the information is redundant, it is acceptable to reference to another chapter or section, to document or to state its redundancy but the chapter or section should not be deleted.

The term ‘clinical investigation’ is used in the template as a synonym of ‘clinical study’ or ‘clinical trial’.

The **CIP** has to be signed by the principal investigator, the sponsor *(if applicable)* and in case of a multicentric project by the different local principal investigators as well. Electronic signatures are accepted under the following conditions: the service provider used for the electronic signature process must have a system that verifies that the electronic signature is correct and genuine and properly embedded in the document. Copy-paste of scanned signatures are not accepted.

Please remove the ***‘General information and instructions’*** from the final document. Complete the table ***‘Change history’*** as required.

INSERT TITLE OF THE CLINICAL INVESTIGATION

CLINICAL INVESTIGATION PLAN TITLE: [Descriptive title identifying the design of the investigation (e.g. "A(n) [intervention model] [primary purpose], [study phase], [blinding] [number]-arm study to investigate [health measurement/outcome] with [investigational intervention] [intervention form] compared with [investigational intervention] [intervention form] in [male and/or female] participants [X to X years of age] with [condition/disease], population (if relevant), target disease(s), the medical device (MD), and, if the investigation is multi-centre (-country)]

SHORT TITLE and / or acronym / or translation (if relevant; title used in the informed consent)

Type of investigation:	Early Feasibility Study (EFS), Clinical Investigation of a medical device (MD).
Registration:	Name of the primary registry (if not yet registered name the intended registry) and the registration number. If applicable: EUDAMED-number, names of other registries, and the registrations numbers
Identifier:	Investigation ID (e.g., institutional or Sponsor CIP identifier) [make sure this corresponds to the Investigation ID in the footer]
Principal Investigator and Sponsor, or Sponsor-Investigator:	Name of Principal Investigator (PI) and of the Sponsor, if the roles are separated, add their full contact details. Name of Sponsor-Investigator, if the PI and the Sponsor are the same person, add his/her full contact details. Indicate the coordinating Investigator if the investigation is multicentric, add his/her full contact details.
Legal Representative (if applicable):	Name of the Legal representative including contact details and address.
CRO (if applicable):	Name of the CRO including contact details and address.
Medical Device:	Identification of the MD, including name, model/type, including software version and accessories, if any, to permit full identification.
CIP Version and Date:	CIP Version number and version date [make sure they correspond to the version number and version date in the footer]. Add if applicable, the Amendment number, from (date), replaces version number from (date). Track the changes in the table "summary of the revision history in case of amendments".

CONFIDENTIAL

Add, if applicable, an institutional confidentiality statement here respecting that it is not in conflict with applicable transparency rules.

e.g., "The information contained in this document is confidential and the property of the xx (or "Sponsor"). The information may not - in full or in part - be transmitted, reproduced, published, or disclosed to others than the applicable Competent Ethics Committee(s) and Regulatory Authority(ies) without prior written authorisation from the Sponsor except to the extent necessary to obtain informed consent from those who will participate in the clinical investigation.

Protocol Change History

Type	Version	Version Date DDMMYYYY	Description of Changes
Original	1.0	24Mar2023	NA, original protocol
Amendment (substantial/non-substantial)	2.0	24Mar2025	Added XXX, Global/Country-Specific/Regional

Signature Page(s)

Complete the signature pages with name and title of the person(s) authorised to sign the CIP and the CIP amendment(s): Sponsor, medical expert, Principal Investigator responsible for conducting the investigation.

Add more lines, functions and pages as needed.

ID number of the investigation:	Investigation ID Registry and registration number (to be filled in once available, in any case before the start of the investigation).
Title:	Full title as written out on title page

The Sponsor and the Principal Investigator have approved the CIP title, ID and version *[x (dated DD.MM.YYYY), make sure this corresponds to the CIP version and date in the footer]*, and confirm hereby to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, EU MDR, ICH-GCP as far as applicable, and the local legally applicable requirements.

Sponsor: If the Sponsor and PI are the same person, replace both lines with Sponsor-Investigator

Place/Date [DD.MM.YYYY]	Signature

Principal Investigator: ***If the Sponsor and PI are the same person, replace both lines with Sponsor-Investigator***

Place/Date [DD.MM.YYYY]	Signature

Principal Investigator at the local investigational site*:

I have read and understood this CIP version *[x (dated DD.MM.YYYY), make sure this corresponds to the CIP version and date in the footer]*, and agree to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, EU MDR, ICH-GCP as far as applicable, and the local legally applicable requirements.

Site:	Name and address of site
Principal investigator at the local investigational site:	Printed name of Principal investigator

Place/Date [DD.MM.YYYY]	Signature

***Note:** In multicentre investigations, this page must be individually signed by all participating Local Principal Investigators.

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Abbreviations

Provide a list of abbreviations used in the CIP – to be completed/adapted

AE	Adverse Event
ADE	Adverse Device Effect
AIMDD	Active Implantable Medical Devices Directive
ASADE	Anticipated Serious Adverse Device Effect
ASR	Annual Safety Report
CA	Competent Authority
EC	Ethics Committee
CEC	Clinical Events Committee
CIP	Clinical investigation plan
COV	Close Out Visit
CRF	Case Report Form (pCRF: paper CRF; eCRF: electronic CRF)
CRO	Contract Research Organisation
DD	Device Deficiency
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EFS	Early Feasibility Study
EUDAMED	European Database on Medical Devices
H0	Null hypothesis

H1	Alternative hypothesis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonisation – Guidelines of Good Clinical Practice
IFU	Instructions For Use
ISF	Investigator Site File
ISO	International Organisation for Standardisation
ITT	Intention to treat
MD	Medical Device
MDR	Medical Device Regulation (EU) 2017/745 of 5 April 2017
N/A	Not Applicable
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SDV	Source Data Verification
SOP	Standard Operating Procedure
SQV	Site Qualification Visit
SRN	Single Registration Number
USADE	Unanticipated Serious Adverse Device Effect

1. Investigation Administrative Structure

1.1. Sponsor, Sponsor-Investigator

Provide the complete contact details of the Sponsor (name and address), the role in the investigation, the role in the investigation design, collection, management, analysis, and interpretation of data, writing of the report.

If applicable, this must also include legal representative(s) in foreign countries.

1.2. Principal Investigator(s)

If available, provide information on the PI at each investigational site, the coordinating investigator for the investigation, the address details for each investigational site and the emergency contact details for the PI at each site. Note: In multicentric investigations, there is one PI only at each investigational site.

Name, title, address, and telephone number(s) of the qualified investigator(s), who is/are responsible for all investigational site related medical decisions (if other than the PI). If you refer to another document, this document should be annexed to the CIP (Annex XV, chapter 2, Art. 3.1.3 MDR).

1.3. Core Laboratory (if applicable)

Provide if applicable the name of the Core laboratory that is involved in the investigation (may be referred to different document, e.g., agreement between Sponsor and Core Laboratory).

1.4. Monitoring institution

Provide the name of the institution, place and country that monitors the investigation, if other tan the Sponsor (may be referred to different document, e.g. agreement between Sponsor and the Monitoring Institution).

1.5. Data Safety Monitoring Board

If applicable this should comprise the composition of data safety monitoring board (DSMB); summary of its role and reporting structure; statement of whether it is independent from the Sponsor and competing interests; and reference to where further details about its charter can be found, if not in the CIP. Alternatively, provide an explanation of why a DSMB is not needed.

1.6. Clinical Events Committee

To avoid bias in certain assessments an independent committee may be used to determine eligibility, classification of events, endpoint adjudication.

Please, provide a summary of its role and reporting structure; statement of whether it is independent from the Sponsor and competing interests; and reference to CEC charter.

1.7. Any other relevant Committee, Person, Organisation, Institution

If applicable e.g., coordination, data management, Patient organization, etc. Alternatively, write “not applicable”.

1.8. Funding

Provide brief statement of sources and types of financial support for the investigation. If applicable, reference to other places or contracts/documents where this information is captured.

Provide brief statement of any other type of support received to conduct the investigation (MD, comparator, investigation material, software’s, …). If applicable, reference to other places or contracts/documents where this information is captured. (MDR Annex XV Chapter II, Section 3.1.4)

2. Synopsis

Provide a structured synopsis containing all important information, preferably in tabular view:

Title:	Full title of the CIP
Short title / Investigation ID:	Short title of the CIP and Investigation ID
Clinical Investigation Plan, version and date:	The version number and the date of the valid CIP. Make sure they correspond to the version number and version date in the footer, on the first page and on the signature pages as well as amendment number
Sponsor / Sponsor-Investigator	Name of Sponsor / Sponsor-Investigator and address
Registration:	Name of the primary registry (if not yet registered name the intended registry) and the registration number. If applicable: EUDAMED-number, names of other registries, and the registrations numbers.
Name of the MD, Unique Device Identification (UDI), name of the manufacturer	Provide name of the MD, model/type, including software version and accessories, if any, to permit full identification. If available, provide the Unique Device Identification (UDI). The UDI is mandatory for category A investigations. Name of the manufacturer and the SRN number (Art. 31 MDR), Include traceability (e.g., lot numbers, serial numbers)

Stage of Development:	State the "clinical development stage" of the MD (early-stage investigations to explore feasibility and gather preliminary data; EFS, pilot stage, pivotal stage, Annex I.1 ISO14155). State if the clinical investigation is conducted for a conformity assessment purpose
Intended Use:	Insert intended use (this can be taken from IFU/IB)
Clinical Need:	Insert information about the clinical need, disease to be treated (this can be taken from Literature Review Report)
Study Design:	Insert details of the study design: Type of the study (prospective, controlled, non-randomized, multicentre study) Study phase Study population (Number and characteristics of patients, age, condition) Aim of the study Number of the sites (if known, put countries) Study duration including follow-up Schedule Any other relevant information The minimum content to be provided is type and aim of the study.
Study Objective(s): Note: Mandatory per ISO 14155:2020	Brief statement of objective of the study
Primary Endpoints Note: Mandatory per ISO 14155:2020	Insert primary endpoints specifying time point of measurements
Secondary Endpoints Note: Mandatory per ISO 14155:2020	Insert secondary endpoints specifying time point of measurements
Subject Population	Insert characteristics of target population

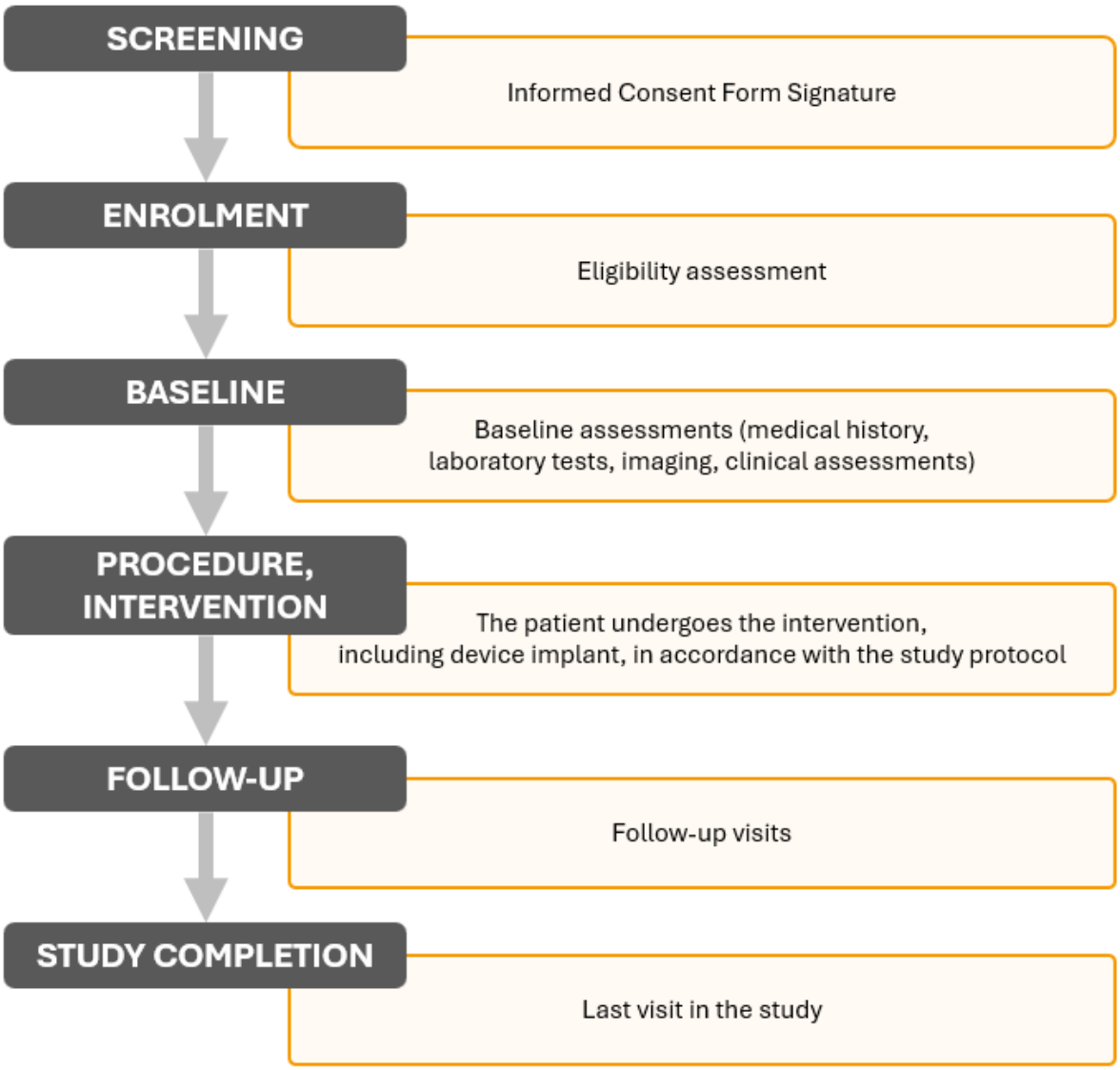
Number of subjects with rationale: Note: Mandatory per ISO 14155:2020	Number of subjects projected for the entire investigation (all sites combined). Give the total and the numbers for each treatment group, and the explanation for this sample size, if there is no power analysis possible, according to precedents and similar studies.
Site Selection	<<Insert number and location of study centres>> (The Sponsor or its designee shall maintain an updated list of principal investigators, investigational Sites and institutions. This list shall be kept separately from this protocol.
Study Timelines: Note: Mandatory per ISO 14155:2020	Estimated First patient in: (Insert date/year of the first patient in) Expected Time to Complete Enrolment: (Insert date/year of study enrolment completion) Expected Time of each Subject to Complete the Study: (Insert number of months/year of the FU duration) Total Expected Duration of the Study: (Insert number of months or years) Planned study end: (Insert date of study end) Regulatory submission: Once all subjects have reached their <<XX>> year follow up time point.
Inclusion / exclusion criteria: Note: Mandatory per ISO 14155:2020	The key inclusion and exclusion criteria and if applicable, the reasons for inclusion of vulnerable subjects (i.e. minors, pregnant and breastfeeding women). If applicable, create different categories.
Screening and Enrolment:	Insert relevant information regarding screening process If the Patient Screening Committee is present, insert description For the purposes of enrolment, subjects will only be considered enrolled after informed consent has been obtained.
Intervention:	Brief description of the investigation specific intervention (mode of action, route) used in the investigation, duration of intervention (treatment, observation), (also run-in phase, if applicable)

Control intervention (if applicable):	Describe if applicable the comparator(s) (e.g. sham- active control, reference therapy, historical)
Additional Assessments:	If applicable, insert specific assessment (e.g., imaging assessment)
Follow-up Schedule: Note: Mandatory per ISO 14155:2020	The Follow up Schedule is presented at the end of this synopsis as schedule of assessment. Insert timeline of the required FU visits/unscheduled visits. Adverse events will be monitored throughout the whole clinical investigation period. At each follow-up visit, the clinical personnel related to the study will assess the patients for the occurrence of adverse events. All adverse events reported by the patient must be recorded on the source documents and case report forms (CRF) provided by the sponsor.
Risk Mitigation and Risk Benefit Considerations	Description of Risk Mitigation and Risk Benefit Considerations.
Compliance statement:	This investigation will be conducted in compliance with the CIP, the current version of the Declaration of Helsinki, ISO14155, ICH-GCP (as far as applicable) as well as all national legal and regulatory requirements.
Study Governance:	Provide names, roles, workplaces of committees/safety boards involved.
Core Labs:	If applicable, add details of Core Lab members (Echo, CT, …)
Sponsor Contact:	Insert name and address of the sponsor
CRO Contact (if applicable):	Insert name and address of the CRO (If applicable)
Investigator(s):	Name(s) of Investigator(s); Full contact details.

Data Safety Monitoring Board/other relevant Committees (Clinical Events Committee (CEC)) **To be added/adjusted as required**	Give details as needed,

2.1. Study Workflow

Provide a graphic flowchart or table detailing the clinical investigation design and stages of the EFS study, like the following example:



2.2. Schedule of Assessments

Insert a flow chart (graphic) or tabular listing of schedule of events and assessments and procedures of the investigation (an example is provided below, amend and expand according to the specific investigation). To be repeated in chapter 9.1.

Investigation Periods	Patient information	Consent (ICF) Screening	Pre-procedure	Treatment, Intervention	Follow-up (e.g. 1 year +/- 30 days)
Patient Information	x				
Patient consent (ICF)		x			
Demographics		x			
Medical History		x			
In- /Exclusion Criteria		x		x	
Physical Examination		x			x
Vital Signs		x		x	x
Laboratory Tests		x			x
Pregnancy Test		x			(x)
Other examinations, tests…		x			x
Other examinations, tests…		x			
Medical Device application				x	
Primary Variables (variable 1, variable x)		x		x	x
Secondary Variables (variable 1, variable x)		x		x	x
Concomitant Therapy, Intervention				x	
(Serious) Adverse Events, Adverse device effects evaluation		x		x	x
Protocol Deviations		x		x	x
Device Deficiencies				x	x
Subject Completion/Discontinuation					x

3. Background

3.1. Background and Rationale for the Clinical Investigation

Describe the relevance of the clinical investigation in the context of the state of the art of clinical practice and the proposed benefits of the new device (Annex XV, chapter 2, Art. 3.2 MDR).

Describe the research question, including summary of relevant investigations (published and unpublished) examining benefits and harms for each intervention, including disease background, e.g., epidemiology and current standard of care (if relevant). Refer to literature where is the current lack of information, why the investigation will be done and establish its context by giving a clear statement on its purpose.

4. Investigational Device

4.1. Identification and Description of the Investigational Medical Device

In case of systems that consist of several devices, list all the devices.

Medical Device(s) (MD): brand name(s), manufacturer(s), name or number of the model(s)/type(s), incl. software version(s), software algorithms, and accessories if any, to permit full identification (e.g., add a picture of the MD). Whether the device is CE marked for a medical use or for other uses (electrical equipment, pressure vessels, other), give the intended purpose of the MD. See Art. 120 Abs 2 MDR for the period of validity of certificates there were issued in accordance with the European directives, specifically 93/42/EEC (Medical Devices Directive) and 90/385/EEC (Active Implantable Medical Devices Directive). Describe the populations for which the MD is intended. For CE marked devices, give all deviations from the original CE-marked instructions for use (off-label use) or statement that there are no such deviations. If the MD has a modular design, indicate to which module modifications have been made, and which module/modification is the focus of the investigation. Include description of device materials in contact with body tissues and/or fluids; this shall include details of any medicinal substances, human or animal tissues or their derivatives, or other biological active substances and reference to compliance with applicable national regulations.

Indicate the necessary training and experience required for the use of the MD and the medical and/or surgical procedures involved in the use of the MD.

Include risk management steps to minimize risks through design and manufacturing.

ISO 14155:2020 A.2.j: Give reference to the IB.

4.2. Device Changes during EFS Studies

Refer to the following guidelines:

MDCG 2021-6 Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation

MDCG 2020-3 Guidance on significant changes regarding the transitional provision under Article 120 of the MDR with regard to devices covered by certificates according to MDD or AIMDD.

In Early Feasibility Studies (EFS) and First-in-Human (FIH) studies, device modifications may occur throughout the course of the clinical investigation as part of the iterative process of refining and optimizing the device. Manufacturers are responsible for ensuring that any changes to the device during the EFS study are properly documented, evaluated, and reported in compliance with regulatory requirements. Below, we outline the procedures for managing and reporting device changes that may arise during the course of an EFS study.

4.3. Types of Device Changes

Device changes during an EFS study may involve any modifications to the design, materials, manufacturing processes, or intended use of the investigational device. These changes need to be listed and may include, but are not limited to, the following:

- Design modifications: Alterations to the device's components, structure, or functionality.
- Material changes: Substitution or modification of materials used in the device, which may affect its safety or performance.
- Manufacturing process changes: Adjustments to the methods used in manufacturing the device, which could impact consistency, quality, or device performance.
- Labelling changes: Modifications to the device's instructions for use (IFU) or packaging, which might affect the device's proper handling, use, or safety.
- Intended use changes: Changes that involve modifying the device's intended use or indications for use, which may require additional regulatory submissions.
- Software changes: Updates or modifications to embedded software, which can impact the device's operation or data management capabilities.

4.4. Regulatory Requirements for Device Changes

Manufacturers must evaluate whether a device change is substantial or non-substantial and whether it requires additional submission to the regulatory authorities for review and approval. The determination of whether a change is substantial will depend on factors such as the potential impact on the safety and effectiveness of the device and whether the change affects the fundamental nature of the investigational device.

This evaluation shall be conducted in accordance with:

- **EU MDR** (Regulation (EU) 2017/745) – Annex XV, Chapter II, which defines requirements for the conduct of clinical investigations and substantial modifications
- **MDCG 2020-3** – Guidance on significant changes regarding the transitional provisions under Article 120 of the MDR, which provides clear decision-making criteria and examples for legacy devices under MDD (where applicable).

- **ISO 14155:2020**, Clause 6.5, Clause 7.5, and Annex A.9.

A distinction is made between:

- Device modifications, which relate to changes in design, materials, manufacturing processes or software of the investigational device; and
- Clinical protocol amendments, which relate to changes in study design elements such as endpoints, population, procedures or follow-up schedules, and are managed separately under clinical investigation governance.

All changes will be documented, risk-assessed, and appropriately escalated as per internal procedures and applicable regulatory requirements.

➢ Substantial Changes:

Changes that have the potential to significantly affect the device's safety, effectiveness or performance, or intended use will be considered substantial. Examples of substantial changes include:

- Changes that alter the fundamental design or intended use of the device.
- Significant modifications to device materials that could impact biocompatibility or device performance.
- Changes to the manufacturing process that could affect device performance or quality control.
- Alterations to the patient population or clinical endpoints defined in the IDE application.

➢ Non-Substantial Changes:

Non-substantial changes may not require regulatory notification but must still be documented and communicated to the regulatory authorities if necessary. These changes should be assessed to determine if they could affect the study's scientific integrity or subject safety. Examples of non-substantial changes include:

- Minor modifications to the labelling that do not impact the device's clinical application.
- Minor adjustments to device parameters that do not fundamentally change device performance or intended use.
- Modifications to the clinical protocol that do not introduce new risks or alter primary objectives.

4.4.1. Documentation and Reporting of Device Changes

Any device changes, whether substantial or non-substantial, must be **adequately documented** in the clinical investigation records. The following actions should be taken to ensure compliance with the applicable regulations:

1. **Documentation**:
   Manufacturers must keep detailed records of all device changes made during the study. Documentation should include the **rationale** for the change, **design specifications**, and **evaluation of risk**, including how the change affects **safety**, **performance**, and **patient outcomes**. These records must be made available to the EU MDR and local CAs upon request.

2. **Evaluation and Risk Assessment**:

   For each change, the manufacturer must conduct a **risk analysis** to assess the potential impact of the change on the **safety** and **performance** of the device. This includes reviewing whether the change could introduce **new risks** or **compromise the device's ability** to meet its intended clinical outcomes.

4.4.2. Impact on Clinical Study

The **clinical protocol** must be reviewed to assess whether any device change necessitates a modification to the study design, clinical endpoints, or **patient population**. Key considerations include:

- **Informed Consent**: The informed consent documents must be updated to reflect any changes in the device that could affect the **patient's understanding** of potential risks, complications and benefits. For example, if a change introduces new risks, the informed consent form must be updated and changes clearly communicated to **inform participants** of those risks.
- **Safety Monitoring**: The study team should assess whether any device change impacts the study's **safety monitoring plan**, including **adverse event reporting**, **monitoring frequency**, or **device handling procedures**.
- **Investigational Data Integrity**: Any changes to the device must be evaluated for their potential impact on the **scientific integrity** of the study. This includes reviewing whether the changes may affect **data comparability** or **generalizability** of the study's findings.

4.4.3. Timing and Communication of Device Changes

Device changes should be communicated to the study team and regulatory authorities in a timely manner to ensure that the investigation continues in compliance with both regulations and study protocols. Timely communication allows for **revised risk assessments** and **appropriate adaptations** to the study design. Manufacturers must notify the authorities of any substantial changes and obtain approval prior to their implementation, ensuring that the study can proceed in a manner consistent with the original regulatory approval.

4.5. Storage of Biological Material and Related Health Data

In the event the data of the investigation is stored in a data-registry: add here that the coded data of the subjects who consented for the further use of their data (independently of the investigation

specific consent) will be stored in a registry for an undetermined length of time, and the data could be re-used for other research projects (provided previous approval by the CEC).

If applicable, describe for how long and where the samples and personal data are stored, or state that samples are destroyed, and data anonymised after the end of the storage period. The information provided here must match the information given in chapters 8.4 and 9.2.5.

In the event of Biobank or registry storage, confirm that coded samples and/or data are only stored if the subject consent for further use has been obtained. This consent is given (or withheld) independently of the participation in the investigation.

5. Justification for the Design of the Clinical Investigation

Provide the justification for the use of the MD (use, method of application, regimen, period of intended use, …), which shall be based on the conclusions of the evaluation, as specified in ISO 14155:2020 A.3).

Specific elements to consider:

- **Patient Input into Design**
- **Justification for dose or Exposition Regime (when applicable)**
- **Rationale for Study Design**
- **Intervention Model**
- **Duration**
- **Objectives**
- **Endpoints**
- **Interim Analysis (when applicable)**
- **Comparator**
- **Other**
- **Start of Study / End of Study Definition**
- **Access to Study Intervention After End of Study**

5.1. Preclinical Evidence

ISO 14155:2020 A.3.a: Summarise, if applicable, the available non-clinical data (published or available unpublished data) that could have clinical relevance and justify its use in humans.

Preclinical evidence details are provided in IB, however the CIP should include a summary, as recommended in MDCG 2024-3.

Relevant information to summarize and justify pre-clinical testing in the EFS CIP, should be located in the clinical evaluation plan and in the Investigator Brochure. Refer to the following MDCG Guidances.

MDCG 2024-3 Guidance on the Content of the CIP - 3.4: The justification for the design of the clinical investigation should be based on the conclusions of the clinical evaluation.

- Summarize the **evaluation of the relevant pre-clinical testing/assessment** and any prior clinical investigations, to justify the use of the investigational device in human subjects.
- Provide an evaluation of clinical data that are relevant to the proposed clinical investigation.
- Describe where the clinical investigation fits into the clinical development of the device (i.e., is this a pilot study an EFS, a pivotal study or a post-market clinical investigation?).
- The informative Annex I in ISO 14155:2020 has information on clinical development stages.

MDCG 2024-5, Guidance on Investigator Brochure- 2.3. **Pre-clinical evaluation** According to section 2.3, chapter II, Annex XV of the MDR, the **IB should include a pre-clinical evaluation based on relevant pre-clinical testing and experimental data**, in particular in-design calculations, in vitro tests, ex vivo tests, animal tests, mechanical or electrical tests, reliability tests, sterilisation validation, software verification and validation, performance tests, evaluation of biocompatibility and biological safety, as applicable.

MDCG 2024-5, Guidance on Investigator Brochure - 2.1.8. Reference to previous and similar generations of the device. An overview of the previous and similar versions of the device (e.g., in table format) is recommended, if applicable. This overview should specifically focus on the devices used clinically and **in confirmatory pre-clinical testing**, i.e. the late stages of development. Preferably, this table contains for each iteration the version number, a photograph/drawing and a brief overview and rationale of changes with regards to the previous iteration.

5.2. Clinical Evidence to Date

Clinical evidence details are provided in IB, however the CIP should include a summary, as recommended in MDCG 2024-3.

ISO14155:2020 A.3.b: Summarise the available clinical experience with relevance to the investigation (published or available unpublished data that should be based on or referred to a systematic review). This shall include an analysis of adverse device effects, benefits, and any history of modification or recall. If none is available, include a statement that there is no available clinical experience to date on the MD. Also include post-market experience if applicable.

Any statements that rely on existing knowledge or published information shall be adequately referenced.

6. Benefits and Risks of the Investigational Device, Clinical Procedure, and Clinical Investigation

6.1. Expected Benefits

ISO14155:2020

Annex A.4.a: Insert anticipated clinical benefit).

Annex H: Application of ISO 14971 to Clinical Investigations.

RISK MANAGEMENT FRAMEWORK

ISO 14971 provides a general framework to systematically manage risks associated with the use of medical devices. The risk management process associated with a clinical investigation allows the hazards and hazardous situations associated with the investigational device to be identified. The associated risks are estimated (risk analysis) and evaluated (benefit-risk analysis), and risks are reduced to an acceptable level where necessary (risk control). The effectiveness of risk control is evaluated throughout the product's lifecycle, including during clinical investigations.

EXPECTED BENEFITS IN EFS

The expected benefits of the investigational device, clinical procedure, and overall clinical investigation should be clearly defined. In the context of **Early Feasibility Studies (EFS)**, the anticipated benefits often include gathering initial data on the safety and performance of the device, which will inform its future development and clinical use. Additionally, expected benefits can encompass advancements in the understanding of the device's interaction with human physiology, its potential to improve clinical outcomes, and how it may serve as a new treatment option for the patient population under investigation.

In **ISO 14971**-based risk management, these benefits should be weighed against the risks, with an emphasis on both clinical and scientific value. The **benefit-risk profile** for EFS studies should ensure that the benefits outweigh the risks at this early stage of the device's lifecycle.

The expected clinical benefits of the investigational device in an Early Feasibility Study (EFS), particularly for high-risk devices, are primarily focused on gathering crucial early-stage data to understand the safety and performance of the device. Given the investigational nature of these studies, the anticipated benefits are more about gathering essential data that could ultimately lead to clinical acceptance and regulatory approval in the future, rather than providing direct therapeutic benefits to the patients involved.

However, these benefits should be balanced with the uncertainty surrounding the device's clinical effects. In EFS for high-risk devices, the primary objective is to assess safety and performance characteristics that are largely unknown at the start. ISO 14971 requires that the expected benefits be clearly articulated, including both immediate and long-term clinical implications as the device progresses through clinical development.

6.2. Anticipated Adverse Device Effects

ISO1415:2020 A.4.b: Insert anticipated adverse device effects.

Adverse device effects (ADEs) are potential unintended consequences resulting from the use of the device.

In **EFS for high-risk devices**, the risks associated with participating in the clinical investigation are often **significantly amplified and** are harder to predict, as the device is still in the early stages of clinical testing. As the device is in an **early stage of evaluation**, the potential for unforeseen risks, both device-related and procedure-related, is substantial. Risks may include **device malfunction**, life-threatening **complications related to the device's novel features**, and **unpredictable patient responses**.

An essential part of **ISO 14971** risk management is identifying these effects early and implementing safeguards. Even though EFS studies often involve novel or untested devices, proactive identification and **classification of potential ADEs** should take place. This would include documenting known risks from similar devices or technologies, along with any predicted adverse outcomes based on preclinical and in vitro studies.

Under ISO 14971, anticipated ADEs should be based on the device's design, technology, and clinical context, which may include increased device failure rates, potential for long-term complications, or unexpected biological responses. The risk analysis should also account for the interactions between the device and human physiology, as well as the devices' interactions with patient-specific conditions.

Given the novelty and high-risk nature of the device, the ADEs occurring during the study should be carefully categorized according to their severity, probability, and clinical impact. Importantly, in such studies, the risk of undetected or previously unknown adverse effects may exist, which makes it essential to rely on rigorous preclinical data, post-market surveillance, and extensive monitoring throughout the study.

From the **patient's perspective**, risks could include exposure to an **experimental treatment** that is not yet proven safe or effective. These risks are heightened by the fact that many of the **specific risks** are still unknown at this stage, making the patient's role essential in helping to understand the **unanticipated** impacts of the device. These unknowns require careful **patient selection**, **clear informed consent**, and **continuous monitoring**.

A particular group of patients in EFS is the Roll-In Population, **Roll-in patients** refer to those enrolled early in the clinical trial who are typically treated with the investigational device during the **learning curve** phase. During this phase, the study team may be gaining familiarity with the device's operation, patient interaction, and clinical procedures. This can increase the potential for **user errors**, **device-related complications**, or **adverse events**, as both the investigational device and the clinical procedures may not yet be fully optimized or refined. The risk associated with Roll-in patients is higher due to this learning curve, which includes both the **investigator's familiarity** with the device and the **patients' responses** to the device's application. It is critical to **disclose** these potential risks in both the **clinical investigation protocol** and the **Informed Consent Form (ICF)**

to ensure transparency and that patients are fully informed of the evolving nature of the study. The protocol should include a detailed explanation of the **risk management strategies**, such as increased monitoring, **safety precautions**, and **contingency plans** in place to address potential device-related complications. Additionally, the ICF should explicitly outline the potential for **initial learning challenges** that may affect the device's performance and the clinical outcomes, emphasizing that the data collected in this early phase will contribute to improving future applications of the device. Ensuring clear communication of these risks to both patients and investigators is essential to maintain patient safety and regulatory compliance throughout the study.

Under the framework of **ISO 14971**, these risks should be identified through a **risk management process** that considers all potential harms, including **device failure**, malfunction, **infection**, and **delayed or adverse biological responses**. The **severity** and **probability** of these risks should be **quantified** based on available data (e.g., pre-clinical data, **animal studies**, **in vitro testing**), but this information will be limited in **EFS studies**. Therefore, a **conservative approach** to patient safety is necessary, including **closer monitoring** and contingency planning for any **adverse events** that arise during the study.

6.3. Potential Risks of Study Participation

ISO14155:2020 A.4.c: Insert risks associated with participation in the clinical investigation.

In addition to risks related to the device itself, participation in the clinical investigation introduces **risks tied to the clinical procedures and investigation protocols**. Potential risks to participants may include procedure-related complications (e.g., anaesthesia risks, surgical risks) or risks related to required examinations (e.g., X ray exposure) or concomitant medications that are recommended for use with the device (e.g., anticoagulation).

ISO 14971 framework provides a structured approach to identifying, assessing, and classifying these risks in terms of likelihood, severity, and severity duration.

6.4. Minimization of Risks

ISO14155:2020 A.4.e: Insert steps that will be taken to control or mitigate the risks.

Given the high-risk nature of the device, minimizing risks in EFS studies must be a top priority. Risk management, as outlined in ISO 14971, requires the implementation of multiple **strategies to control and mitigate the identified risks**. This may involve both device design improvements and clinical safety measures.

For example, in the case of device malfunctions, risk mitigation may include ensuring redundant safety features in the device (e.g., backup systems, automatic shutoffs), increased training for clinical staff to ensure correct application, and enhanced monitoring systems to detect device failures early. Patient management is also critical, including pre-screening to exclude individuals with conditions that could increase the risks of adverse events, and closely monitoring patients' post-procedure.

Moreover, ISO 14971 mandates that risks must be regularly reassessed throughout the clinical investigation, and corrective actions should be implemented immediately if new risks are identified.

In the context of high-risk devices, continuous patient monitoring (e.g., real-time data collection, frequent follow-ups) is necessary to detect potential adverse effects early and prevent escalation.

6.5. Risk/Benefit Considerations

ISO14155:2020 A.4.f: Rationale for benefit-risk ratio.

MDR Annex XV Chapter II, Section 3.3: Insert risks and clinical benefits of the device to be examined, with justification of the corresponding expected clinical outcomes in the clinical investigation plan.

ISO14155:2020 A.4.d: Insert possible interactions with concomitant medical treatments as considered under the risk analysis.

MDR Annex XV, Chapter II, section 3.3: Add a justification of the corresponding expected clinical outcomes.

The risk-benefit rationale includes a clear statement of the anticipated clinical benefits, considering the device's safety and performance history, including any modifications or recalls. For investigations that do not provide direct benefit to subjects, the rationale must explain how the results could contribute to future advancements, such as improved treatment options or a better understanding of the disease. Risk mitigation strategies are outlined, with references to the risk analysis report. These measures include protective barriers, safe device design, effective communication of safety information, and comprehensive safety training. Plans for post-investigation care, such as addressing adverse outcomes or device deficiencies, are also detailed to ensure participant safety and prevent further harm.

The evaluation identifies and assesses all risks associated with the device and clinical procedures, specifying the type, likelihood, severity, and duration of potential harm. Residual risks are defined and addressed, and mechanisms to monitor risk thresholds and distress levels during the study are established. By thoroughly evaluating risks, benefits, and mitigation measures, this section ensures compliance with regulatory standards while prioritizing participants' safety and well-being.

In **EFS for high-risk devices**, the **benefit-risk ratio** is a delicate balance. The **anticipated benefits** are often uncertain or indirect and may not immediately translate into **patient-specific therapeutic outcomes**. Instead, these studies aim to gather data that will inform **future trials**, device **optimization**, and broader **clinical applications**.

The **risk-benefit ratio** should clearly acknowledge the **novelty** and **unpredictability** of the device's risks. Although some risks may not be fully understood at the beginning of the study, the **long-term benefits** (e.g., improved treatment options for broader patient populations) should be emphasized. In cases where **direct patient benefit** is uncertain or unlikely, the **risk-benefit rationale** should explain how the **knowledge gained from the study** will contribute to the development of better devices and therapies in the future. This could include **improved efficacy**, better **safety profiles**, or the ability to address unmet medical needs.

The **ISO 14971** risk management process should include an assessment of all potential known risks to the patient, including **device malfunction**, **procedure-related complications**, and **long-term**

health impacts. This should be coupled with clear and **comprehensive informed consent** forms that inform patients of the potential risks, including unknowns that may arise during the study.

Plans for **post-investigation care**, including addressing **adverse outcomes** or **device deficiencies**, should also be in place, providing **additional safety nets** for patients once they have completed their participation in the study. Monitoring and **follow-up care** will be essential in ensuring patient safety and managing any **long-term consequences** of participating in an early-phase trial with a high-risk device.

By **thoroughly evaluating** the potential risks, benefits, and risk-mitigation strategies, this section ensures that all regulatory and ethical requirements are met, prioritizing **patient safety**, **informed decision-making**, and **scientific progress**.

7. Objectives and Hypotheses of the Clinical Investigation

ISO14155:2020 A.5.b and MDR Annex Chapter II, Section 3.5: Provide the purpose of the clinical investigation, claims for the clinical performance, effectiveness or safety of the investigational device that are to be verified.

EFS studies are early phase clinical studies not designed for statistical rigor or hypothesis testing. Rather EFS are designed to evaluate early device safety and performance prior to further clinical work or device iteration.

Describe the overall, primary and secondary objective(s) of the investigation in a clear and simple form. The primary objective should be clearly marked as such.

7.1. Overall Objective

Provide a clear, simple statement describing the overall purpose(s) of the investigation, explaining why the investigation is performed.

7.2. Safety Objectives

In investigations with efficacy as primary and secondary endpoints safety is always an additional objective.

Provide a clear, simple statement describing the safety objectives of the investigation. (e.g., the investigation aims to assess long-term safety of Device A and its tolerability in terms of allergic reactions against the component B of the device and use of rescue medication).

7.3. Device Functionality, Performance and Technical Success Objectives

This section defines specific objectives related to the functionality, initial performance and technical success of the device under investigation. In EFS, these aspects are essential for evaluating the feasibility and the safety of the device.

Provide specific, measurable objectives related to device functionality and performance (how the device is expected to operate and achieve its intended preliminary effect); technical success (successful execution of the device implantation or intervention procedure, and the device's immediate operational status post-procedure). Justify the choice of these objectives, explaining their relevance for assessing the feasibility and initial performance of the device in this preliminary phase.

Description of Study Design

Per ISO 14155:2020 A.5.a, add the purpose of the clinical investigation, claims for clinical performance, effectiveness or safety of the investigational device that are to be verified.

Per ISO 14155:2020 A.5.c, provide the scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits, where applicable.

Per ISO 14155:2020 A.5.e, provide any risks and anticipated adverse device effects that are to be assessed.

7.4. Study Hypothesis (if applicable)

Provide primary and secondary hypotheses, if applicable, per ISO 14155:2020 A.5.d and MDR Annex XV Chapter II, Section 3.5.

8. Design of the Clinical Investigation

8.1. General Clinical Investigation Design and Justification of Design

Note: The scientific integrity of the investigation and the credibility of the data from the investigation depend substantially on the design of this investigation.

The EFS study design should be fit for purpose, meaning it must be appropriately tailored to the specific developmental stage of the device and the critical questions being addressed.

Per ISO 14155:2020 A.6.1.a, and MDR Annex XV, Chapter II, Section 3.6.1, describe the design of the investigation and its rationale, the type (e.g., blind – who is blinded, with comparator, parallel design), allocation ratio and framework (e.g., superiority, equivalence, non-inferiority, exploratory). Provide a description of intended procedures and stages, the expected duration of subject's participation, description of sequence and duration of all investigation periods, incl. follow-up. Provide a discussion of the known or potential problems and limitations of the design.

The following information should be included in this chapter:

MDR Annex XV, Chapter II, Section 3.6: Evidence of scientific robustness and validity of clinical investigation design.

ISO 14155:2020 A.6.1.b: Description of the measures to be taken to minimize or avoid bias, such as randomization, concealment of allocation, blinding/masking, and management of potential confounding factors.

ISO 14155:2020 A.6.1.d: Methods and timing for assessing, recording, and analysing variables and relevant rationale.

ISO 14155:2020 A.6.1.e: Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration.

ISO 14155:2020 A.6.1.h: Definition of completion of the clinical investigation.

8.2. Study Duration

ISO14155:2020 A.6.3.c: Expected duration of subject participation and a description of the sequence and duration of all investigation periods, including follow-up, if any.

8.3. Methods for Minimising Bias (if applicable)

Describe measures to be taken in order to minimise or avoid bias; if applicable describe randomisation, blinding and other measures in the chapters below.

Remove if not applicable

8.3.1. Randomisation (If applicable)

Describe the exact randomisation method (unit, what, allocation ratio, number generation mechanisms, block randomisation, stratification, how it is done and concealment of list). You can refer to chapter 7.3 as appropriate.

Remove if not applicable

8.3.2. Blinding Procedures (if applicable)

Describe how blinding is ensured, and who will be blinded after subjects' assignment to the intervention(s) (e.g., investigation subjects, care providers, outcome assessors, data analysts).

Remove if not applicable

8.3.3. Other Methods for Minimising Bias (if applicable)

Describe other methods if applicable (e.g., the use of validated questionnaires).

Remove if not applicable

8.3.4. Unblinding Procedures (Code Break) (if applicable)

If the investigation is blinded, describe under which circumstances unblinding is permissible and the unblinding procedures. Describe the unblinding procedure in case of suspension or premature termination of the investigation.

Remove if not applicable

8.4. Clinical Investigation Outcomes

Describe the outcomes in the corresponding chapters below, including the specific measurements and variables, analysis metric (e.g., change from baseline, final value, time to event, any evaluation criteria), time point for each outcome etc. Explanation of the clinical relevance of chosen efficacy and safety outcomes is strongly recommended.

8.4.1. Safety Outcomes

The safety outcomes (or endpoints) is the main result that is measured at a precise time-point or at the end of treatment/intervention to verify whether a given treatment was successful or not.

Provide a short description of the safety outcomes variable (usually only one and with regard to efficacy) and the rationale for the choice of outcome. (Safety can also be a primary endpoint in a safety investigation.)

There is only one primary safety and one primary performance endpoint.

Other endpoints will be listed as secondary endpoints.

8.4.2. Device Functionality and Performance Outcomes

Provide a short description of the Device Functionality and Performance Outcome variables and the rationale for the choice of outcomes.

8.4.3. Other Outcomes

Provide a short description of other outcome variables (such as human factors and usability: observation on how clinicians interact with the device).

9. Study Population

Describe in the subchapters below the population to be studied; this should include a description of the investigation settings if relevant (e.g., out-patients, community clinic, academic hospital) and list of centres/countries where data will be collected (or reference to where list of investigational sites can be obtained). Provide plan of actions to be taken if the enrolment goals are not met.

9.1. Eligibility Criteria

Describe in detail the inclusion and exclusion criteria for the subjects' eligibility to the investigation (if applicable, for example for cluster randomized investigations, eligibility criteria at the investigational sites level and individuals who will perform the interventions (e.g., surgeons, …)). Create a list of criteria and be as specific as possible.

9.1.1. Inclusion criteria

Subjects fulfilling ALL the following inclusion criteria are eligible for the investigation:

Etc. continue as applicable for this investigation

9.1.2. Exclusion criteria

Exclusion criteria are characteristics that make an individual ineligible for participation.

The presence of any ONE or MORE of the following exclusions criteria will lead to the exclusion of the subject.

(The following list is given as an example only. Please indicate here the exclusion criteria applicable to the investigation):

Contraindications to the class of MD under investigation, e.g., known hypersensitivity or allergy to the device material. Do not merely write a generic sentence here but clearly state the names of the substances that have a known potential for allergies, include the trade names where applicable. For example: “Patients with known iodine allergy, including previous reactions to Betadine™ or other iodine-based disinfectants”.

Vulnerable subjects (except the objectives of the investigation concern vulnerable subjects specifically),

Known or suspected non-compliance, drug or alcohol abuse,

Inability to follow the procedures of the investigation, e.g., due to language problems, psychological disorders, dementia, etc. of the subject,

Previous enrolment into the current investigation,

Enrolment of the PI, his/her family members, employees and other dependent persons,

Specific exclusions for the disease under investigation,

Etc. adapt the list and continue as applicable for this investigation.

Note: In line with the recommendations of the EU GCP Inspector‘s Working Party (web-Link) the inclusion and exclusion criteria must all be mapped individually in the CRF. An overall statement regarding a subject's eligibility in the trial such as 'Did the subject satisfy all study entry criteria?' is not accepted.

9.2. Eligibility Assessment

A qualified physician, acting as the investigator or sub-investigator, will assess each potential subject against all protocol-defined eligibility criteria, which may include medical, behavioural, and lifestyle-related factors such as diet, caffeine intake, alcohol consumption, tobacco use, and physical activity, if relevant to the safe use of the device or validity of study data. Any lifestyle-related restrictions necessary to ensure subject safety or data integrity will be clearly documented. If no lifestyle restrictions apply, this will be explicitly stated.

The final decision to include a subject in the trial will be made by the investigator or sub-investigator and must be documented prior to the subject receiving the first study intervention. This process is

conducted in accordance with the principles outlined in ISO 14155:2020 (Section 6.3) and ICH E6(R3) (Section 4.3.1).

9.3. Recruitment and Screening

Describe how, where and by whom subjects are recruited / preselected for the investigation. Subjects must be given enough time to consider and to council with relatives and indicate the expected duration of the recruitment period. Mention details in case of advertisement; describe any screening requirements (e.g., laboratory or diagnostic tests), if the investigation foresees a screening visit. Describe any payment or compensation given to subjects (ISO14155). Refer to section 9.3. for description of screening procedures.

9.4. Criteria for Withdrawal / Discontinuation of Subjects

Describe the criteria and procedures when and how subjects are withdrawn from the investigation and if and under which circumstances subjects will be replaced. Describe reasons that would lead to investigation discontinuation (voluntary withdrawal, non-compliance, …) and the reasons that would lead to intervention discontinuation.

Refer to chapter 9.2.5 for description of follow-up procedures (e.g., withdrawal of informed consent, non-compliance, disease progression, safety, etc. or investigation or routine procedure must be stopped, e.g., due to safety concerns).

9.5. Justification of the Choice of the Investigation Population

This section provides a detailed justification for selecting the investigation population, ensuring its relevance and representativeness of the target population, as outlined in Annex XV, Chapter 2, Article 3.6.3 of the MDR. The rationale for the inclusion criteria considers the clinical context, the investigational device's intended purpose, and the indications for use. If the device's intended use differs from its approved purpose, this distinction is clarified.

For investigations involving vulnerable populations, such as minors, individuals incapable of judgment, or those under tutelage, the inclusion rationale must demonstrate why comparable results cannot be obtained from adults capable of judgment, in compliance with EU MDR Article 64(2)(d), ISO 14155:2020 Clause 4.8, and the Declaration of Helsinki (Paragraphs 19–20, 28) The specific aspects of the research question that pertain to vulnerable subjects are identified, along with the scientific necessity for their inclusion based on risk–benefit assessment. Ethical safeguards and protections should be applied in accordance with the applicable regulation. Recruitment strategies shall ensure the appropriate inclusion of vulnerable and non-vulnerable subjects. Stratification and enrolment procedures must be clearly defined to support ethical and scientifically valid study conduct. This process should allow for appropriate subject representation and facilitate meaningful analysis across both for pilot and pivotal phases of investigations.

This section summarizes the investigational device's intended purpose, target population, and indications, ensuring alignment with the investigation's objectives and the overarching goals of clinical research.

10. Study Conduct

Describe the Informed consent procedure, clinical procedures, diagnostic methods, collection, storage of samples taken, etc. relating to the clinical investigation and in particular highlighting any deviation from normal clinical practice (Annex XV, chapter 2, Art. 3.6.5 MDR).

10.1. Procedures at Each Visit

Describe the procedures at each visit according to investigation phase: e.g., Informed consent procedure, screening, baseline, visits during intervention, close-out visit, follow-up visits. Include additional tasks as scheduling of next visit, time windows permitted, etc.

10.2. Split Into Subtitles by Type of Visit

E.g. Screening visit, Day (e.g., -10 to 0): List all exams/tests and other actions to be performed.

E.g. Visit 1, Baseline (Day e.g., 1): List all exams/tests, actions to be performed according to flow chart (chapter 9.1) including also e.g., application of the MD, Scheduling of next visit.

E.g. Visit 2-5 (± indicate the window), if they are identical, otherwise describe each visit separately. Final visit, safety follow-up visits 7-9 (± indicate the window). Mention the hand-over of the implant card in case of implantable MD.

10.3. Adverse Events

Recording of adverse event information and the information to be collected: time of onset, duration, resolution, action to be taken, assessment of intensity, relationship with the MD and with the procedures of the investigation, expectedness, seriousness. Define specific process to ask the subject at the visits about adverse events, collection of spontaneous reports including follow-up after investigation completion.

Refer to chapter 14.1 for AE definition and reporting procedures to EC, CA and CEC.

10.4. Device Deficiencies

This section should describe how device deficiencies will be managed, documented, and reported. In EFS the timely identification and characterization of device deficiencies is critical to the design optimization process and risk management. Deficiencies are distinct from adverse events, but they can be the cause of them.

Provide a clear definition of what constitutes a device deficiency within the context of this specific investigational device. Detail the procedures for their identification, assessment, and reporting during the clinical investigation.

10.5. Imaging and Core Laboratory Parameters

Specify imaging and laboratory parameters to be assessed; define time-points of assessment; describe sampling if deviating from hospital routine; specify tests to be used (e.g., for pregnancy:

blood, urine; urinalysis); describe analysis of samples: local or abroad, if abroad, describe procedure for shipment, storage until shipment; if not yet known, refer to instruction to be written for the investigation team and to be part of the investigation manual.

10.6. Vital Signs (If applicable)

Describe how and when they will be assessed (e.g., heartbeat, blood pressure, body temperature, ECG) (e.g., in supine position after 5 minutes resting).

10.7. Concomitant Interventions (Treatments)

Clearly state any specific or relevant concomitant care and interventions that are permitted (additional treatments) during the investigation including contraindications and interactions for the investigational device, comparators, and required treatments. Their use should be recorded in the CRF. Describe their potential impact on the objectives of the investigation.

10.8. Clinical Investigation Specific Preventive Measures

Describe any specific preventive measures, including rescue medication for the subjects or treatments that are prohibited (restrictions). Their use should be recorded in the CRF. Describe their potential impact on the objectives of the investigation.

10.9. Follow-up of the Subjects After the Regular Termination of the Clinical Investigation

Describe the arrangements for taking care of the subjects after their participation in the clinical investigation has ended, where such additional care is necessary because of the subjects' participation in the clinical investigation and where it differs from that normally expected for the medical condition in question.

10.10. Assessments of Outcomes

If not already described under chapter 5: Describe for each endpoint (if applicable) what variables will be assessed/observed and how it will be done (e.g., questionnaires, laboratory tests), including any related processes to promote data quality (e.g., duplicate measurements, training of assessors; equipment to be used and arrangements for maintenance and calibration). Provide the rationale or justification to use certain methods and not others etc. Define the time windows allowed.

10.10.1. Assessment of Safety Outcomes

If not already described under chapter 8.4.1: What will be assessed, when and how (e.g., The primary outcome, change of diastolic blood pressure at Day 21, will be measured as first item of the visit. The equipment xy will be used. The subject should be in supine position and 5 minutes at rest. In case the measurement needs to be repeated, it should be waited for at least 10 minutes. A repeated measurement needs to be recorded in the CRF.).

10.10.2. Assessment of Device Functionality, Performance Outcomes

If not already described under chapter 8.5.2: What will be assessed, when and how (e.g., The secondary outcome, change of diastolic and systolic blood pressure at the various time-points, will be measured as described for the primary endpoint.).

10.10.3. Assessment of Other Outcomes of Interest

If not already described under chapter 8.5.3: What will be assessed, when and how (e.g., demographic characteristics, physical examination, quality of life, biomarkers: describe sample kind, preparation, storage (in biobanks and the appropriate procedure with separate ICF) or destruction, shipment to other labs/ countries if applicable. In case of pharmacokinetic parameters: describe condition of subject (e.g., fasting, x hours after treatment with MD), time-points of sampling, size of sample taken, sample processing, storage, shipping, substances to be analysed, how their concentration is measured, validation of analytical system).

10.11. Site and Data Monitoring

Site and Data Monitoring activities (e.g., SQV (Site Qualification Visit), SIV (Site Initiation Visit), COV (Close Out Visit) and Source data verification) are described in detail in the Monitoring Plan which is a separate document.

Alternatively, the extent and nature of monitoring activities and all the details described in the above paragraph, based on the objective and design of the investigation, can be written in a Monitoring Plan.

Provide a statement that the source data/documents are accessible to monitors and questions are answered during monitoring by the PI and the site staff.

10.12. Protocol Deviations

The Investigator is not allowed to deviate from the Clinical Investigation. The use of waivers from the CIP is prohibited as per MDR Annex XV Chapter II, Section 3.9 and 3.10.

Exceptions are allowed under emergency circumstances to protect the rights, safety and well-being of the subjects. These deviations may proceed without prior approval but must be promptly documented, reported to the Sponsor and relevant authorities within (insert timeframe, e.g., 24-72 hours), and justified.

The Annual Study Report shall include any deviations from the CIP that may have affected the rights, safety or well-being of the subject or the scientific integrity of the investigation (ISO14155).

ISO14155:2020 A.10a: Write a statement that the investigator is not allowed to deviate from the CIP, except as specified in 5.6.4 letter c) (deviations from the CIP to protect the rights, safety and well-being of human subjects under emergency circumstances).

ISO14155:2020 A.10b: Describe the procedure for recording, reporting and analysing CIP deviations.

MDR Annex XV Chapter II, Section 3.10: Provide Policy regarding follow-up and management of CIP deviations.

ISO14155:2020 A.10c: Provide notification requirements and time frames.

ISO14155:2020 A.10d Describe corrective and preventive actions and investigator disqualification criteria.

11. Statistical Design and Analysis

This section describes the statistical plan for managing, analysing, and presenting data from this clinical study. In EFS studies, the statistical design is predominantly descriptive and exploratory, focusing on preliminary safety, initial performance, and feasibility. Demonstrations of statistical significance or formal hypothesis testing for the primary objectives are not envisaged, but rather the identification of trends and issues.

11.1. Statistical Design and Considerations

Describe the statistical considerations done for the investigation

Discuss/justify the chosen study design - demonstrate "fit for purpose"

Describe the planned data summaries/analyses

Justify the sample size: special reasoning and sample sizes may apply for early clinical investigations (e.g., feasibility studies [ISO14155]).

11.2. Planned Analyses

Make brief statements of the analyses that are planned, the methods and types and which variables and with what data sets and when (a detailed statistical analysis plan may be written as a separate document after finalisation of the CIP and may be referred to this document, e.g., statistical analysis plan), including timing of any planned interim analysis(ses).

11.2.1. Datasets to be Analysed, Analysis Populations

Describe the analysis populations, evaluation groups (i.e., the selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects) and data sets to be used for analysis and methods for any additional analyses (e.g., subgroup and adjusted analyses). This applies to all endpoints / outcomes to be analysed.

11.2.2. Primary Analysis

Describe the intended primary analysis that will be done, when and how and by whom it will be done. Indicate the pass and fail criteria to be applied to the results of the investigation.

11.2.3. Secondary Analyses

Describe the intended secondary analysis that will be done, when and how and by whom it will be done. Indicate the pass and fail criteria to be applied to the results of the investigation.

Describe the intended subgroup analyses, if applicable, that will be done, when and how and by whom they will be done, add hypothesis related to each subgroup.

11.2.4. Exploratory / Tertiary / Other Objectives

Describe the intended Analysis of Exploratory / Tertiary / Other Objectives.

11.2.5. Safety Analysis

Describe the intended Analysis of Safety Objectives.

11.2.6. Other Analysis

Describe any additional analysis of variables and/or parameters and subgroup analyses.

11.2.7. Interim Analysis

Describe the intended interim analysis that will be done, why, when and how and by whom it will be done, taking into consideration their purpose, frequency, timing, scope, statistical procedures, Data Monitoring Committee involvement, and stopping guidelines (refer to chapter 11.3). Explain the methods that will be used to adjust for interim analysis, or give a rationale for why adjustment is not necessary.

11.2.8. Deviation(s) from the Original Statistical Plan

Describe the procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the CIP and/or in the final report, as appropriate).

11.3. Data Management

According to ISO14155:2020 A.18 and MDR Annex XV Chapter II, Section 3.8, describe plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). In case electronic data capture systems are used, this chapter shall include a description of procedures for verification, validation and securing the database.

If data will not be anonymised after the statistical analysis, describe in which form they will be stored (e.g., coded). If the data is anonymised, describe how this is done.

Reference to where details of data management procedures can be found, if not in the CIP.

11.3.1. Data Management System

Describe what system (including cloud services and software) is being used and who is responsible and how it is tested before the investigation begins (may include a description of where the system is hosted).

11.3.2. Data security, Access and Back-up

Describe who has access to data, how, where and when – and which backup systems are in place (if applicable).

11.4. Analysis and Archiving

Describe how data are extracted and where they are stored, database status recording, duration and place of storage.

11.5. Data Handling and Record Keeping / Archiving

Describe how data are handled and that all investigation related documents are archived. A list of the essential clinical investigation documents which should be maintained in the investigation site and sponsor file is given in ISO14155 Annex E.

11.5.1. Handling of Missing Data and Drop-outs

Describe how missing data will be handled (e.g., multiple imputation, last observation carried forward, complete case analysis, consider primary and secondary outcomes…).

Describe efforts taken in case of lost to follow-up. European Considerations are available for ISO 14155. Reference MEDDEV 2.7/2 rev.2, chapter 7.2 Annex A.7, link.

Describe if dropouts are replaced. If sensitivity analyses are planned, specify them. All subjects shall be accounted for and documented, including those withdrawn from the investigation or lost to follow-up.

11.6. Electronic and Central Data Validation

Describe how data are validated.

11.7. Case Report Forms

ISO14155:2020 A.8.a

Describe how the investigation data is recorded, e.g., with paper or electronic Case Report Forms (p-/e-CRF). A CRF is maintained for each enrolled subject. CRFs must be kept current to reflect subject status at each phase during the course of the investigation. Subjects must not be identified in the CRF through the use of names, initials, or date birth. If paper-CRFs are used, describe how data is entered into an electronic database for analysis (e.g., double data entry).

Note: The person(s) authorized by the PI to enter the data in the CRF must be listed on the delegation log.

11.7.1. Specification of Source Data and Source Documents

Source data should be available at the site to document the existence of the investigation subjects. Source data must include the original documents relating to the investigation, as well as the medical treatment and medical history of the subject. In case of electronic source data (e.g., from Apps or from automatic recording devices), describe how the data is handled, transferred, stored and accessed by the PI and authorised staff.

Describe what is considered the source documents in the investigation (specify what is the source document for each data collected in the CRF, e.g., demographic data, visit dates, participation in investigation and ICFs, SAEs, SADEs, USADEs, AEs, and concomitant medication, results of relevant examinations. Identify data that are directly recorded in the CRF, which should also be considered being source data. Also describe where original source data are kept at the site.

Additionally, at the Sponsor's request, certain source data relevant to the assessment of AEs, Device Deficiencies, and other events of interest may be sent to the Sponsor to support safety and performance evaluation.

You can also refer to a separate document in the Appendices ('source data description and source data location').

11.7.2. Archiving of Essential Clinical Investigation Documents

All the documents of the clinical investigation must be archived for a minimum of (time according to local legislation) years after regular or premature termination of the clinical investigation.

Describe Sponsor and PI responsibilities for archiving essential documents in accordance with ISO 14155:2020 Section 8.3 and EUMDR Annex XV, Chapter II, Section 3.7. Specify location and length of storage.

11.7.3. Audits and Inspections

Describe the frequency and procedures for auditing the investigation, if any, and whether the process will be independent from the PI and the Sponsor. Provide a statement that the documentation of the investigation and the source data/documents are accessible to auditors/inspectors (also EC and CA) and questions are answered during inspections. All involved parties must keep the subject data strictly confidential.

11.7.4. Confidentiality, Data Protection

Data protection; should include the statement that direct access to source documents will be permitted for purposes of monitoring (chapter 12.3), audits and inspections (chapter 12.4) and should declare who will have access to the documents of the investigation, dataset, randomization code, etc. during and after the investigation (refer to chapter 13 for publication and dissemination of the results of the investigation).

12. Device Accountability

Provide plans of accurate and adequate records maintenance from shipment to the sites until return or disposal including the quantities, the dates of receipt, use, and return, identification of each MD (batch number/serial number or unique code), the expiring date if applicable, the subject identification, the physical storage location, the date on which the MD was returned by the patient/explanted, if applicable, the date of return of unused, expired or malfunctioning MDs, if applicable.

The accountability includes the accountability of the comparator(s).

ISO 14155:2020 A.11. and MDR Annex XV Chapter II, Section 3.11: Insert Description of the procedures for the accountability of investigational device and information on the control of access to the device.

ISO 14155:2020 A.11.b: Insert Procedures and particular materials and instructions for the safe return of investigational devices, including those that are potentially hazardous.

12.1. Return, Analysis or Destruction of the Medical Device

Provide a statement if the MD under investigation is shipped back to the Sponsor disposed/destructed at the hospital at the end of the investigation. Add procedures for preparation and shipment of used MD at the end of the investigation.

For MD already in use at the hospital "return or disposed/destructed" are according to standard procedures and mentioning this in the CIP is enough (no details needed).

In case of device deficiencies, including malfunction, usability issues, or inadequacy in the information supplied by the manufacturer including labelling, the devices will be returned to the sponsor for analysis.

Add procedures for documentation by the centre (e.g., pictures that need to be taken in situ and of the explant), and for preparation and shipment of used devices and explants.

12.2. Labelling and Supply (Re-supply)

Describe how the MD under investigation and the comparator, if applicable, are labelled and are provided to the investigational site. If applicable describe logistics of re-supply. For post-market device investigations labelling is not mandatory. Describe deviation from the commercial products if applicable. The label of the MD must be done according to Art. 6.10 ISO 14155 and indicate that the investigational device is exclusively for use in an investigation, unless this is not required (for example depending on the clinical development stage and of the design of the investigation).

12.3. Storage Conditions

Describe how the MD under investigation and the MD/medicinal products for the

standard/routine/comparator therapy are stored (e.g., temperature range, exposure to light, sterile environment, etc.). MD supplies must be kept in a secure, limited access storage area under the recommended storage conditions.

(For devices already in use: "supply, "storage", "return or destruction" are according to standard procedures and may be simply mentioned in the CIP without specific details.)

13. Ethical and Regulatory Aspects

Describe here the ethical considerations relating to the investigation:

Before the investigation is conducted, the CIP, the ICF as well as other investigation-specific documents shall be submitted to a properly constituted Ethics Committee (EC) and to the competent authorities (name the authority.) in agreement with local legal requirements, for formal approval. Any amendment to the CIP must as well be approved (if legally required) by these institutions.

The final positive decision of the EC and of the CA on the conduct of the investigation will be made and given in writing to the Sponsor before the investigation can start.

13.1. Ethical Conduct of the Investigation

The investigation will be carried out according to the CIP and with principles enunciated in the current version of the Declaration of Helsinki, the European Regulation on medical devices 2017/745 (MDR), the Norms ISO 14155 and ISO 14971, the ICH-guidelines of Good Clinical Practice (GCP) as applicable, The EC and the CA will receive the Annual Safety Report (ASR) and interim reports and be notified about investigation stop/end in agreement with local requirements.

The investigation will also be conducted in compliance with all applicable regional and national regulations, including but not limited to EU MDR Annex XV and data protection laws such as the General Data Protection Regulation (GDPR).

Add other national/local requirements, as applicable.

13.2. Declaration of Interests

Declare any conflict of interest if applicable or provide a statement of no conflict of interest (independence, intellectual, financial, proprietary etc.). A conflict of interest /competing interest is defined as “a set of conditions in which professional judgment concerning a primary interest (such as patients’ welfare or the validity of research) tends to be unduly influenced by a secondary interest” (DF Thompson, NEJM, 1993).

13.3. Insurance

<ISO 14155:2020A12.e>

Give proof of insurance cover or indemnification of subjects in case of injury. E.g., "Insurance is provided by the Sponsor and fulfils the legal provision of art. 3 ClinO-MD. A copy of the insurance certificate is filed in Investigator's file and in the Sponsor's file."

It can be referred here to another place where the document is found, e.g., chapter 17 or elsewhere.

13.4. Registration of the Investigation

Provide a statement of registration of the investigation. In which primary register is the investigation registered (or will be registered)? Include the registry entry number and registration date; include details on further registrations if the investigation is registered in other registries.

The investigation must be registered in a registry listed in the WHO International Clinical Trials Registry Platform (ICTRP, http://www.who.int/ictrp/en/).

13.5. Competent Authorities (CA) and Ethics Committees (EC)

The Sponsor (or The Sponsor-Investigator, as applicable) will submit the clinical investigation to the CA and EC and obtain regulatory and ethical committee approval before the start of the investigation. The PI (for multicentre investigations: 'Each PI at each participating investigational site') ensures that approval from the CA and EC is obtained and filed in the Investigator site file before the investigation starts.

CA approval is necessary for all EFS.

13.5.1. Reporting Duties to the Competent Authorities and Ethics Committees

Mention the reporting duties and the allowed time frame for the reporting (changes to the investigation including the reporting duties in case of planned or premature end of the investigation and the final report) and that no changes are made to the CIP without prior Sponsor and EC approval, except where necessary to eliminate apparent immediate hazards to subjects. Refer to

chapter 10 for safety reporting.

The regular or premature end of the clinical investigation as well as the interruption of the clinical investigation is reported to the EC within 15 days. The reasons for a premature end or an interruption have to be explained.

A guidance document on how to prepare, write, and translate, summaries of clinical trial results in lay language is given here. The lay summary is **not** the study report synopsis.

Add other local requirements in case of international investigations.

13.6. Protocol Amendments

State who is allowed to amend the CIP or to provide suggestions for a CIP amendment.

Provide plans for communicating important CIP modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., PIs, EC, CA, subjects, registries, journals, regulators etc.), to the medical device, etc.

13.7. Informed consent process

<ISO 14155:2020 A.13.a>

Explain that subjects will be informed about the investigation (what, how, by whom) and that consent is obtained from each subject; include the mention of compensation if any. Describe the process specific to the investigation including processes for vulnerable subjects (e.g., children assent) or subject lacking capacity of judgment, if applicable.

Check that the layout of the information respects the epicene language, or is it written in an inclusive format. If applicable, ensure that the issue of contraception and pregnancy are fully and clearly presented; If appropriate, address the issue of potential extra costs that may deter women/parents to participate in the study, e.g. childcare and custody.

The PI explains to each subject the nature of the clinical investigation, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each subject is informed that the participation in the clinical investigation is voluntary and that he/she may withdraw from the investigation at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The subjects are informed that he/she can ask any question, and consult with family members, friends, their treating physicians or other experts before deciding about their participation in the investigation. Enough time is given to the subjects.

Important note: Enough time needs to be given to the subject to give an informed consent. The time depends on the type of intervention, the risks, and other factors. If necessary, specify the timeframe given.

The subjects are informed that authorised individuals other than their treating physician may examine his/her medical records.

All subjects a given a subject information sheet and a consent form describing the clinical investigation and providing sufficient information for the subjects to make an informed decision about their participation in the investigation.

The formal consent of a subject, using the approved consent form, is obtained before the subject is submitted to any clinical investigation procedure.

The subject should read, understand, and voluntarily agree before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is signed and dated by the subject and the PI (or her/his designee). The signed consent form it is retained as part of the investigation records.

For subjects who are unable to read or write, the process for obtaining informed consent shall follow the guidance of ISO 14155 and MDR. This includes providing the information verbally in the presence of an impartial witness who will attest to the subject's informed consent. The witness will sign and date the consent form, confirming that the information was accurately conveyed and understood by the subject before consenting. The investigator must document this procedure thoroughly to ensure compliance with ethical and regulatory standards. In case of vulnerable populations the following aspects should be addressed and described:

- Describe how the legal representative is informed regarding the procedures of the investigation and how his or her consent is obtained;

In the event of a subject lacking capacity of judgment, mention that signs and symptoms showing that the subject is unwilling to participate in the investigation will result in the subject being excluded from participation.

<ISO 14155:2020 A.13.b>

Additionally, for emergency situations, the following aspects should be addressed and described

- How the will of the subject can be elucidated without unjustified delay (e.g., patient's provision);
- Mention that signs and symptoms showing that the subject is unwilling to participate in the investigation will result in the subject being excluded from participation;
- The guarantee that a physician not participating in the investigation, safeguards subject interest and insures proper medical care;
- How to get an informed consent for the use of the data from the subjects after regaining capacity of judgement, and in case of death of the subjects before they regain capacity of judgment;
- How to obtain an informed consent from the legal representative of subjects that are permanently lacking capacity of judgement, minors or subjects under tutelage.

13.8. Subject Privacy and Confidentiality

The Sponsor and the PI affirm and uphold the principle of the subjects' right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the subjects shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals. Individual subject medical information obtained as a result of this clinical investigation is considered confidential and disclosure to third parties is prohibited.

Specify here how the subjects' confidentiality is guaranteed (for example: the assignment to each subject of a unique subject identification number ensures subject confidentiality. Describe how the unique identification number is generated.

Specify in the CIP or in another written agreement that the PI(s)/institution(s) will permit investigation-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents. For data verification purposes, authorised representatives of the Sponsor, the CA or a EC may require direct access to parts of the medical records relevant to the investigation, including subjects' medical history.

14. Safety Reporting

Describe plans for collecting, documenting, assessing, reporting, and managing solicited and spontaneously reported adverse events, adverse device effects and other unintended effects of the interventions or conduct of the investigation. Detail additional safety measures for high-risk devices, including close monitoring, independent safety monitoring, and phased approaches.

14.1. Definition and Assessment of (Serious) Adverse Events and Other Safety Related Events

Adverse Event (AE) (ISO 14155:2020 A.14.a; EU MDR 2017/745, Art. 2(57))

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether related to the MD.

This includes events related to the MD under investigation or the comparator and to the procedures involved. For users or other persons this is restricted to events related to the MD.

Serious Adverse Event (SAE) (ISO 14155:2020 A.14.b; EU MDR 2017/745, Art. 2(58) & 80(2))

Any adverse event that led to any of the following:

a) death,

b) serious deterioration in the health of the subject that resulted in any of the following:

   I. life-threatening illness or injury,

   II. permanent impairment of a body structure or a body function,

   III. hospitalisation or prolongation of patient hospitalisation,

   IV. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

   V. chronic disease,

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Note: planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration of the health status of the subject, is not considered an SAE.

Device deficiency (ISO 14155: 2020 A.14.b; EU MDR 2017/745, Art.2(59) & 80(1))

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, of an investigational device, including malfunction, user errors and inadequate information supplied by the manufacturer.

The definition includes deficiencies related to the investigational MD or the comparator MD.

Device deficiency with Serious Adverse Device Effect (SADE) potential (Art. 80 Abs 1 letter c MDR; ISO14155)

Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Adverse Device Effect (ADE) (ISO14155:2020, Clause 3.1)

Adverse event possibly, probably or causally related to the use of an investigational device or procedures.

This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the MD under investigation. This includes any event that is a result of a use error or intentional misuse.

Serious Adverse Device Effect (SADE) (ISO 14155: 2020 Clause 3.49; EU MDR 2017/745, Art. 80 (2))

Adverse device effect (ADE) that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) (ISO 14155:2020, Clause 3.53; EU MDR 2017/745, Art. 80(1–2))

Serious adverse device effect (SADE) which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated SADE (ASADE) is an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Adverse Event Causality Assessment (MDCG 2020-10/1)

A causal relationship towards the medical device or the procedure of the investigation should be rated by the PI and the Sponsor as follows:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Possible:** The relationship with the use of the investigational device or the relationship with the implant procedure, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment, cases where relatedness cannot be assessed, or no information has been obtained).
- **Probable:** The relationship with the use of the investigational device or the relationship with the implant procedure seems relevant and/or the event cannot reasonably be explained by another cause.
- **Related:** The adverse event is associated with the investigational device and or with procedures beyond reasonable doubt.

14.2. Adverse Events Categorization

The adverse events are categorized by the PI and the Sponsor using the following algorithm:

Does the AE meet the seriousness criteria?

- No, it is not serious
  - Is the relationship to the device or the procedure possible, probable or causal?
    - No: non-related AE
    - Yes: **ADE**
- Yes, it is serious: **SAE**
  - Is the relationship to the device or the procedure possible, probable or causal?
    - No: non-related SAE
    - Yes: **SADE**
- Is it anticipated (within expected type, severity and frequency of the complications)?
    - No: unanticipated SADE (USADE)
    - Yes: **anticipated SADE (ASADE)**

14.2.1. Foreseeable Adverse Events and Anticipated Adverse Device Effects

List here foreseeable AE and anticipated adverse device effects, together with their likely incidence, mitigation or treatment. The SAEs and adverse device effects, together with their likely incidence, can be presented in a tabular form.

14.2.2. Reporting of (Serious) Adverse Events, Device Deficiencies, and Other Safety Related Events

Describe how, by whom and in what time frame the serious and other reportable AE (health hazards, laboratory abnormalities, pregnancies if applicable, etc.) are reported. Note: The Sponsor is responsible for the notifications to CA and to the ECs. The Sponsor may delegate the task, but not the responsibility. Describe the reporting responsibilities of the PI to the Sponsor in case of a multicentre investigation, when the Sponsor and the PI are not the same person. Similarly, define the reporting roles and responsibilities to the manufacturer when the Sponsor and the PI are the same person. Describe if there are exceptions for the reporting.

Reporting to the Sponsor:

The following events are to be reported to the Sponsor by the PI (or authorized designee) within 24 hours and 3 days (give reporting deadlines as applicable. These depend on stage of development and severity of possible consequences. Refer to the European guidance document MDCG 2020-

10/1, ISO 14155:2020 (9.2.5) and EU MDR 2017/745 (Art. 80) for details) after becoming aware of the event:

- *All SAEs*
- *DDs with SAE potential*
- *Other AEs and DDs identified in this CIP as being critical to the evaluation of the results of the investigation*

The Sponsor will evaluate all AEs including SAEs with regard to causality and seriousness. Device deficiencies are also assessed regarding their potential to lead to an SAE (DD with SADE potential).

Pregnancies

Note: Depending on the investigation, reporting of pregnancies may not be necessary.

If reporting is needed, include in the CIP how pregnancies will be reported (usually within 24 hours to the Sponsor), and how occurrence of pregnancy will be handled in the investigation (patient is withdrawn, outcome of the pregnancy should be followed-up, etc). If it is suspected that the MD may have interfered with the effectiveness of a contraceptive medication/device, specify how this should be reported. Details can depend on the type of investigation and intervention.

Reporting to the National CA and EC

The following events are to be reported by the Sponsor to the EC and to the CA promptly in accordance with EU MDR 2017/745 (Art. 80, 87), ISO 14155:2020 (9.2.5, 9.3 & 9.4), MDCG 2020-10/1:

a) **any serious adverse event** that has a causal relationship with the MD to be investigated, the comparator or the investigation procedure, or where such causal relationship is reasonably possible; (SADE);

b) **any device deficiency** that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; (DD with SADE potential);

c) **any new findings** in relation to any event referred to in points (a) and (b).

In order to ensure prompt notification, the Sponsor may initially submit an incomplete notification.

If applicable: For conformity-related clinical trials in sub-categories C1 and C2 that are also being conducted abroad:

The sponsor notifies the EC and CA without delay of all events, DD deficiencies and findings as specified above which arise from the conduct of the clinical trial abroad as per local requirement.

If safety and health hazards that require measures must be taken immediately during the conduct of the investigation (as for ADE and USADE), the Sponsor notifies the EC within the time frames specified in ISO 14155, MDCG guidance, and EU MDR and the circumstances which made them necessary.

If applicable: For clinical trials that are also being conducted or are also due to be conducted in EU or EEA states, the Sponsor notifies the EC and CA of all imposed or voluntary safety and protective measures that are being implemented in EU or EEA states, along with the circumstances that necessitated them, in accordance with applicable regulations in the respective member states.

Periodic safety reporting:

An Annual Safety Report (ASR) is submitted by the Sponsor to the EC and to the CA on an annual base. The ASR contains a list of all SADEs and DDs and a report on their degree of seriousness, causal relationship with the MD and procedure and on subjects' safety.

For investigations that are also being conducted abroad, the list and report must also include AEs and DDs that occurred abroad. The report must also include the status of the investigations in EU or EEA states in question.

14.2.3. Follow-up of (Serious) Adverse Events

Describe the follow-up of subjects terminating the investigation (either regularly or prematurely) with reported ongoing SAE, or any ongoing AEs of laboratory values or of vital signs. Describe how and what is done to follow-up on ongoing SAE and AES, and what is documented. Describe efforts taken in case of loss to follow-up.

14.2.4. Documentation and Reporting

Important note concerning all following sections of this chapter: add, respectively adapt to other local requirements in case of international investigations.

Device deficiencies (DD) and all **adverse events (AE)** including all **serious adverse events (SAE)** are collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire investigation period, i.e., from patient's informed consent until the last CIP-specific procedure, including a safety follow-up period until study exit ((i.e., completion of study, lost to follow-up, withdrawal of consent, or patient has died).

- Documentation of AEs (including SAEs) by the PI includes diagnosis and/ or symptoms description, start and stop dates of event, event treatment/action taken, event resolution, assessment of seriousness and causal relationship to MD and/or investigation procedure (ISO14155).
- Documentation of DDs by the PI includes description of event, start date, investigational device information, action taken with regard to the investigational device, and whether the DD led to an AE. The Sponsor shall review all DDs and determine and document in writing whether they could have led to a SAE (DD with SADE potential) (ISO14155).

Specify here how the information on AEs is systematically collected (e.g., by clinical safety assessment at the regular visits, as applicable and clinically justified in the context of the specific CIP). Also specify here the follow-up period, if applicable (also in case of premature withdrawal of the subject). If no such safety follow-up is needed, please specify and justify.

15. Suspension/Premature Termination of the Clinical Investigation

Describe the "stopping rules" for parts of the investigation or the entire investigation and provide a statement that the Sponsor (the EC and any competent authority) may terminate the investigation prematurely according to certain circumstances (name the reasons). <ISO 14155:2020 A.16.a-c>

The Sponsor may terminate the investigation prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient subject recruitment,
- when the safety of the subjects is doubtful or at risk, respectively,
- early evidence of harm of the experimental intervention.

15.1. Discontinuation or Modifications of the Intervention

Describe criteria for discontinuing or modifying allocated interventions for a given subject (e.g., removal of the implanted MD in response to harms, subject request, or improving/worsening disease).

15.2. Compliance with Clinical Investigation Intervention

Describe the procedures for monitoring subject compliance and the strategies to improve adherence to the intervention, and any procedures for monitoring adherence (e.g., return of unused MD, laboratory tests). Define non-compliance and how such subjects should be handled. Describe the ensured use of compliance with GCP, EC, regulatory approvals, etc.

16. Publication Policy

<ISO 14155:2020 A.17a-c>

Describe plans to communicate the results of the investigation to the subjects, healthcare professionals, the public, and other relevant groups (e.g., via a summary in lay language, publication, reporting in results databases, or other data sharing arrangements); anticipate for authorship eligibility guidelines and any intended use of professional writers and, if any plans for granting public access to the full CIP, subject-level dataset, and statistical code, including who will have ultimate authority over any of the activities. Mention the protection of trade secrets, if applicable.

17. Bibliography

<ISO 14155:2020 A.18 and MDR Annex XV, Chapter II, section 3.19>

1. Provide a list of the references pertaining and cited in the CIP.
2. Declaration of Helsinki, Version October 2013 (http://www.wma.net/en/30publications/10policies/b3/index.html)
3. Medical Device Regulation (EU) 2017/745 of 5 April 2017 (MDR) (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745)
4. EN ISO 14155:2020 Clinical investigation of medical devices for human subjects - Good clinical practice (www.iso.org)
5. EN ISO 14971:2019 Application of risk management to medical devices (www.iso.org)
6. MDCG 2024-3 Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices
7. MDCG 2024-5: Guidance on Investigator's Brochure
8. MDCG 2021-6 Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation
9. MDCG 2021-28 Substantial modification of clinical investigation under Medical Device Regulation
10. MDCG 2020-5 Clinical Evaluation – Equivalence A guide for manufacturers and notified bodies
11. MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 (https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-1_guidance_safety_reporting_en.pdf)
12. FDA Guideline: Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies (2013)
13. WHO, International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
14. 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)

18. Appendices

NOTE: Further relevant information can be found in the ISO 14155, Annex A Clinical Investigation Plan (CIP)

Documents that frequently change during the course of the investigation can be mentioned as ‘documents provided separately’ and listed here.

The section headings can be renamed accordingly.

1. Investigator's Brochure
2. General Insurance Conditions, insurance certificate
3. List of norms
4. List of investigational sites / PIs (List of countries or centres where data will be collected)
5. Specific protocols (e.g. MRI)
6. Case Report Form (ISO14155 Annex C)
7. Other material handed over to the patients
8. Definitions
9. Rates of foreseeable AE
10. Labels
11. ICF
12. Monitoring plan

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