Template for a Clinical Investigation Plan (CIP) for clinical investigations involving Medical Devices (MD)

General information and instructions

This document is the Clinical Investigation Plan (CIP) template for clinical investigations of medical devices (MD). swissethics recommends using this template to write a CIP for investigations to be submitted to the Swiss ethics committees and Swissmedic.

This template is suitable for investigations:

- initiated by (academic) investigators,
- performed in Switzerland, respectively where the Sponsor is located in Switzerland,
- where the questions of the investigation do relate to the investigation of a MD,
- where the Federal Act on Medicinal Products and Medical Devices (TPA) applies,
- where the Swiss law on human research (Federal Act on Research involving Human Beings (HRA)) and the ordinance ClinO-MD (KlinV-Mep, OClin-Dim, OSRUm-Dmed) apply.

The template is based on:

- HRA and the ordinance ClinO-MD (KlinV-Mep, OClin-Dim, OSRUm-Dmed).
- ISO14155
- EU Medical Devices Regulation 2017/745 (MDR)

This template provides a general format applicable to all investigations with MD. Investigations with MD of category A1 and A2 do not need Swissmedic approval, the CIP must be adapted accordingly.

The CIP must be adapted in case of international investigations.

Ensure that the criteria for selecting the persons intended to participate and the trial design allow an appropriate representation of the groups of persons who are relevant for answering the scientific question; in particular, they must take into account the distribution of genders and age groups. All applications submitted to the Ethics Committee should also address the issue of **sex and gender** (unless totally irrelevant). Based on the recommendations “sex and gender in research involving humans according to the HRA” (swissethics.ch / topics / sex and gender equitable research), a set of instructions has been elaborated by a group of experts to guide researchers in the writing of their research documentation, including a grid inspired by the SAGER guidelines. Researchers need to know that the check-up grid provided in the instructions are used by ethics committees’ members to review all protocols and related documents.

Instructions are indicated in *blue italics* and they need to 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].

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 synonymous of ‘clinical study’ or ‘clinical trial’.

The CIP must be submitted via BASEC in an Optical Character Recognition (OCR) PDF format, i.e. in a searchable PDF format.

The CIP must be signed by the principal investigator, the sponsor (if applicable) and in case of a

multicentric project by the principal investigators of each participating research center as well. Electronic signatures of the CIP 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. If the protocol is signed by hand, the scans of the wet-ink signed signature pages are uploaded to BASEC separately

The content of the CIP has to be consistent with the content of the research project application form in BASEC. You can refer to the CIP in the research project application form in BASEC to avoid redundancies but not vice versa.

Change history

Version Nr	Version date	Modified without version change	Description, comments	Control
1.0	15.04.2021		Initial version	PG
		x	Corrected few typos Added note to gender research to chapter 11.4 and 13.	PG
2.0	27.06.2022		Chapter 10 Safety: adapted to the revised ClinO-MD status 26.05.2022. Chapter 11.5 Describe efforts taken in case of lost to follow-up. Chapter 15 Insurance: total revision.	PG
		X	Additions to the section general information and instructions. Added notes to reporting deadlines to the sponsor in chapter 10.3.2 Chapter 2.3.1 and 2.4.1: Added notes for the submission to the ethics committee and to Swissmedic of the summary of the final report in lay language.	PG
		X	Added instructions on “sex and gender”-equitable research.	PG
3.0	16.09.2024		New version adapted to the amended ClinO-MD, status as of November 1, 2024.	PG
		X	Added reference to Clinicaltrials.gov in chapter 2.1 and reference to art. 5 ClinO-MD in chapter 2.8. Confidentiality	PG

✂ Remove the ‘General information and instructions’, and the table ‘Change history’ ✂

Clinical Investigation Plan (CIP)

INSERT TITLE OF THE CLINICAL INVESTIGATION

[Descriptive title identifying the design of the investigation (e.g. randomised, sham controlled, etc.), 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:	*Clinical investigation concerning medical devices (MD).*
Categorisation:	*Category according to Art 6 ClinO-MD (A1, A2, C1, C2 or C3).*
Registration:	*Name of the primary registry (if not yet registered name the intended registry) and the registration number.* *Swiss National Clinical Trials Portal (SNCTP): SNCTP-Number (this number is not available when the investigation is initially submitted to the CEC. It should be added once available).* *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.*
Sponsor representative (if the Sponsor is not located in Switzerland)	*Name of the Sponsor representative in Switzerland.*
Medical Device:	*Identification of the MD, including name, model/type, including software version and accessories, if any, to permit full identification.* *If available: Unique Device Identifier (UDI, the UDI system is detailed in Part C of Annex VI of the EU Medical Devices Regulation 2017/745 (MDR)).*
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".*

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, Statistician.

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 on title page*

The Sponsor, the Principal Investigator and the Statistician have approved the CIP 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 [indicate version/year], ICH-GCP as far as applicable, and the local legally applicable requirements.

The Investigator has received the ICF and consider it appropriate for use.

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

Place/Date	Signature

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

Place/Date	Signature

Statistician

Place/Date	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 [indicate version/year], ICH-GCP as far as applicable, and the local legally applicable requirements.

I have received the ICF and consider it appropriate for use.

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

Place/Date	Signature

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

Table of Contents

SYNOPSIS

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

Sponsor / Sponsor-Investigator	*Name of Sponsor / Sponsor-Investigator*
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.*
Registration:	*Name of the primary registry (if not yet registered name the intended registry) and the registration number. SNCTP-Number (this number is not available when the investigation is initially submitted to the CEC. It should be added once available). If applicable: EUDAMED-number, names of other registries, and the registrations numbers.*
Category and its rationale:	*Provide the investigation category determined by Art. 6 ClinO-MD with the rational/justification for this category*
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)*
Stage of development:	*Indicate the "clinical development stage" of the MD (pilot stage, pivotal stage, or post-market stage, Annex I.1 ISO14155). Indicate if the clinical investigation is conducted for a conformity assessment purpose*
Background and rationale:	*Provide a short background and the rationale for the investigation, this includes the health condition studied.* *Are "sex and gender" dimensions relevant to the topic of the study (specifying genetic/biological or social mechanisms at play)? To address this question, refer to the recommendations "sex and gender in research involving humans according to the HRA" (swissethics.ch / topics / sex and gender equitable research). If it is considered that "sex and gender" dimensions are not relevant, provide a justification.*
Objective(s):	*Brief statement of primary objectives and the main secondary objectives*
Outcome(s):	*Brief statement of primary outcome and the main secondary outcome measures*
Design:	*Design attributes such as open label; randomised; parallel; cross-over; factorial design, etc.*
Inclusion / exclusion criteria:	*Brief description of the population under investigation, the key inclusion and exclusion criteria and if applicable, the reasons for inclusion of vulnerable subjects* *Are "sex and gender" dimensions relevant to the topic of the study? To address this question, refer to the recommendations "sex and gender in research involving humans according to the HRA" (swissethics.ch / topics / sex and gender equitable research).*
Measurements and procedures:	*Brief description the measurements and procedures (methodology, procedures, sampling, …)*
Intervention:	*Brief description 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)*
Number of subjects with rationale:	*Number of subjects projected for the entire investigation (all sites combined). Give the total and the numbers for each treatment group*
Duration of the investigation:	*Estimated duration for the main investigation plan (e.g. from start of screening of first subject to last subject processed and finishing the investigation)*
Investigation schedule:	*Month Year of First- subject –In (planned)* *Month Year of Last- subject –Out (planned)*
Investigator(s):	*Name(s) of Investigator(s); Full contact details.*
Investigational Site(s):	*Single- or multicentric investigation. If multicentric give the number of projected sites to be involved. Indicate also the countries if the investigation is multi-national*
Statistical considerations:	*A very brief description of the main elements of the statistical methodology to be used in the investigation. Explanation of the sample size*
Compliance statement:	This investigation will be conducted in *full* compliance with the CIP, the current version of the Declaration of Helsinki, *ISO 14155 [indicate version/year],* ICH-GCP (as far as applicable) as well as all national legal and regulatory requirements. *If safety reporting in this investigation is not fully compliant to the version of ISO 14155, details must be described in section 10.3.*

ABBREVIATIONS

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

AE	Adverse Event
ADE	Adverse Device Effect
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CIP	Clinical investigation plan
ClinO	Ordinance on Clinical Trials in Human Research *(in German KlinV, in French Oclin, in Italian OSRUm)*
ClinO-MD	Ordinance on Clinical Trials with Medical Devices *(in German: KlinV-Mep, in French: Oclin-Dim, in Italian: OSRUm-Dmed)*
CRF	Case Report Form (pCRF paper CRF; eCRF electronic CRF)
DD	Device Deficiency
DMC / DSMC	Data Monitoring Committee, Data Safety Monitoring Committee
Ho	Null hypothesis
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonisation – guidelines of Good Clinical Practice
IFU	Instruction For Use
ISF	Investigator Site File
ISO	International Organisation for Standardisation
ITT	Intention to treat
MedDO	Medical Devices Ordinance *(in German: MepV, in French: Odim, in Italian: Odmed)*
MD	Medical Device
MDR	Medical Device Regulation (EU) 2017/745 of 5 April 2017
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDV	Source Data Verification
SNCTP	Swiss National Clinical Trials Portal
SOP	Standard Operating Procedure
USADE	Unanticipated Serious Adverse Device Effect

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr, Version Date	Chapter	Description of change	Reason for the change

INVESTIGATION SCHEDULE

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.

e.g.:

Investigation Periods	*Patient information*	*Consent (ICF) Screening*	*Treatment, Intervention Period*				*Follow-up*
Visit	*0*	*1*	*2*	*3*	*4*	*5*	*6*
Time (hour, day, week)	*-10*	*-7*	*0*	*1*	*8+/-1d*	*15+/-2d*	*22*
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*	*x*	*x*	*x*
Laboratory Tests		*x*				*x*	*x*
Pregnancy Test		*x*					*(x)*
Randomisation			*x*				
Other examinations, tests…		*x*			*x*		*x*
Other examinations, tests…		*x*					
Medical Device application			*x*	*x*	*x*	*x*	
Primary Variables (variable 1, variable x)		*x*	*x*	*x*	*x*	*x*	*x*
Secondary Variables (variable 1, variable x)		*x*	*x*	*x*	*x*	*x*	*x*
Concomitant Therapy, Intervention			*x*	*x*	*x*	*x*	
(Serious) Adverse Events, Adverse device effects			*x*	*x*	*x*	*x*	*X*
Device Deficiencies			*x*	*x*	*x*	*x*	*x*

1. INVESTIGATION ADMINISTRATIVE STRUCTURE

Provide complete contact details (address, phone, e-mail) of all individuals or groups/committees and their composition, roles, and responsibilities overseeing the investigation (e.g. Sponsor, PI, statistician, monitor, coordinator, data management team, and other individuals or groups, laboratories if applicable).

Provide complete contact details of any committee(s) involved in the investigation (e.g., Data Monitoring Committee, Data Safety Monitoring Committee, etc.).

If critical personnel involved in the investigation is not determined at the moment of writing the CPI, refer to other documents, e.g. staff list.

Note: Refer to Art. 4 ClinO-MD for the general obligations of the Sponsor and PI.

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 may also include legal representative(s) in foreign countries, in case of a multi-national investigation with a Swiss Sponsor-Investigator.

1.2 Principal Investigator(s)

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 must be annexed to the CIP (Annex XV, chapter 2, Art. 3.1.3 MDR).

Note: Required professional qualifications of the PI and other persons conducting the clinical investigation is given in Art. 5 ClinO-MD.

1.3 Statistician ("Biostatistician")

Name, title, address, email and telephone number(s) of the qualified statistician involved in the investigation.

1.4 Laboratory

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

1.5 Monitoring institution

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

1.6 Data Safety Monitoring Committee

If applicable this should comprise the composition of data safety monitoring committee (DSMC); 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 DSMC is not needed.

1.7 Any other relevant Committee, Person, Organisation, Institution

If applicable e.g. coordination, data management, etc. Alternatively, write "not applicable".

2. ETHICAL AND REGULATORY ASPECTS

Describe here the ethical considerations relating to the investigation:

Please refer to the ethical requirements in clinical research of E. Emanuel (Emanuel E et al., What makes clinical research ethical? JAMA 2000; 283:2701-2711): 1. Value, 2. Scientific validity, 3. Fair subject selection, 4. Favourable risk-benefit ratio, 5. Independent review, 6. Informed consent, 7. Respect for enrolled subjects.
Describe and evaluate the ethical implications for individuals and the society as a whole. Make a careful risk benefit evaluation.

Before the investigation is conducted, the CIP, the ICF as well as other investigation-specific documents shall be submitted to a properly constituted Competent Ethics Committee (CEC) and to the competent authorities (name the authority, e.g. Swissmedic / FOPH / foreign competent authorities.) 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 CEC 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 (Category C investigations: In Switzerland the national approval is issued by Swissmedic and includes the approval of the CEC). Additional requirements set by the authorities must be implemented.

2.1 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 primary registry recognized by the WHO (International Clinical Trials Registry Platform: https://www.who.int/clinical-trials-registry-platform), or in the registry of the U.S. National Library of Medicine (https://clinicaltrials.gov). In addition, registration in SNCTP (via BASEC) in the national languages of Switzerland in which recruitment is intended is required for clinical trials conducted in Switzerland (Art. 41 ClinO-MD, Art. 56 HRA).

Note: The data of the clinical investigation entered in BASEC will be automatically published in SNCTP no later than six months after the investigation has been granted approval by the CEC and CA.

2.2 Categorisation of the investigation

Describe the category and the rationale for the categorisation (Art. 6 ClinO-MD): (note: this is a non-official translation in English of Art 6, the text of the ordinance in English was not available when this template was written in March-April 2021)

1 Clinical trials correspond to category A if:

a. the product to be investigated bears a conformity mark in accordance with Art.13 MedDO;

b. the product to be investigated is used in accordance with the instructions for use; and

c. the making available on the market, the putting into service or the use of the product to be investigated is not prohibited in Switzerland.

2 Category A clinical trials correspond to the following subcategories:

a. if the subjects concerned are not subjected to any additional invasive or stressful procedures compared with those applied under normal conditions of use of the product: subcategory A1;

b. if the subjects are subjected to additional invasive or stressful procedures compared to the procedures used under normal conditions of use of the device: subcategory A2.

3 Clinical trials correspond to category C if:

a. the device bears a mark of conformity in accordance with Article 13 MedDO, but is not used in accordance with the instructions for use (subcategory C1);

b. the product does not bear a conformity mark according to Article 13 MedDO (subcategory C2); or

c. the making available on the market, the putting into service or the use of the product in Switzerland is prohibited (subcategory C3).

2.3 Competent Ethics Committee (CEC)

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

2.3.1 Reporting duties to the Competent Ethics Committee

Mention the reporting duties and the legal 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 CEC approval, except where necessary to eliminate apparent immediate hazards to subjects. Refer to chapter 10 for safety reporting.

Amendments are reported according to Art. 15 ClinO-MD (see also 2.10).

The regular or premature end of the investigation as well as the interruption of the investigation is reported to the CEC within 15 days (within 24 hours if it is due to security reasons) (Art. 36 ClinO-MD). The reasons for a premature end or an interruption have to be explained.

A final report shall be submitted within one year after the regular end of the investigation and within 3 months after a premature end of the investigation. A summary in easily understandable terms must be included with the final report (Art. 37 ClinO-MD). *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.

2.4 Competent Authorities (CA)

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

CA approval is necessary for all investigations category C (C1, C2, C3).

2.4.1 Reporting duties to the competent authorities

Mention the reporting duties and allowed time frame for the reporting to the CA including the reporting duties in case of planned or premature end of the investigation and the final report. Reporting duties and timelines are the same as for CEC, except of non-substantial amendments that shall be reported as soon as possible (Art. 20 ClinO-MD). Refer to chapter 10 for safety reporting. Amendments are reported according to Art. 20 ClinO-MD (see also 2.10). A final report shall be submitted within one year after the regular end of the investigation and within 3 months after a premature end of the investigation. A summary in easily understandable terms must be included with the final report (Art. 38, resp. 37 ClinO-MD).

Amendments to the CIP are reported according to Art. 20 ClinO-MD (see also chapter 2.10).

For safety reporting including reporting of safety and protective measures, as well as the safety and general progress report (jointly "annual report") refer to chapter 10.

The regular or premature termination of the investigation as well as the interruption of the investigation is reported to the CA within 15 days and within 24 hours if it is due to safety reasons (Art. 36 ClinO-MD). The reasons for a premature termination or an interruption shall be explained.

*A final report is submitted within one year after the regular end of the investigation and within 3 months after a premature end of the investigation. A summary in easily understandable terms will be included with the final report (Art. 37 ClinO-MD). 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.

2.5 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 ISO14155 and ISO14971, the ICH-guidelines of Good Clinical Practice (GCP) as applicable, the Swiss Human Research Act (HRA) and its Ordinances and Swiss regulatory authority's requirements.

Add other national/local requirements, as applicable.

2.6 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).

2.7 Patient Information and Informed Consent

swissethics strongly recommends to exclusively use the swissethics templates for writing the patient information documents and informed consent forms (ICF). They meet the legal requirements of Switzerland. The templates can be downloaded in German, French and Italian from swissethics.ch/templates and checklists/patient information and declaration of consent.

A Guidance document on "How to write comprehensible patient information and consent forms for research" and a "Glossary for medical terms and abbreviations" are available on swissethics.ch/templates/patient information and declaration of consent. swissethics strongly recommends to read the guidance document before writing the ICF.

If the sponsor or investigator plan to develop an electronic ICF for the study, swissethics strongly recommends to refer to the Guidance document on the development and use of an Electronic Informed Consent (eIC), published on swissethics.ch/topics/position papers, to meet international and national requirements.

Explain that subjects will be informed about the study (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 study (see also HRA and Art. 7-9 ClinO), 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. Make sure that the information covers the study's aspect related to "sex and gender" appropriately. If applicable, ensure that the issue of contraception and pregnancy are fully and clearly presented. If applicable, ensure that the issue of contraception and pregnancy are fully and clearly presented.

The PI explains to each subject the nature of the 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 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 (see the guidance document "Guideline of swissethics for the time for consideration between information and consent" published on swissethics.ch/topics/position papers, available in German and French). If necessary, specify the time-frame 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 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 consent form approved by the CEC, is obtained before the subject is submitted to any study 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, when applicable).

The subjects are informed, with their approval, that their personal physicians are informed about the

subjects' participation in the clinical investigation, when applicable.

The signed consent form it is retained as part of the clinical investigation documents. The subject's medical records are clearly marked to indicate that the subject is enrolled in the clinical investigation.

The subject is provided with well-defined procedures for possible emergency situations related to the performance study. The PI makes the necessary arrangements for emergency treatment. If the clinical performance study involves a blinding/masking technique: *chapter 6.9 gives the procedures for breaking the blinding/masking code in emergency situations and describes under which circumstances unblinding/unmasking is permissible.*

In case incidental findings are expected in the clinical investigation (e.g., radiological findings) that directly affect the study participants health care provided to the participants, describe how they will be informed (Art. 7, Abs 1, lit. e^{bis}).

In case of in case of vulnerable population 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 that the minor and / or subject under tutelage is capable of judgment, describe how their consent (or assent) is collected in addition to the consent of their legal representative;*
- *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.*

Additionally, for emergency situations, the following aspects should be addressed and described (a guidance document and templates for writing ICF for investigations in emergency situations are available on swissethics.ch/topics/research in an emergency situation, link*):*

- *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.*

2.8 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.

The investigator has appropriate knowledge and skills in the areas of data security and data protection or is able to ensure compliance by calling in appropriate expertise (Art. 5, ClinO-MD).

Individual subject medical information obtained as a result of this 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 CEC may require direct access to parts of the medical records relevant to the investigation, including subjects' medical history.

2.9 Early termination of the investigation

Describe the "stopping rules" for parts of the investigation or the entire investigation and provide a statement that the Sponsor (the CEC and any competent authority) may terminate the investigation prematurely according to certain circumstances (name the reasons).

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,
- alterations in accepted clinical practice that make the continuation of the investigation unwise,
- early evidence of benefit or harm of the experimental intervention.

2.10 Clinical investigation plan 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, CEC, CA, subjects, registries, journals, regulators etc.).

Substantial amendments are only implemented after approval by the CEC (Art. 15 ClinO-MD) and, for category C investigations, after approval by the CA also (Art. 20 ClinO-MD). The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR).

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of the subjects may proceed without prior approval by the Sponsor and the CEC (and for category C investigations without prior approval by the CA). Such deviations shall be documented and reported to the Sponsor and the CEC (and to the CA for category C investigations) within 2 days (Art. 34 ClinO-MD).

All non-substantial amendments are communicated to the CEC annually together with the safety report / general progress report of the clinical investigation (Art. 15 ClinO-MD), and for category C clinical investigations to the CA as soon as possible (Art. 20 ClinO-MD). The report will 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).

2.11 Deviation from the Clinical Investigation Plan

The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR).

Write a statement that the investigator is not allowed to deviate from the CIP, except as specified in 2.10. Describe the procedure for recording, reporting and analysing CIP deviations. Describe corrective and preventive actions and investigator disqualification criteria.

3. BACKGROUND AND RATIONALE

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

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.

Are "sex and gender" dimensions relevant to the topic of the study (specifying genetic/biological or social mechanisms at play)? To address this question, refer to the recommendations "sex and gender in research involving humans according to the HRA" (swissethics.ch / topics / sex and gender equitable research). If it is considered that "sex and gender" dimensions are not relevant, provide a justification.

3.2 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 (link) for the period of validity of certificates there were issued in accordance with the European directives directive 93/42/EEC or 90/385/EEC. 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.

Give reference to the IB and IFU.

3.3 Preclinical Evidence

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 can be omitted in the CIP if the MD is CE marked as medical device and if there is no off-label use.

3.4 Clinical Evidence to Date

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 postmarked experience if applicable.

3.5 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 the above chapters

3, 3.1-3.4).

3.6 Explanation for choice of comparator

Explain the rationale for the comparator (other MD, other therapy (e.g. active control), sham MD/intervention or no treatment, or historical data) used in the control group. In addition to the scientific rational, give the ethical justification for the choice of the comparator.

3.7 Risk evaluation (Risk-to-Benefits rationale)

Note: The risk management process, which includes risk analysis, risk-to-benefit assessment and risk control is described in ISO14971.

Describe in this chapter the anticipated adverse device effects, residual risks associated with the MD and the procedures involved in its use. Indicate the risks due to interaction with concomitant treatments. Risks associated with participation in the investigation shall be described and possible interactions with concurrent medical interventions shall be listed. A statement of the anticipated clinical benefit shall be given, as well as the risk-benefit rationale. This shall include an analysis of adverse device effects and any history of modification or recall in relation to safety and clinical performance in relation to both the device under investigation and the comparator(s).

For investigations without immediate benefit to the subjects, a rationale should be provided stating how the results of the investigation could be beneficial for future subjects due to e.g. improved treatment options a better understanding of the disease, etc.

Describe and discuss measures to control or mitigate the risks (give the reference to the risk analysis report) and how post-investigation care is organised.

Include harm caused directly by the MD, invasive procedures carried out for using the devices (for implantable devices indicate risks for implantation and removal), medical consequences of device deficiencies and side effects (risks due to rescue surgery, etc.), insufficient efficacy, withholding proven therapies from subjects, wrong diagnostic output (false positive or false negative results obtained with diagnostic MD), delaying correct screening/ diagnosis/ treatment in subjects.

3.8 Justification of the choice of the investigation population

Describe the choice of the investigation population and the rationale for it. Provide information on the representativeness of the investigation population in relation to the target population (Annex XV, chapter 2, art 3.6.3 MDR).

Ensure that the criteria for selecting the persons intended to participate and the trial design allow an appropriate representation of the groups of persons who are relevant for answering the scientific question; in particular, they must take into account the distribution of genders and age groups. The exclusion or intended underrepresentation of relevant groups of persons must be stated and justified (Art. 4a ClinO).

Describe how recruitment of the subjects is conducted to ensure “sex and gender” balance is achieved, or give an explanation why this would not be possible and how this imbalance would impact the scientific validity of the investigation result. Refer to the recommendations “sex and gender in research involving humans according to the HRA” (swissethics.ch / topics / sex and gender equitable research) to address “sex and gender” issues in this chapter. *If it is considered that “sex and gender” dimensions are not relevant, provide a justification.*

For vulnerable subjects (e.g. minors, subjects incapable of judgment or subjects under tutelage), the following aspects need to be addressed in the CIP: Rationale for the inclusion of vulnerable subjects (i.e. reasons why comparable results / findings cannot be obtained from adults capable of judgment, Art. 11 HRA).

If both vulnerable and non-vulnerable subjects are foreseen for recruitment: Describe the aspects of the research question that are specific to the vulnerable subjects. Describe in chapter 11, the numbers needed to evaluate those aspects (for pilot investigations) and the sample size calculation (for pivotal investigations), the stratification process for recruitment of the correct number of vulnerable and non-vulnerable subjects.

4. CLINICAL INVESTIGATION OBJECTIVES

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.

4.1 Overall Objective

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

4.2 Primary Objective

Provide one clear, simple statement describing the primary objective of the investigation (e.g., The investigation seeks primarily to determine the performance of an implanted subcutaneous insulin pump on glucose levels in blood compared to Insulin Pen A).

4.3 Secondary Objectives

Provide a clear, simple statement describing the secondary objectives of the investigation (e.g., Secondary objectives are to assess usability of an implanted subcutaneous insulin pump on glucose levels in blood compared to Insulin Pen B).

4.4 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).

5. CLINICAL INVESTIGATION OUTCOMES

Describe the primary, secondary, and other outcomes, in the corresponding chapters below, including the specific measurements and variables (e.g., blood sugar levels), 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.

5.1 Primary Outcome

The primary outcome (or endpoint) 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 primary outcome 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.

Note: a pivotal investigation is carried out for risk/benefit assessment. Both risks and benefits generally need to be primary endpoints and sufficiently powered. Separate sample size calculations are carried out for both parameters (efficacy and safety), the higher n needs to be taken. Note: the statistical analysis needs to be carried out on each specific population separately. A detailed description of the statistical analysis must be given in chapter 11. Statistical Methods.

Other endpoints will be listed as secondary endpoints.

5.2 Secondary Outcomes

Provide a short description of the secondary outcome variables and the rationale for the choice of outcomes.

5.3 Other Outcomes of Interest

Provide a short description of other outcome variables of interest. If applicable, describe how 'other outcomes of interest' are assessed in chapter 9.2.3. If statistical analysis is done, describe it in chapter 11.

5.4 Safety Outcomes

Provide a short description of the safety outcome variables referring to e.g. specific adverse events, rate of adverse events in general, laboratory parameters and/or vital signs.

6. CLINICAL INVESTIGATION DESIGN

6.1 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.

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:

Intervention to be studied (MD and procedures),

Population to be studied and the number of subjects to be included (if known or applicable),

Level and method of blinding/masking (e.g. double-blind, open, blinded evaluators and unblinded subjects and/or PI(s)),

Kind of comparator(s), (e.g. sham, no treatment, active drug, dose-response, historical and investigation configuration (parallel, cross-over)). Describe the control group(s)

Method of assignment to intervention (randomisation, stratification),

Expected duration of subject participation and a description of the sequence and duration of all investigation periods, including follow-up, if any.

6.2 Methods for minimising bias

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

6.2.1 Randomisation

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.

6.2.2 Blinding procedures

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).

6.2.3 Other methods for minimising bias

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

6.3 Unblinding Procedures (Code break)

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.

7. CLINICAL INVESTIGATION 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.

7.1 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.

Refer to the recommendations "sex and gender in research involving humans according to the HRA" (swissethics.ch / topics / sex and gender equitable research) to address "sex and gender" issues in this chapter, if relevant.

Subjects fulfilling all of the following inclusion criteria are eligible for the investigation:

- Informed Consent signed by the subject
  - *Etc. continue as applicable for this investigation*

The presence of any one of the following exclusion criteria will lead to the exclusion of the subject *(following list is given as an example only. Please indicate here the exclusion criteria applicable to the investigation)*:

- *Contraindications and limitations of the MD as described in the instructions for use.*
- *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".*
- *Clinically significant concomitant disease states (e.g., renal failure, hepatic dysfunction, cardiovascular disease, etc.),*
- *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,*
- *Participation in another investigation with an investigational drug or another MD within the 30 days preceding and during the present investigation,*
- *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.

It is the expectation that a qualified physician who is an investigator or a sub-investigator for the trial has assessed each individual eligibility criteria and has taken the final decision to include the subject in the trial (ICH GCP 4.3.1). This decision should be documented prior to the subject receiving the first intervention.

7.2 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 experts (see the guidance document "Guideline of swissethics for the time for consideration between information and consent" published on swissethics.ch/topics/position papers, available in German and French). 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.

7.3 Assignment to investigation groups

Describe how subjects are randomised (tools, by whom, when) and how associated treatment assignment will be made. Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned. Refer to chapter 6.2.1, if appropriate).

7.4 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).

8. CLINICAL INVESTIGATION INTERVENTION

8.1 Identity of the medical device under investigation

Describe all treatments for each arm of this investigation. Methods, equipment and timing for assessing, recording and analysing variables.

8.1.1 Experimental Intervention (medical device)

Describe the experimental intervention, the specific medical or surgical procedures involved in the use of the MD, route and place of implantation, and any deviation from the commercial product, if applicable. Do not repeat here the information provided in the chapter 3.2.

Include a description (especially for pre-market investigations) of how the MD is used or implanted, the necessary training and experience needed for its use (e.g. may also be supported by pictures or sketches of the handling, application, implantation), proctoring during the intervention.

8.1.2 Control Intervention (standard/routine/comparator)

If applicable: Describe the intervention with the comparator(s): routine (standard) MD, or medicinal product, or any other intervention used as comparator, as applicable. Give and describe the name, material, model/type, including software version and accessories, if any, etc. of the routine (standard) MD (e.g. add a picture of the MD), route and place of implantation, and any deviation from the commercial product, if applicable. Describe any other comparators (medicinal products, interventions, …).

Describe the procedure in case of sham-interventions.

Include a description of the necessary training and experience needed for its use (e.g. may also be supported by pictures or sketches of the handling, application, implantation).

8.1.3 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 ISO14155, 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).

8.1.4 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.)

8.2 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).

8.3 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.

8.4 Data Collection and Follow-up for withdrawn subjects

Describe the type and timing of data to be collected for withdrawn subjects. Note: If a subject withdraws from the investigation and gives the reason(s), this/these shall be recorded. If such withdrawal is due to problems related to the MD safety or performance, the PI shall ask for the subjects' permission to follow his/her status/condition outside the investigation.

Data and material already collected will be evaluated as far possible according to Art. 3 Abs. b ClinO-MD. In case of withdrawal, after the evaluation the data will be a) anonymised (if possible) or b) not anonymised (i.e. the data remains coded). Please specify which one. The biological material will be anonymised (if possible) or destroyed after evaluation.

The medical follow-up of withdrawn subjects, or of subjects that drop out from the investigation prematurely is described in chapter 9.2.5 and chapter 9.2.6.

8.5 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.

8.6 Concomitant Interventions (treatments)

Describe any specific or relevant concomitant care and interventions that are permitted (additional treatments) during the investigation. Their use should be recorded in the CRF. Describe their potential impact on the objectives of the investigation.

8.7 Medical 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).

8.8 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.

9. CLINICAL INVESTIGATION ASSESSMENTS

Describe the 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)

9.1 Clinical investigation flow chart(s) / table of clinical investigation procedures and assessments

Provide a detailed graph, chart or table of flow of the investigation and for the subject ("assessment schedule") with what is measured and how, grouped according to primary and/or secondary endpoints. Include the allowed time frames for each visit. The flow chart should comprise all investigation procedures during the whole course of the investigation, not only the assessed endpoints. It may be referred to the chapters "clinical investigation procedures" in case all these details are provided there. It is recommended that the flow chart is repeated here.

9.2 Assessments of outcomes

In 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.

9.2.1 Assessment of primary outcome

If not already described under chapter 5.1: 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.).

9.2.2 Assessment of secondary outcomes

If not already described under chapter 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.).

9.2.3 Assessment of other outcomes of interest

If not already described under chapter 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 PIC) 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).

9.2.4 Assessment of safety outcomes

If not already described under Chapter 5.4: What will be assessed, when and how.

9.2.4.1 Adverse events

Recording of adverse event information, what information needs 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.

Refer to chapter 10.1 for AE definition and reporting procedures to CA and CEC.

9.2.4.2 Laboratory parameters

Specify 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.

Define when abnormal laboratory parameters are considered as adverse events in chapter 10.3.1 for category C investigations and in chapter 10.4.1 for category A investigations. Refer to chapter 10 for reporting procedures to CA and CEC.

9.2.4.3 Vital signs

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).

9.2.5 Assessments in subjects who prematurely stop the clinical investigation

Describe follow-up procedures and assessments in subjects who withdrew/drop out from the investigation prematurely (e.g., recording of adverse events, physical examination, laboratory parameters, vital signs). The information provided here should not contradict the information provided under chapter 7.4. clinical investigation discontinuation criteria. Define follow-up period.

Indicate if and how the collected data of subjects withdrawing their consent during the course of the investigation is used and analysed. Indicate what happens to the data after the analysis. The details given here must match the information given in the patient information and consent form and in chapter 8.4 and 12.6.

9.2.6 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.

9.3 Procedures at each visit

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

9.3.1 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.

9.3.2 Split into subtitles by type of visit

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.

9.3.3 Split into subtitles by type of visit

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

10. SAFETY

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.

10.1 Definition and Assessment of (Serious) Adverse Events and other safety related events

Adverse Event (AE) (Art. 2 Abs 57 MDR)

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 or not 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) (Art. 2 Abs 58 MDR)

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 (Art. 2 Abs 59 MDR)

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.

Malfunction (ISO14155)

Failure of an investigational device to perform in accordance with its intended purpose when used in accordance with the instructions for use or the CIP.

Device deficiency with Serious Adverse Event (SAE) 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)

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) (ISO14155)

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

Unanticipated Serious Adverse Device Effect (USADE) (ISO14155)

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.

Causal Relationship of SAE (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 is weak but cannot be ruled out completely. Alternative causes are also possible. Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

10.2 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)

10.3 Documentation and reporting in Medical Device Category C clinical investigations

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

10.3.1 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.

10.3.2 Documentation of device deficiencies and adverse events by the investigator

All **device deficiencies (DD),** all **serious adverse events (SAE)** and *choose the applicable* all non-serious **adverse events (AE)** *or* non-serious adverse events (AE) identified in this CIP as being critical to the evaluation of the results of the investigation *(please phrase the compliance statement in the Synopsis accordingly)* are collected, fully investigated and documented in the source document and appropriate 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.

- Documentation of AEs (including SAEs) by the PI includes diagnosis or symptoms, start and stop dates of event, event treatment, event resolution, assessment of seriousness and causal relationship to MD and/or investigation procedure (ISO14155 *[please indicate version/year]*).
- 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 (ISO14155 *[please indicate version/year]*).

Specify here how the information on AEs is systematically collected (e.g., by clinical safety assessment and/or safety lab 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 from the investigation). If no such safety follow-up is needed, please specify and justify.

*In case that AEs identified as being critical to this evaluation and not **all** AEs shall be recorded as defined above, please include a list of the AEs evaluated as being critical and that shall be recorded. Please note that in this case full compliance with ISO 14155:2020 **cannot** be claimed.*

10.3.3 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 CECs. 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 of stage of development and severity of possible consequences. Refer to the European guidance document MDCG 2020-10/1 for details)* after becoming aware of the event:

- All SAEs
- Health hazards that require measures
- 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 shall define the timelines for reporting of non-serious AEs and DDs to the Sponsor.

The sponsor shall review the investigator's assessment of adverse events and determine and document in writing the seriousness and relationship to the investigational device and procedures required by the CIP (ISO 14155). The Sponsor shall evaluate AEs and SAEs with regard to causality and seriousness. Device deficiencies are also assessed regarding their potential to lead to an SAE (DD with SAE potential) (Art 32. ClinO-MD, ISO 14155).

Pregnancies

Note: Depending of 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 Competent Ethics Committee and to Swissmedic:

The following events are to be reported to the CEC and to the CA promptly (Art. 33 ClinO-MD):

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;
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.

In line with European guidance document MDCG 2020-10/1 Rev. 1, reportable SAE and DD must be sent to Swissmedic within 7 days, or 2 days for SAE requiring prompt action for the safety of other study subjects.

If applicable: For conformity-related clinical trials in sub-categories C1 and C2 that are also being conducted abroad: The sponsor notifies the CEC and CA without delay of all events, device deficiencies and findings as specified above which arise from the conduct of the clinical trial abroad.

If safety and health hazards that require measures must be taken immediately during the conduct of the investigation, the Sponsor notifies the CEC and CA within 2 days of these measures and the circumstances which made them necessary (Art. 34 ClinO-MD).

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 CEC and CA within 2 days of all imposed or voluntary safety and protective measures that are being implemented in EU or EEA states and the circumstances that necessitated them (Art. 34 ClinO-MD).

Periodic safety reporting (Art. 35 ClinO-MD):

Once a year, the sponsor submits to the CEC and CA a list of all SAEs and DDs and provides it with a report on their severity, causal relationship with the device and/or the intervention and on the safety of the participants (outcome, event status). The sponsor informs the CEC and CA annually about the general progress and status of recruitment of the clinical investigation *(also abroad)*. Any safety-relevant measures taken by the sponsor or imposed by ethics committees *or authorities anywhere in the world as well as results from other clinical investigations with the investigational device (if applicable)* shall be described. Based on the data presented in the report, the sponsor will draw his/her conclusions regarding the safety of the subjects and the continuation of the investigation. *The safety report and the general progress report can be merged in one single report.*

The cumulative list of reportable serious adverse events and device deficiencies (MDCG 2020-10/2 Rev. 1) per cut-off dateis submitted in parallel.

10.3.4 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.

10.4 Documentation and reporting in Medical Device Category A clinical investigations

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.

- Documentation of AEs (including SAEs) by the PI includes diagnosis or symptoms, start and stop dates of event, event treatment, event resolution, assessment of seriousness and causal relationship to MD and/or investigation procedure (Art. 32 ClinO-MD, 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) (Art 32. ClinO-MD, 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.

10.4.1 Foreseeable adverse events and anticipated adverse device effects

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

10.4.2 Reporting of Safety related events

Reporting to the Sponsor:

All SAEs, DDs with SAE potential and health hazards that require measures are reported to the Sponsor by the PI (or authorized designee) without delay after becoming aware of the event. DD are assessed regarding their potential to lead to an SAE.

Pregnancies

Depending of the investigation, reporting of pregnancies may not be necessary. If reporting is needed, include in the CIP how pregnancies will be reported (usually within a maximum of 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.). Details can depend on the type of investigation and intervention.

Reporting to the Competent Ethics Committee:

The Sponsor reports to the CEC without delay any SAE for which a causal relationship between the event and the test procedure used in the clinical trial has been ascertained (Art. 33 ClinO-MD).

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

If safety and health hazards that require measures must be taken immediately during the conduct of the investigation, the Sponsor notifies the CEC within 2 days of these measures and the circumstances which made them necessary (Art. 34 ClinO-MD).

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 CEC within two days of all imposed or voluntary safety and protective measures that are being implemented in EU or EEA states and the circumstances that necessitated them (Art. 34 ClinO-MD).

Periodic safety reporting (Art. 35 ClinO-MD):

Once a year, the sponsor submits to the CEC a list of the SAEs and DDs and provides it with a report on their severity, causal relationship with the device and the intervention, as well as on the safety of the participants. The sponsor informs the CEC about the general progress of the clinical investigation, annually. *The safety report and the general progress report can be merged in one single report.*

Materiovigilance reporting to Swissmedic:

The Sponsor is responsible for ensuring that Swissmedic is informed of serious incidents in accordance with Art. 66 MedDO.

Materiovigilance reports are not sent to the CEC.

If the Sponsor is the manufacturer of the investigational device or Swiss representative of the manufacturer:

- *the Sponsor has to send reportable incidents to Swissmedic (materiovigilance@swissmedic.ch) with the form available at www.swissmedic.ch/md-materiovigilance-manufacturers (Art. 66 para. 1 to 2bis MedDO).*

If the Sponsor is not the manufacturer of the investigational device or Swiss representative of the

manufacturer:

- *In case of incidents, check whether the event is subject to materiovigilance reporting duties for users acc. to Art. 66, para. 4 MedDO (using guidance MU680_20_008e_WL). If the clinical investigation/performance study is conducted in a hospital, the materiovigilance contact person of the hospital may also be contacted (Art. 67 para. 2 MedDO)*
- *The Sponsor has to ensure that reportable incidents are sent to Swissmedic with the form MU680_20_015d_FO (materiovigilance@swissmedic.ch). Guidance and forms are available at www.swissmedic.ch/md-materiovigilance-users.*
- *Users are legally obliged to inform the suppliers of the devices about serious incidents (Art. 66, para 4 MedDO).*

10.5 Assessment, notification and reporting on the use of radiation sources

In investigations involving therapeutic or diagnostic products capable of emitting ionising radiation and/or medical exams that use ionizing radiation (X-rays, CT scans, PET scans, fluoroscopy, …), the Sponsor shall assess compliance with the dose guidance value in accordance with Art. 45 of the Radiological Protection Ordinance of 26 April 2017. The dose guidance values for investigations without expected direct benefit for the subjects is 5 mSv effective dose per year.

If the permitted dose guidance value is exceeded at any time, the Sponsor or the PI notifies the CEC within 7 working days after becoming aware of the event [Art. 39 ClinO-MD].

When applicable, in the case of Category C clinical investigation with MDs that emit ionising radiation:
If in the case of Category C clinical investigations with MDs that emit ionising radiation, if the permitted dose guidance value is exceeded at any time, the Sponsor or the PI notifies the CA within 7 working days after becoming aware of the event [Art. 39 ClinO-MD].

Within one year of the completion or discontinuation of the investigation involving examinations with radioactive sources, the Sponsor sends to the CEC and to the CA a final report containing all information relevant to radiation protection, in particular an estimate of the doses to which the subjects were exposed [Art. 39 ClinO-MD].

11. STATISTICAL METHODS

Describe the statistical considerations done for the investigation, with justification, including a power calculation for the sample size, the statistical methods to be employed, the level of significance that will be used, including timing of any planned interim analysis(ses).

Special reasoning and sample sizes may apply for early clinical investigations (e.g. feasibility studies [ISO14155]).

11.1 Hypothesis

If a Null Hypothesis is tested, state explicitly both Null and Alternative Hypotheses in terms of the primary endpoint(s) and justify them in regard of the subject population and dose. The stated safety and benefit hypotheses have to be used in the determination of Sample Size. Relate these hypotheses to the investigation objectives.

If hypothesis testing is not used, then discuss how the approach used (e.g. Bayesian methods) will address the objectives.

11.2 Determination of Sample Size

Provide the number of subjects planned to be enrolled. Reason for choice of sample size with justification, including a power calculation for the sample size. Provide the estimated number of subjects for each investigation site and investigation arm (if applicable) needed to achieve the safety and benefit objective, how it was determined, including clinical and statistical assumptions supporting any sample size calculations, the power of the investigation, the type I error (one- or two-sided) and the related risk, the clinical justification.

If "sex and gender" dimension is of primary interest, does the sample size estimation integrate this aspect? Are the statistical analyses appropriate?

11.3 Statistical criteria of termination of the investigation

Describe the statistical criteria for the termination of the investigation ("discontinuation criteria") or the stopping rules, for example in case of evidence of early benefits or harm for parts of investigation and for the entire investigation). If applicable, describe the 'stop/go' rules for temporarily discontinuing the investigation.

11.4 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).

Include a statement that analyses of "sex and gende"r differences are planned. If such an analysis is not possible, please state the reasons.

11.4.1 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.

11.4.2 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.

11.4.3 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.

11.4.4 Interim analyses

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 analyses, or give a rationale for why adjustment is not necessary.

11.4.5 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).

11.5 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).

12. QUALITY ASSURANCE AND CONTROL

Describe how quality is assured and controlled. The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions, at all sites in case of multicentric investigations. Indicate the software used. The PI is responsible for proper training of all involved investigation personnel.

12.1 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.

12.1.1 Case Report Forms

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 by name or initials and birth date. Describe the coding used for the investigation, e.g. subject number in combination with year of birth (see the guidance document published on swissethics.ch "coding of trial subject accepted by swissethics and secure storage of subject identification list" https://swissethics.ch/assets/Themen/akzeptierte_verschluesselung_e.pdf)

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.

12.1.2 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, randomisation codes, SAEs, SADEs, USADEs, 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. You can also refer to a separate document in the Appendices ('source data description and source data location').

12.1.3 Archiving of essential clinical investigation documents

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

Describe Sponsor (Art. 40 Abs 1 ClinO-MD) and PI (Art. 40 Abs 2 ClinO-MD) responsibilities. Specify location and length of storage. Archiving for 10 years, in the case of an implantable device 15 years in Switzerland (Art. 40 ClinO-MD).

12.2 Data management

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.

12.2.1 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).

12.2.2 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).

12.2.3 Analysis and archiving

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

12.2.4 Electronic and central data validation

Describe how data are validated.

12.3 Monitoring

Describe the regular monitoring visits at the PI's site prior to the start and during the course of the investigation organised by the Sponsor. Give a detailed description of what, which data and documents will be monitored and to which extent (these points are given here as examples only: subject enrolment logs, informed consents and informed consent process, source data verification, inclusion and exclusion criteria, subjects' visit schedule, safety, processing of subjects' data, preservation of subjects confidentiality, reporting to CEC and RA and approvals, provisions of records and data retention, etc…). Indicate which organisation or person does the monitoring; specify monitor qualification and training. Describe procedure to review the monitoring visit reports, follow-up on monitoring findings and corrective actions.

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. The Monitoring Plan must be annexed to the CIP (Annex XV, Chapter 2, Art. 3.6.6. MDR).

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.

12.4 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 CEC and CA) and questions are answered during inspections. All involved parties must keep the subject data strictly confidential.

12.5 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 investiation, dataset, randomization code, etc. during and after the investigation (refer to chapter 13 for publication and dissemination of the results of the investigation).

12.6 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 subjects consent for further use has been obtained. This consent is given (or withheld) independently of the participation in the investigation (Art. 17. ClinO).

13. PUBLICATION AND DISSEMINATION POLICY

Give the publication policy of the results of the investigation, if not addressed in a separate agreement, according to Art. 42 ClinO-MD.

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.

Confirm that if "sex and gender" effects are observed, they will be published in the final study report. If an analysis is performed but no "sex and gender" effects are observed, this should also be published in the final study report.

The Sponsor will enter and publish a summary of the results of the clinical investigation in a public recognized register (as specified in Art. 64 Abs. 1 lit a or b ClinO) *(complete the paragraph as appropriate)*:

a) immediately after submitting the final report *(for completed clinical trials with devices that already bear a conformity marking and were used in accordance with the instructions, or in the event of an early termination or interruption of a clinical trial: in accordance with Article 37)*

or b) at the latest before the device is placed on the market or one year after submitting the final report if the device has not been placed on the market by this point in time. *(for all other completed clinical trials, in accordance with Article 37).*

The Sponsor also ensures that a lay summary of the results is entered in BASEC within the period specified in the paragraph above. The entry is made at least in the national languages of Switzerland in which the study participants were recruited.

If publication of the results is not possible within the specified period for scientific reasons, the sponsor will explain this in the application documents and indicate when publication will take place. Adapt this paragraph accordingly.

The investigator will provide each participant with the lay summary of the results of the clinical investigation at the end of the study, directly. *The investigator should ensure that participants are adequately informed about this in the patient information document and also that they are informed where the lay summary of the results of the clinical investigation will be published online.*

14. FUNDING AND SUPPORT

14.1 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.

14.2 Other Support

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.

15. INSURANCE

Give proof of insurance cover or indemnification of subjects in case of injury, pursuant to Art. 3 ClinO-MD. 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."

Note: Category A1 performance studies are exempt from liability coverage requirements (ClinO Art. 12). Categories A2 and C performance studies need to document the guarantee of liability (insurance certificate or equivalent guarantee) (ClinO Art. 13).

The insurance must cover damage occurring up to 20 years after the end of the clinical investigation.

The policy value shall be set in accordance with ClinO Annex 2.

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

16. REFERENCES

Provide a list of the references pertaining and cited in the CIP.

1. Declaration of Helsinki, Version October 2013 (http://www.wma.net)
2. Humanforschungsgesetz, HFG Bundesgesetz über die Forschung am Menschen (Bundesgesetz über die Forschung am Menschen, HFG) vom 30. September 2011/ Loi fédérale relative à la recherche sur l'être humain (loi relative à la recherche sur l'être humain, LRH) du 30 septembre 2011 / Legge federale concernente la ricerca sull'essere umano (Legge sulla ricerca umana, LRUm) del 30 settembre 2011
3. Verordnung über klinische Versuche mit Medizinprodukten (KlinV-Mep) vom 1. Juli 2020 / Ordonnance sur les essais cliniques de dispositifs médicaux (OClin-Dim) du 1er juillet 2020 /. Ordinanza sulle sperimentazioni cliniche con dispositivi medici (OSRUm-Dmed) del 1 luglio 2020
4. Verordnung über klinische Versuche mit Ausnahme klinischer Versuche mit Medizinprodukten (Verordnung über klinische Versuche, KlinV) vom 20. September 2013 / Ordonnance sur les essais cliniques hors essais cliniques de dispositifs médicaux (Ordonnance sur les essais cliniques, OClin) du 20 septembre 2013. Ordinanza sulle sperimentazioni cliniche ad eccezione delle sperimentazioni cliniche con dispositivi medici (Ordinanza sulle sperimentazioni cliniche, OSRUm) del 20 settembre 2013
5. Medizinprodukteverordnung (MepV) vom 17. Oktober 2001 / Ordonnance sur les dispositifs médicaux (ODim) du 17 octobre 2001 / Ordinanza relativa ai dispositivi medici (ODmed) del 17 ottobre 2001
6. Medical Device Regulation (EU) 2017/745 of 5 April 2017 (MDR)
7. MDCG 2024-3 Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices
8. 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)
9. EN ISO 14155: Clinical investigation of medical devices for human subjects - Good clinical practice (www.iso.org)
10. EN ISO 10993: Biological evaluation of medical devices (www.iso.org)
11. EN ISO 14971: Application of risk management to medical devices (www.iso.org)
12. WHO, International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
13. Strahlenschutzverordnung (StSV) vom 26. April 2017 / Ordonnance sur la radioprotection (ORaP) du 26 avril 2017 / Ordinanza sulla radioprotezione (ORaP) del 26 aprile 2017.
14. International Conference on Harmonization (ICH) Guideline for Good Clinical Practice E6(R2), (www.ich.org).
15. Zz
16. Yy

17. APPENDICES

NOTE: Further relevant information can be found in the ISO14155, Annex A Clinical Investigation Plan (CIP)

Documents that do 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. *Monitoring Plan*
8. *Other material handed over to the patients*