Clinical Protocol template for Investigator initiated trials (IIT):

General information and instructions

This document is the Clinical Protocol template for IIT (Investigator initiated Trials) studies. swissethics strongly recommends using this template to develop clinical research protocols for trials testing an investigational medicinal product (IMP) or a medical device (MD) to be submitted to Swiss authorities.

This template is suitable for studies:

- involving IIT,
- performed in Switzerland, respectively where the Sponsor-Investigator is located in Switzerland
- where the study question does relate to the use of drug(s) or medical device effect(s),
- where the Swiss law on therapeutic products (HMG/LPTh and Federal Act on Medicinal Products and Medical Devices) applies,
- where the Swiss law on human research (Federal Act on Research involving Human Beings (HRA)) and its applicable ordinance ClinO/KlinV/OClin/OSRUm applies,
- that are interventional*

*health related interventional studies include research in preventive, diagnostic, therapeutic, palliative or rehabilitation activities that are examined in the context of a clinical trial.

The current template is based on:

- the Federal Act on Research involving Human Beings (HRA) and its applicable ordinance (ClinO e/KlinV d/OClin f/OSRUm i)
- the SPIRIT statement and
- ICH-GCP E6, section 6
- EN ISO14155:2011: Annex A
- MEDDEV 2.7/3 revision 3, May 2015

This template attempts to provide a general format applicable to all clinical trials evaluating an investigational product (drugs or medical devices).

Note that *instructions* are indicated in *blue italics* and they need be deleted (or alternatively may be formatted as "hidden text" that will not show in printing).

Section headings and template text formatted in **regular type red** gives you reference to the legal requirements. This text may be deleted.

Section headings and template text formatted in regular type (black) should be included in your protocol document as provided in the template.

Header and footer should contain the following information (on all pages): [Protocol Title], [Page x of xx], [version x, DD/MM/YYYY], [Study ID]

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

Refer questions regarding use of this protocol template to swissethics, info@swissethics.ch, phone: +41 31 306 93 95, www.swissethics.ch.

This template was developed by a task force initiated by the Federal Office of Public Health (FOPH) and the AGEK (called swissethics today) / CT CER during 2013 and under the lead and coordination of the Swiss Clinical Trial Organisation (SCTO). Clinical research experts from 8 institutions reviewed the template. swissethics actualizes it on a regular base and recommends its use.

Please be aware that the content of the protocol has to be identical to the content of the BASEC research project application form. You can refer to the protocol in the research project application form of BASEC to avoid redundancies but not vice versa.

Change history

Version Nr	Version date	Modified without version change	Description, comments	Control
1.0	2013		Initial version	
3.0	30.05.17		Added change history box. Few minors administrative changes	PG
3.1	24.07.17		Insert change history, minor changes in the General information and instructions pages (title, footer, logo).	PG
3.2	17.01.18		Added reference to MEDDEV 2.7/3 revision 3 for the causality assessment of the SAE to the investigational medical device or procedures. Obligation to collect and investigate safety events and device deficiencies, and document them in CRF. Added reporting obligations for Cat. A clinical trials with medical devices, some additional simplifications.	PG
		X	Clarified the obligation for the submission of safety reports for Cat. A clinical trials to Swissmedic. Replaced reference EU directive on medical devices 93/42EEC with European Regulation on medical devices 2017/745 in chapter 2.5.	PG
3.3	28.05.18		Changed definition of SAE according to the European Regulation on medical devices 2017/45 art. 58, in chapter 10.2.1. Added chapter 10.4 Assessment, notification and reporting on the use of radiation sources.	PG
3.4	15.08.18		Added obligation to report device deficiencies to the Ethics Committees and to Swissmedic (ClinO Art. 42), in chapter 10.2.2 Category C resp. chapter 10.3.2 Category A clinical trials with medical devices.	PG
		X	Updated weblinks	PG

✂ **….. Please remove the 'General information and instructions'**

and the table 'Change history' ….. ✂

<<Protocol template: Interventional study with investigational medicinal product (IMP) / medical device (MD)>>

Clinical Study Protocol

INSERT TITLE OF THE PROTOCOL
(SPIRIT #1)

[Descriptive title identifying the study design (e.g. randomised, placebo controlled, etc.), population (if relevant), phase (if applicable, e.g. phase I, phase II...), target disease(s), the investigational drug or medical device, and, if the study is multi-centred (-country)]

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

Study Type:	*Clinical trial with Investigational Medicinal Product (IMP), Medical Device (MD)*
Study Categorisation:	*Risk category according to HRA (A, B or C)*
Study Registration:	*Name of study registry (if not yet registered name the intended registry)*
	Registration number (from FOPH portal) eventually other registries and numbers if applicable
Study Identifier:	*If additional identifier applies (e.g. institutional or Sponsor protocol identifier)*
Sponsor, Sponsor-Investigator or Principal Investigator:	*Name of Sponsor, Sponsor-Investigator or Principal Investigator (any who is applicable)*
	Contact details (full details)
Investigational Product:	*Study Drug – Generic, followed by marketed name if applicable; Medical Device Name*
Protocol Version and Date:	*Version number and validity date*
	Add if applicable, the Amendment number, from (date), replaces version number from (date)

CONFIDENTIAL

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

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

Signature Page(s)

(ICH E6 6.1)

ICH E6: Have signature pages with name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the sponsor or of the medical expert (if applicable), the investigator responsible for conducting the trial, the statistician (if applicable)

Note: Add more lines, functions and pages if relevant, e.g. for trial statistician, if relevant or protocol contributors

Study number	*Study registry and registration number*
Study Title	*Full study title as written out on title page*

The Sponsor-Investigator and trial statistician have approved the protocol version [x (dated DD.MM.YYYY)], and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-Investigator:

Printed name of Sponsor-Investigator (if Sponsor and PI is not the same person please add an additional signature line for the PI of the study)

Place/Date	Signature

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	*Name and address of site*
Principal investigator	*Printed name of Principal investigator*

Place/Date	Signature

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

Table of Contents

STUDY SYNOPSIS

(ClinO, Appendix 3, 1.1, 2.1, 3.1, 4.1; Appendix 5, 2b)

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

Sponsor / Sponsor-Investigator	*Name of Sponsor / Sponsor-Investigator*
Study Title:	*Full title of protocol*
Short Title / Study ID:	*Short title of protocol or Study ID, if applicable*
Protocol Version and Date:	*The version number and the date of the valid study protocol.*
Trial registration:	*Provide the name of the study registry and the registration number and date (if not registered then indicate the anticipated registry)*
Study category and Rationale	*Provide the determined study category with explanation for this category*
Clinical Phase:	*For clinical trials with drugs: Clinical study phase or phase of clinical development (e.g. Phase 1, 2, 3 or 4; or according to ICH E8 para 3.1.3 Human Pharmacology, Therapeutic Exploratory, Therapeutic Confirmatory or Therapeutic Use); in case of Medical Device study rename and use e.g. "Phase of development"*
Background and Rationale:	*Provide a short background and the rationale for the study, this includes the health condition studied*
Objective(s):	*Brief statement of primary study objectives and the main secondary study objectives.*
Outcome(s):	*Brief statement of primary study outcome and the main secondary study outcome measures.*
Study design:	*Design attributes such as open label; randomised, placebo or active control; cross-over design, etc.*
Inclusion / Exclusion criteria:	*Brief description of the anticipated study population, the key inclusion and exclusion criteria and if applicable, the reasons for inclusion of vulnerable participants*
Measurements and procedures:	*Describe the study intervention (methodology, procedures, sampling if applicable)*
Study Product / Intervention:	*Describe the study specific intervention (product (drug / device name (generic), dose, route, regimen) used in the study). Duration of product administration (also run-in if applicable)*
Control Intervention (if applicable):	*Describe if applicable the comparator(s) (e.g. active control, reference therapy, placebo)*
Number of Participants with Rationale:	*Number of participants projected for the entire study (e.g. not for simply one site, rather for entire study, all sites combined). Give the total and the numbers for each treatment group.*
Study Duration:	*Estimated duration for the main investigational plan (e.g. from start of screening of first participant to last participant processed and finishing the study)*
Study Schedule:	*Month Year of First-Participant-In (planned)* *Month Year of Last-Participant-Out (planned)*
Investigator(s):	*Name(s) of Investigator(s)* *Full contact details*
Study Centre(s):	*Single-centre or multi-centre. If multi-centre note number of projected centres to be involved. Or countries if multi-national study*
Statistical Considerations:	*A very brief description of the main elements of the statistical methodology to be used in the study. Explanation to sample size*

GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

Provide a list of abbreviations used on the protocol - to be completed

AE	Adverse Event
BASEC	Business Administration System for Ethical Committees, (https://submissions.swissethics.ch/en/)
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
DSUR	Development safety update report
GCP	Good Clinical Practice
IB	Investigator's Brochure
Ho	Null hypothesis
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
ISO	International Organisation for Standardisation
ITT	Intention to treat
MD	Medical Device
MedDO	Medical Device Ordinance *(in German: MepV, in French: ODim)*
PI	Principal Investigator
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

STUDY SCHEDULE

(SPIRIT #13; ICH E6 6.4.2)

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

e.g.:

Study Periods	*Screening*	*Treatment, Intervention Period*				*Follow-up*
Visit	*1*	*2*	*3*	*4*	*5*	*6*
Time (hour, day, week)	*-7*	*0*	*1*	*8+/-1d*	*15+/-2d*	*22*
Patient Information and Informed Consent	*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*					
Administer Study Medication, Medical Device		*x*	*x*	*x*	*x*	
Primary Variables	*x*	*x*	*x*	*x*	*x*	*x*
Secondary Variables	*x*	*x*	*x*	*x*	*x*	*x*
Concomitant Therapy, Intervention		*x*	*x*	*x*	*x*	
Adverse Events		*x*	*x*	*x*	*x*	*x*

1. STUDY ADMINISTRATIVE STRUCTURE

(ICH/E6 6.1.2-6.1.7; SPIRIT 5a-d)

Any committee(s) to be formed should be mentioned here (e.g., safety committees, data monitoring committees, etc.). Subsections may be expanded if necessary but shall not be deleted if not relevant.

Describe a solution, if not all personnel involved are determined at this stage and may be referred to other documents than the protocol.

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

1.1 Sponsor, Sponsor-Investigator

(ICH/E6 6.1.2; SPIRIT 5b)
ICH: Name and address of the sponsor …..

Provide the complete contact details of the Sponsor, its role in the study; its role in the study 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 study with a Swiss Sponsor-Investigator.

1.2 Principal Investigator(s)

(ICH/E6 6.1.5, 6.1.6; SPIRIT 5a-d)
ICH: Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

Name, title, address, and telephone number(s) of the qualified physician (or other qualified person, if applicable), who is responsible for all trial-site related medical decisions (if other than investigator).

Provide the complete contact details of the investigator(s) or reference to where a list of investigators and study sites can be obtained (some can be covered in contracts).

1.3 Statistician ("Biostatistician")

(ICH/E6 6.1.7; SPIRIT 5a-d)
ICH: Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

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

1.4 Laboratory

(ICH/E6 6.1.7; SPIRIT 5a-d)
ICH: Name(s) and address(es) of the clinical laboratory(ies) ……. involved in the trial.

Provide if applicable the name of the laboratory that is involved in the trial (may be referred to different document, e.g. separate agreement).

1.5 Monitoring institution

(ICH/E6 6.1.2; SPIRIT 5a-d)
ICH: Name and address of the …. monitor (if other than the sponsor).

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

1.6 Data Safety Monitoring Committee

(ICH/E6 6.1.7; SPIRIT 5a-d)
ICH: Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

(if applicable, also for MD pre-market products)

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 protocol. Alternatively, provide an explanation of why a DSMC is not needed.

1.7 Any other relevant Committee, Person, Organisation, Institution

(ICH/E6 6.1.7; SPIRIT 5a-d)
ICH: Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

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

2. ETHICAL AND REGULATORY ASPECTS

(ICH/E6 6.12; SPIRIT #24, 5)
ICH: Description of ethical considerations relating to the trial.

Before the study will be conducted, the protocol, the proposed patient information and consent form as well as other study-specific documents shall be submitted to a properly constituted Competent Ethics Committee (CEC) and/or competent authorities (name the authority, e.g. Swissmedic / FOPH / foreign competent authorities; Note that clinical studies of category A do not need a Swissmedic approval, please delete respective passage) in agreement with local legal requirements, for formal approval. Any amendment to the protocol must as well be approved (if legally required) by these institutions.

The decision of the CEC and Swissmedic/foreign competent authority concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

(ClinO, Art. 1d, 64; SPIRIT #2a-b)

Provide a statement of study registration, where it is, or is intended to be, registered, include the number and date; include further registrations if registered in other registries.

The study must be registered in a registry listed in the WHO International Clinical Trials Registry Platform (ICTRP, http://www.who.int/ictrp/en/). In addition, registration in a national language in the Swiss National Clinical trial Portal (SNCTP via BASEC) is required.

2.2 Categorisation of study

(ClinO, Art. 19, 20, App 3, 1.1)

Describe the risk category and the rationale for the categorisation;

Article 19 Categorisation of clinical trials of medicinal products

[1] Clinical trials of medicinal products come under Category A if the medicinal product is authorised in Switzerland and its use:

- *a. is in accordance with the prescribing information;*
- *b. is in an indication or dosage different from that specified in the prescribing information, but in accordance with the following criteria:*
  1. *the indication is within the same disease group of the International Classification of Diseases (ICD), as specified in Annex 1, number 3,*
  2. *the disease in question is self-limiting and the dosage of the medicinal product lower than that specified in the prescribing information; or*
- *c. is recognised as standard in guidelines prepared in accordance with internationally accepted quality criteria.*

[2] Clinical trials of medicinal products come under Category B if the medicinal product:

- *a. is authorised in Switzerland; and*
- *b. is not used as specified in paragraph 1.*

[3] They come under Category C if the medicinal product is not authorised in Switzerland.

[4] In justified cases, a clinical trial of a medicinal product authorised in Switzerland may be assigned to a different category if this is possible or necessary with regard to medicinal product safety or protection of the participants' safety and health.

Article 20 Categorisation of clinical trials of medical devices

[1] Clinical trials of medical devices come under Category A if:

- *a. the medical device bears a conformity marking; and*
- *b. it is used in accordance with the instructions.*

[2] They come under Category C if:

- *a. the medical device does not have a conformity marking;*

b. it is not used in accordance with the intended purposes recognised in the conformity assessment and specified in the instructions; or

c. use of the medical device is prohibited in Switzerland.

2.3 Competent Ethics Committee (CEC)

(ClinO, Art 24-29; SPIRIT #24)

Mention that the responsible investigator at each site ensures that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the clinical study.

Mention the reporting duties and allowed time frame (all changes in the research activity and all unanticipated problems involving risks to humans; including in case of planned or premature study end and the final report) and that no changes are made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

(ClinO, Art. 23, 27, 30-39, 42, 43, 46-48, 57; SPIRIT #24)

Mention that the Sponsor will obtain approval from the competent authority (e.g. Swissmedic) before the start of the clinical trial. CA approval is necessary for all studies category B and C (IMP and MD).

Mention the reporting duties and allowed time frame to CA including the reporting duties in case of planned or premature study end 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. Amendments are reported according to chapter 2.10.

Add other local requirements in case of international studies.

2.5 Ethical Conduct of the Study

(ClinO, Art. 5; ICH E6 6.12, 6.2.5)
ICH: A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Regulation on medical devices 2017/745 and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

Add other local requirements in case of medical device or international studies.

2.6 Declaration of interest

(ClinO, Art. 3b; SPIRIT #28)

Declare any conflict of interest if applicable, otherwise provide a statement of no conflict of interest (independence, intellectual, financial, proprietary etc.).

2.7 Patient Information and Informed Consent

(ClinO, Art. 7-9, Art. 15-17, Appendix 3, 1.4, 2.4, 3.4, 4.3, Appendix 4, 3.6; SPIRIT #26, 32)

Explain that participants will be informed about the study (what, how, by whom) and that consent is sought from each participant (e.g. sample text below); include the mention of compensation if any; describe special approaches in case of vulnerable population (e.g. children assent). Describe the process specific to the trial (see also HFG and respecting ordinances KlinV/OClin para 7-9).

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw

from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. *Enough time needs to be given to the participant to decide whether to participate or not. Please specify the time frame given*.

The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) at the same time as the participant sign, and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

(ClinO, Art. 18; ICH/E6 6.10; SPIRIT #27)
ICH: The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

(ClinO Art. 47; ICH/E6 6.4.6; SPIRIT #21b)
ICH: A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial.

Provide a statement that the Sponsor-Investigator (and any competent authority) may terminate the study prematurely according to certain circumstances (name the reasons).

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

2.10 Protocol amendments

(ClinO, Art. 29, 34, 55; SPIRIT #25)

State, who is allowed to amend the protocol or to provide suggestions for a protocol amendment. Provide plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, CEC, competent authorities, trial participants, trial registries, journals, regulators).

Substantial amendments are only implemented after approval of the CEC and CA respectively.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/CA. Such

deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible.

All non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

(ICH 6.2; SPIRIT #6)

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

3.1 Background and Rationale

(ICH/E6 6.2; SPIRIT #6)

Describe the research question, including summary of relevant studies (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 study will be done and establish its context by giving a clear statement on its primary and secondary purposes.

3.2 Investigational Product (treatment, device) and Indication

(ICH/E6 6.2.1; SPIRIT #6)
ICH: Name and description of the investigational product(s).

This section should contain a description of the investigational product, its class, make-up, chemical properties and any relevant physical properties including any available pharmacologic data (the Investigator's Brochure or the summary of product characteristics, as applicable, should be referred to but not reiterated)

Medical Device (MD): brand name, manufacturer, name or number of the model/type, incl. software version and accessories if any, to permit full identification. Populations and indications for which investigational device is intended. Differences to authorisation (if any) / if applicable, mention CE Declaration of Conformity including the intended purpose defined in the instruction manual. Include description of device materials in contact with body tissues and/or fluids, summary of necessary training and experience to use device and medical and/or surgical procedures involved in the use of the device (ISO 14155 Annex A).

3.3 Preclinical Evidence

(ICH/E6 6.2.2; SPIRIT #6a)
ICH: A summary of findings from nonclinical studies that potentially have clinical significance …..

Summarise, if applicable, the available non-clinical data (published or available unpublished data) that could have clinical relevance and justify its use in humans.

Medical devices: only applicable if needed for pre-marketed / marketed devices needing Swissmedic notification (Guidance on the biological evaluation of medical devices is given in ISO 10993).

3.4 Clinical Evidence to Date

(ICH/E6 6.2.2; SPIRIT #6a)
ICH: A summary of findings from … and from clinical trials that are relevant to the trial.

Summarise the available clinical study data with relevance to the protocol under construction (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 and any history of modification or recall. If none is available, include a statement that there is no available clinical research data to date on the investigational product.

Medical Devices: include postmarked experience if applicable

3.5 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)

(ICH/E6 6.2.4; SPIRIT #6a)
ICH: Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

Provide the rationale used for selection of the dose, route, regimen and dosage period or the intended purpose in the study (medical devices: the application etc.).

3.6 Explanation for choice of comparator (or placebo)

(SPIRIT #6b)

Explain the rationale for the comparator chosen for the study (include an explanation whether placebo is ethically justified or alternatively the comparator proved to be another effective treatment to compare with the investigational product).

3.7 Risks / Benefits

(ClinO, Appendix 4, 3.5; Art 25d2; ICH/E6 6.2.3; SPIRIT #6a; MD: ISO 14155 Annex A & ISO 14971)
ICH: Summary of the known and potential risks and benefits, if any, to human subjects.

Provide a discussion of the known and potential risks and benefits to human, include a description of possible or anticipated adverse effects and a discussion of measures to control or mitigate the risks (if available reference to the risk analysis report should be made) and how post-trial care is organised. For studies without immediate benefit to the study participants, a rationale should be provided stating how the results of the study could be beneficial for future participants due to e.g. a better understanding of the disease, mechanism of action etc.

Describe, if applicable and relevant, the potential threats to the study, e.g. competing trials, and anticipate risk minimisation.

For medical devices a device risk analysis and risk assessment should be included according to EN ISO 14971. This shall describe the anticipated adverse device effects, residual risks associated with the investigational device and the procedures involved in its use. Risks associated with participation in the clinical investigation shall be described and possible interactions with concurrent medical interventions shall be listed. A statement of the anticipated clinical benefit shall be given and a risk to 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).

3.8 Justification of choice of study population

(ClinO, Art 25d4, Art. 15-17; ICH/E6 6.2.6)
ICH: Description of the population to be studied.

Describe the choice of the study population and the rationale for it (mandatory in case of vulnerable participants)

For vulnerable participants (e.g. minors, participants incapable of judgment or participants under tutelage), the following issues need to be addressed in the protocol:

- *Rationale for the inclusion of vulnerable participants (i.e. reasons why comparable results / findings cannot be obtained from adults or those capable of judgment)*
- *Describe how the legal representative is informed regarding the procedures of the study and how his or her consent is obtained.*
- *In the event that the minor and / or participant under tutelage is capable of judgment, describe how their assent is collected in addition to the consent of their legal representative.*
- *In the event of a participant incapable of judgment, mention that signs and symptoms showing that the participant is unwilling to participate in the study will result in the participant being excluded from participation.*

For emergency situations, the following aspects should be described:

- *How to obtain, without unjustified delay, an informed consent by the legal representative of participants that are incapable of judgement, minors or under tutelage*
- *How the will of the participant can be elucidated later (when the participant is capable of judgment) or with the help of accessible relatives*
- *Mention that signs and symptoms showing that the participant is unwilling to participate in the study will result in the participant being excluded from participation.*
- *The guarantee that a physician not participating in the study, safeguards participant interest and insures proper medical care*

4. STUDY OBJECTIVES

(ICH/E6 6.3; SPIRIT #7)
ICH: A detailed description of the objectives and the purpose of the trial.

Describe the overall, primary and secondary objective(s) of the study 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 study, explaining why the study is performed. (e.g., The purpose of this study is to evaluate whether Test Drug A lowers blood pressure with a similar efficacy as known for Comparator Drug B in participants with moderate to severe hypertension. The study aims to describe an efficacy and safety profile for Test Drug A compared to Drug B for the treatment of moderate to severe hypertension).

4.2 Primary Objective

Provide one clear, simple statement describing the primary objective of the study (e.g., The study seeks primarily to determine the effect of Test Drug/Device A on diastolic blood pressure compared to Drug/Device B).

4.3 Secondary Objectives

Provide a clear, simple statement describing the secondary objectives of the study (e.g., Secondary objectives are to assess efficacy of Test Drug A on systolic blood pressure compared to Drug B).

4.4 Safety Objectives

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

Provide a clear, simple statement describing the safety endpoints of the study. (e.g., The study aims to assess long-term safety of Drug/Device A and its tolerability in terms of incidence of gastrointestinal side effects and use of rescue medication).

5. STUDY OUTCOMES

(ICH/E6 6.4.1; SPIRIT #12)
ICH: A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

Describe the primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure or description of surrogate marker for non-measurable variables), analysis metric (e.g., change from baseline, final value, time to event), time point for each outcome etc. Explanation of the clinical relevance of chosen efficacy and harm 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 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 trial. e.g., The primary endpoint will be the change of diastolic blood pressure from baseline to Day 21.)

There is only one primary endpoint. 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. (e.g., Secondary endpoints will be the change of diastolic blood pressure from baseline to Day 10, to Day 60, change of systolic blood pressure from baseline to Day 10, Day 21, Day 60.)

5.3 Other Outcomes of Interest

Provide a short description of other outcome variables of interest and the rationale for the choice of endpoints.

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 (e.g., Incidence and severity of gastrointestinal side effects related to study drug intake during the whole study.)

6. STUDY DESIGN

(ICH/E6 6.4; SPIRIT #8)

6.1 General study design and justification of design

(ICH/E6 6.4.2, 6.4.5; SPIRIT #8)
ICH: The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design.
ICH: A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
ICH: The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

Describe the design of the study and its rationale, the type (e.g., placebo-controlled, parallel design, who is blinded), allocation ratio and framework (e.g., superiority, equivalence, non-inferiority, exploratory). Provide a description of intended procedures and stages, the expected duration of participant's participation, description of sequence and durations of all trial 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 section:

- *treatments/intervention to be studied (drugs/medical device, doses and procedures)*
- *population to be studied and the number of participants to be included (if known or applicable)*
- *level and method of blinding/masking (e.g. open, blinded evaluators and unblinded participants and/or investigators).*
- *kind of comparator(s), (e.g. placebo, no treatment, active drug, dose-response, historical and study configuration (parallel, cross-over))*
- *method of assignment to treatment/intervention (randomisation, stratification)*
- *sequence and duration of all study periods*

6.2 Methods of minimising bias

(ICH/E6 6.4.3; SPIRIT #16, 17)
ICH: A description of the measures taken to minimize/avoid bias, including: Randomization, Blinding.

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

6.2.1 Randomisation

Describe the exact randomisation method (unit, what, allocation ratio, number generation mechanisms, block randomisation, stratification, who generates and concealment of list).

6.2.2 Blinding procedures

Describe how blinding is ensured, and who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts).

6.2.3 Other methods of minimising bias

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

6.3 Unblinding Procedures (Code break)

(ICH/E6 6.4.8; SPIRIT #17b)
ICH: Maintenance of trial treatment randomization codes and procedures for breaking codes.

If blinded, describe circumstances under which unblinding is permissible and procedures for revealing a participant's allocated intervention will be allowed during the trial, also in case of suspension or premature study termination.

7. STUDY POPULATION

(ICH/E6 6.2.6, 6.4.6; SPIRIT #9, 10, 15, 16, 21)
ICH: Description of the population to be studied.

Describe in the subchapters below the population to be studied; this should include a description of the study 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 study sites can be obtained). Provide plan of actions to be taken if the enrolment goals are not met.

7.1 Eligibility criteria

(ClinO, Art 25d5; ICH/E6 6.5.1&6.5.2; SPIRIT #10)
ICH: Subject inclusion and exclusion criteria.

Describe in detail the inclusion and exclusion criteria for the participants' eligibility to the study (if applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)). Create a list of criteria and be as specific as possible. Also describe the control groups in detail.

Participants fulfilling all of the following inclusion criteria are eligible for the study, for example:

- Informed Consent as documented by signature (Appendix Informed Consent Form)
- *Etc. continue as applicable for this study*

The presence of any one of the following exclusion criteria will lead to exclusion of the participant, for example:

- Contraindications to the class of drugs under study, e.g. known hypersensitivity or allergy to class of drugs or the investigational product,
- Define drugs not allowed during the study or for specific periods of time prior to the administration of the test dose,
- Women who are pregnant or breast feeding,
- Intention to become pregnant during the course of the study,
- Lack of safe contraception, defined as: Female participants of childbearing potential, not using and not willing to continue using a medically reliable method of contraception for the entire study duration, such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices, or who are not using any other method considered sufficiently reliable by the investigator in individual cases.
- Female participants who are surgically sterilised / hysterectomised or post-menopausal for longer than 2 years are not considered as being of child bearing potential.
- Other clinically significant concomitant disease states (e.g., renal failure, hepatic dysfunction, cardiovascular disease, etc.),
- Known or suspected non-compliance, drug or alcohol abuse,
- Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant,
- Participation in another study with investigational drug within the 30 days preceding and during the present study,
- Previous enrolment into the current study,
- Enrolment of the investigator, his/her family members, employees and other dependent persons,
- *Specific exclusions for the disease under study,*
- *Specific concomitant therapy washout requirements prior to and/or during study participation,*
- *Dietary restrictions,*
- *Etc. continue as applicable for this study.*

7.2 Recruitment and screening

(ClinO, Art 25, Appendix 3, 1.4 & 1.6; SPIRIT #15)

Describe how, where and by whom participants are recruited / preselected for study, also mention in case of advertisement; describe any screening requirements (e.g. laboratory or diagnostic tests). Refer to section 9.4. for description of screening procedures. Describe any payment or compensation given to study participants.

7.3 Assignment to study groups

(SPIRIT #16)

Describe how participants 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.

7.4 Criteria for withdrawal / discontinuation of participants

(ClinO, Art 9; ICH/E6 6.5.3; SPIRIT #21b)

Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying: a) When and how to withdraw subjects from the trial/ investigational product treatment. c) Whether and how subjects are to be replaced.

Describe the criteria and procedures when and how participants are withdrawn from the study / investigational product treatment and whether or not and how participants will be replaced. Refer to Section 9.2.5 for description of follow-up procedures (e.g., withdrawal of informed consent, non-compliance, disease progression, safety, etc. or study or routine procedure must be stopped, e.g. due to safety concerns).

8. STUDY INTERVENTION

(SPIRIT #11)

8.1 Identity of Investigational Products (treatment / medical device)

(ICH/E6 6.2.1, 6.4.2, 6.4.4)
ICH: A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s).

Describe all trial treatments for each arm of the study.

8.1.1 Experimental Intervention (treatment / medical device)

ICH: Name and description of the investigational product(s).

Describe the investigational product, the name (generic and brand name), its source, formulation/material, strength, colour etc. (e.g. a picture of the medical device), route and mode of administration for medication (medical device: place of implantation) and the deviation from commercial product, if applicable.

8.1.2 Control Intervention (standard/routine/comparator treatment / medical device)

ICH: Name and description of the investigational product(s).

Describe the routine (standard) therapy, the name, its source, formulation/material, strength, colour etc. or if applicable the comparator chosen (e.g. also placebo), route and mode of administration for medication (medical device: place of implantation) and the deviation from commercial product, if applicable.

8.1.3 Packaging, Labelling and Supply (re-supply)

ICH: Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

Describe how the investigational/comparator product is labelled (sample label), packaged (e.g., blisters, capsules, primary package) and how the supply is provided. If applicable describe logistics of re-supply esp. for products with limited shelf life. For post-market device studies labelling is not mandatory. Describe deviation from commercial products if applicable.

8.1.4 Storage Conditions

Describe how the investigational product and those for the standard/routine/comparator therapy are stored (e.g., temperature range, exposure to light, etc.). IMP / 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 protocol without specific details.)

8.2 Administration of experimental and control interventions

(ICH/E6 6.4.4)

8.2.1 Experimental Intervention

ICH: Description of and justification of the treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

Describe the route, dose, regimen and the rationale for timing, doses of the investigational medical product(s) or the device(s) plus a description of the study procedures, use and estimated exposure to humans. Selection of doses in the study, selection of timing for individual participants. These could be optional sections for drug studies to justify different dosages used and individual timing.

Medical Devices: This must include (especially for pre-market studies) a description of how device is used or implanted, and the necessary training and experience needed for its use (e.g. may also be supported by pictures or sketches of the handling, application, implantation).

This chapter can also be merged with chapter 8.1.1.

8.2.2 Control Intervention

ICH: Description of and justification of the treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

Describe the route, dose, regimen and the rationale for timing, doses of the comparator (e.g. standard, routine, placebo) medical product(s) or device(s) plus a description of the study procedures, use and exposure. Selection of doses in the study, selection of timing for individual participants. These could be optional sections for drug studies to justify different dosages used and individual timing.

Medical Devices: This must include (especially for pre-market studies) a description of how device is used or implanted.

This chapter can also be merged with chapter 8.1.2.

8.3 Dose / Device modifications

(SPIRIT #11b)

Describe criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)

8.4 Compliance with study intervention

(ICH/E6 6.6.3; SPIRIT #11c)
ICH: Procedures for monitoring subject compliance.

Describe the strategies to improve adherence to the intervention, and any procedures for monitoring adherence (e.g., return of unused medication, laboratory tests). Define non-compliance and how such participants should be handled.

8.5 Data Collection and Follow-up for withdrawn participants

(ICH/E6 6.5.3; SPIRIT #18b)
ICH: 6.5.3.b) The type and timing of the data to be collected for withdrawn subjects. ICH: 6.5.3.d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

Describe the type and timing of data to be collected for withdrawn participants and how the follow up for withdrawn participants is organised.

8.6 Trial specific preventive measures

(ICH/E6 6.6.2; SPIRIT #11d)
ICH: Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

Describe any specific preventive measures, including rescue medication for the trial participants or treatments that are prohibited (restrictions), (e.g., contraception, pregnancy test, dietary requirements / omissions, concomitant medication etc.). Their use should be recorded in the CRF. Describe their potential impact on study objectives.

8.7 Concomitant Interventions (treatments)

(ICH/E6 6.6.2; SPIRIT #11d)
ICH: Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

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

8.8 Study Drug / Medical Device Accountability

(ICH/E6 6.4.7; SPIRIT 11c)
ICH: Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

Provide plans of accurate and adequate records maintenance from shipment to the sites until return or disposal including the physical location, dates (receipt, expiry, use, return), lot/batch number and quantities (received, used, destroyed).

8.9 Return or Destruction of Study Drug / Medical Device

(SPIRIT 11c)

Provide a statement of the procedures for final reconciliation at the end of the study and whether the product is shipped back to Sponsor or destroyed.

For medical devices already in use at the hospital "return or destruction" are according to standard procedures and mentioning this in the protocol is enough (no details needed).

9. STUDY ASSESSMENTS

(ICH/E6 6.7, 6.8; SPIRIT #18a)

Describe procedures, measurements, collection, storage of samples taken, etc.

9.1 Study flow chart(s) / table of study procedures and assessments

Provide a detailed graph, chart or table of flow of the study and for the study participant ("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 study procedures during the whole course of the study, not only the assessed endpoints. It may be referred to section "STUDY SCHEDULE" in case all these details are provided there. It is recommended that the flow chart is repeated here.

9.2 Assessments of outcomes

ICH: Specification of the efficacy parameters. Specification of safety parameters.

In not already described under 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; medical device: 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

ICH: Methods and timing for assessing, recording, and analysing of efficacy & safety parameters.

If no already described under 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 study visit. The equipment xy will be used. The participant 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

ICH: Methods and timing for assessing, recording, and analysing of efficacy & safety parameters.

If no already described under 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

ICH: Methods and timing for assessing, recording, and analysing of efficacy & safety parameters.

If no already described under 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. This should be a practical instruction; regulatory aspects are described in chapter 12.7; pharmacokinetic parameters: describe condition of participant (e.g., fasting, x hours after treatment with study drug), 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

ICH E6 6.8: Specification of safety parameters. The methods and timing for assessing, recording, and analysing safety parameters

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 study treatment; refer to Section 10 for

AE definition and procedures; define specific process to ask the participant at the visits about adverse events, collection of spontaneous reports.

9.2.4.2 Laboratory parameters

Specify laboratory parameters to be assessed; define when abnormal laboratory parameters will be considered as adverse events, 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 study team and to be part of the study manual.

9.2.4.3 Vital signs

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

9.2.5 Assessments in participants who prematurely stop the study

Describe follow-up procedures and assessments in participants who are withdrawn from the study prematurely (e.g., recording of adverse events, physical examination, laboratory parameters, vital signs). Define follow-up period; refer to Section 10 for procedures for participants who prematurely stop the study.

9.3 Procedures at each visit

Provide a verbal description of procedures at each visit according to study phase: e.g., screening, baseline, visits during intervention, close-out visit, follow-up visits. Include additional tasks as scheduling of next visit, distribution of study medication, what is not a measurement to be described.

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 (9.1) including also e.g., Dispense of trial medication, 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.)

10. SAFETY

(ClinO Art. 37-43; ICH/E6 6.8; ISO14155 8.2.5, A.14; SPIRIT # 22, 30)

Describe plans for collecting, documenting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct.

Fill the section relevant to your study, e.g. either drug studies (10.1) or device studies (10.2).

10.1 Drug studies

The Sponsor's SOPs provide more detail on safety reporting.

During the entire duration of the study, all adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and case report forms (CRF). Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period.

Note: The Swiss law on clinical research (human research act HRA and its ordinance ClinO) does not require the documentation of AEs for Category A drug trials. For Category B trials the documentation of AEs is only mandatory if this is written in the study protocol or requested from the authorities. The documentation of SAEs is mandatory for all categories. Please adapt above sentence according to the categorisation and your needs.

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

ICH: Procedures for eliciting reports of and for recording … adverse event and intercurrent illnesses.

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2]

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

Both Investigator and Sponsor-investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship

	Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Note that other categories can be used. However, a definition has to be provided in the protocol.

Unexpected Adverse Drug Reaction

An "unexpected" adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively). [ICH E2A]

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

Note: In case of double-blinded studies, unblinding is needed in order to determine a SUSAR. Treatment allocation should not be disclosed to the investigator, nor to the study staff, in order not to make the subject ineligible.

Assessment of Severity

Describe the severity grading scale in use for this study, depending on the type of study and disease, the grades for severity described in the "Common Terminology Criteria for Adverse Events CTCAE Version x" terminology may be used and should be referred to here. Other definitions and grades are possible and shall be provided in the protocol (e.g., grading scale with explanation or reference to source).

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

(ClinO Art. 37)
ICH: Procedures for … reporting adverse event and intercurrent illnesses.

Describe how, by whom and in what time frame the serious and other reportable adverse events (safety signals, pregnancies if applicable, etc.) are reported. This should also define the reporting Principal Investigator to Sponsor in case of a multicentre trial, when the Sponsor and the Principal Investigator are not the same person.

Important note concerning all following sections of this chapter 10.1.2: add, respectively adapt to other local requirements in case of international studies.

Reporting of SAEs

All SAEs must be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator of the study. The Sponsor-Investigator will re-evaluate the SAE and return the form to the site.

SAEs resulting in death are reported to the Ethics Committee via BASEC within 7 days.

For multicentre studies, add that:

The other in the trial involved Ethics Committees receive SAEs resulting in death in Switzerland via Sponsor-Investigator via BASEC within 7 days.

Exemptions from expedited reporting may be possible if the SAE is either a clear result of the underlying disease or well known and described in the currently approved product information (mainly for phase IV studies). Please define those SAEs that are exempted from expedited reporting.

Reporting of SAEs or other safety relevant events to the Marketing Approval Holder (MAH) of the drug(s) may be necessary. If so, this should be described either in this section or in the contract with the MAH.

Reporting of SUSARs

A SUSAR needs to be reported to the Ethics Committee (local event via local Investigator) via BASEC and to Swissmedic for category B and C studies (via Sponsor-Investigator) within 7 days, if the event is fatal, or within 15 days (all other events).

In multicentre studies the following should be added:

The Sponsor-Investigator must inform all Investigators participating in the clinical study of the occurrence of a SUSAR. All in the trial involved Ethics Committees will be informed about SUSARs in Switzerland via Sponsor-Investigator via BASEC according to the same timelines.

Reporting of Safety Signals

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so called safety signals, must be reported to the Sponsor-Investigator within 24 hours. The Sponsor-Investigator must report the safety signals within 7 days to the Ethics Committee (local event via local Investigator) via BASEC and to Swissmedic in case of a category B or C study.

In multicenter studies the following should be added:

The Sponsor-Investigator must immediately inform all participating Investigators about all safety signals. The other in the trial involved Ethics Committees will be informed about safety signals in Switzerland via the Sponsor-Investigator.

Reporting and Handling of Pregnancies

If applicable, describe the handling and reporting duties in case of a pregnancy during the study

Pregnant participants must immediately be withdrawn from the clinical study. Any pregnancy during the treatment phase of the study and within 30 days after discontinuation of study medication will be reported to the Sponsor-Investigator within 24 hours. The course and outcome of the pregnancy should be followed up carefully, and any abnormal outcome regarding the mother or the child should be documented and reported.

This section should be adapted based on the type of study and depending on the study drug.

Periodic reporting of safety

Describe any specific periodic safety (and other) reporting duties according to local legislation to the competent authorities (CEC, Swissmedic, foreign CA if applicable, others if applicable).

An annual safety report is submitted once a year to the local Ethics Committee via local Investigator and to Swissmedic in case of a category B or C study via Sponsor-Investigator.

For multicentre studies the annual safety report contains information from all sites including information from sites outside of Switzerland. The Sponsor-Investigator prepares it, and then submits it to the participating Investigators. The participating Investigators submit it to the local committees.

In clinical trials with radiopharmaceuticals the FOPH requests a final report within one year after study termination regarding all aspects of radiation protection (see ClinO Art. 44). Exempted are routine examinations with approved radiopharmaceuticals.

10.1.3 Follow up of (Serious) Adverse Events

(ICH/E6 6.8.4; SPIRIT #30)
ICH: The type and duration of the follow-up of subjects after adverse events.

Describe the follow up of participants terminating the study (either regularly or prematurely) with reported ongoing SAE, or any ongoing AEs of laboratory values or of vital signs being beyond the alert. Describe procedures: when and how and what is done and documented. Describe efforts to be done in case of loss to follow up.

10.2 Medical Device Category C studies

Device deficiencies 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 study period, i.e. from patient's informed consent until the last protocol-specific procedure, including a safety follow-up period [ISO 14155]. Documentation includes dates of event, treatment, resolution, assessment of seriousness and causal relationship to device and/or study procedure.

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

List here foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation or treatment.

10.2.1 Definition and Assessment of (Serious) Adverse Events and other safety related events **(MD: ISO 14155)**

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device [ISO 14155: 3.2].

This includes events related to the investigational device or the comparator and to the procedures involved. For users or other persons this is restricted to events related to the investigational medical device.

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device [ISO 14155: 3.1].

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

Serious Adverse Event (SAE) [European regulation on medical devices 2017/745, art. 58].

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.

This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are submitted to the EC via BASEC within 7 days. A planned hospitalisation for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling [ISO 14155: 3.15].

Health hazards that require measures

Findings in the trial that may affect the safety of study participants and, which require preventive or corrective measures intended to protect the health and safety of study participants SAE [ClinO Art. 37].

Causal Relationship of SAE [MEDDEV 2.7/3 revision 3, May 2015].

A causal relationship towards the medical device or study procedure should be rated as follows:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Unlikely:** The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

Device deficiencies that might have led to an SAE are always related to the medical device.

10.2.2 Reporting of (Serious) Adverse Events and other safety related events

Describe how, by whom and in what time frame the serious and other reportable adverse events (health hazards, pregnancies if applicable, etc.) are reported. This should also define the reporting PI to Sponsor in case of a multicentre trial, when the sponsor and the PI are not the same person. Similarly, define the reporting responsibilities to the manufacturer when the sponsor and the PI are the same person.

Important note concerning all following sections of this chapter 10.2.2: add, respectively adapt to other local requirements in case of international studies.

Reporting to Sponsor-Investigator:

The following events are to be reported to the Sponsor-Investigator within 24 hours upon becoming aware of the event:

- All SAEs
- Health hazards that require measures
- Device deficiencies

The Sponsor-Investigator will evaluate SAEs with regard to causality and seriousness. Device deficiencies are assessed regarding their potential to lead to an SAE.

Pregnancies

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

If reporting is needed, include in the protocol how pregnancies will be reported (usually within a maximum of 24 hours to the Sponsor-Investigator), and how occurrence of pregnancy will be handled in the study (patient is withdrawn, outcome of the pregnancy should be followed-up, etc). Details will depend on the type of study.

Reporting to Authorities [ClinO Art. 42]:

In Category C studies it is the Investigator's responsibility to report **serious adverse events** in Switzerland which are

- related or possibly related to the medical device under investigation
- related or possibly related to study procedures

to the Ethics Committee via BASEC within 7 days. The Sponsor-Investigator reports within the same timeline to Swissmedic (incl. events from abroad).

It is the Investigator's responsibility to report **device deficiencies** via BASEC that could have led to serious adverse events if suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate within 7 days. The Sponsor-Investigator reports within the same timeline to Swissmedic (incl. events from abroad) [ClinO Art. 42].

Health hazards that require measures are reported to the Ethics Committee via BASEC within 2 days [ClinO Art. 37].

Periodic safety reporting:

In Category C studies a yearly safety update-report is submitted by the Investigator to the Ethics Committee and by the Sponsor-Investigator to Swissmedic.

10.2.3 Follow up of (Serious) Adverse Events

(SPIRIT #30)

Describe the follow up of participants terminating the study (either regularly or prematurely) with reported ongoing SAE, or any ongoing AEs of laboratory values or of vital signs being beyond the alert. Describe procedures: when and how and what is done and documented. Describe efforts to be done in case of loss to follow up.

10.3 Medical Device Category A studies

Device deficiencies 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 study period, i.e. from patient's informed consent until the last protocol-specific procedure, including a safety follow-up period. Documentation includes dates of event, treatment, resolution, assessment of seriousness and causal relationship to device and/or study procedure [ISO 14155, 6.4.1.].

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

List here foreseeable serious adverse events and anticipated adverse device effects, together with their likely incidence, mitigation or treatment.

10.3.1 Definition and Assessment of safety related events

See the definition of serious safety events and of causal relationship of SAE assessment in the chapter 10.2.1.

10.3.2 Reporting of Safety related events

Important note concerning all following sections of this chapter 10.3.2: add, respectively adapt to other local requirements in case of international studies.

Reporting to Sponsor-Investigator:

Health hazard that require measures are reported to the Sponsor-Investigator within 24 hours upon becoming aware of the event:

Pregnancies

Depending of the study, reporting of pregnancies may not be necessary. If reporting is needed, include in the protocol how pregnancies will be reported (usually within a maximum of 24 hours to the Sponsor-Investigator), and how occurrence of pregnancy will be handled in the study (patient is withdrawn, outcome of the pregnancy should be followed-up, etc.). Details will depend on the type of study.

Reporting to Authorities:

In Category A studies, the sponsor is subject to the notification requirements specified in Art. 15 of the MedDO of 17 October 2011 (SR 812.213).

It is the Investigator's responsibility to report to the Ethics Committee via BASEC **device deficiencies** that could have led to serious adverse events if suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate within 7 days [ClinO Art. 42].

Health hazards that require measures are reported to the Ethics Committee via BASEC within 2 days [ClinO Art. 37].

Periodic safety reporting:

A yearly safety update-report is submitted by the Investigator to the Ethics Committee via BASEC.

A report is submitted to Swissmedic by the Sponsor-Investigator, as defined in Art. 15a,b of the MedDO

of 17 October 2011 (SR 812.213).

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

(ClinO Art. 44)

In clinical trials involving therapeutic products capable of emitting ionising radiation, and in investigations using radiation sources, the investigator shall assess compliance with the dose guidance value in accordance with Article 45 of the Radiological Protection Ordinance of 26 April 2017. The dose guidance values for clinical trials without expected direct benefit for the participants is 5 mSv effective dose per year.

If the permitted dose guidance value is exceeded at any time, the investigator notifies the Ethics Committee via BASEC within 7 working days of it becoming known.

In the case of Category B and C clinical trials with therapeutic products that emit ionising radiation, if the permitted dose guidance value is exceeded at any time, the Sponsor-Investigator notifies Swissmedic within 7 working days of it becoming known.

11. STATISTICAL METHODS

(ICH/E6 6.9; SPIRIT # 14, 20)
Statistical considerations
ICH: A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

Describe the statistical considerations done for the study, the level of significance that will be used.

11.1 Hypothesis

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

If hypothesis testing is not used, then discuss the manner in which the approach that will be used (e.g. Bayesian methods) will address objectives.

11.2 Determination of Sample Size

ICH: The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

Provide the estimated number of participants for each study site and study arm (if applicable) needed to achieve the objective, how it was determined, including clinical and statistical assumptions supporting any sample size calculations, the power of the trial, the type I error (one- or two-sided) and the related risk, the clinical justification.

11.3 Statistical criteria of termination of trial

ICH: A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial.

Describe the criteria for the termination of the trial or the stopping rules.

11.4 Planned Analyses

ICH: A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

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 protocol and may be referred to this document, e.g. statistical analysis plan)

11.4.1 Datasets to be analysed, analysis populations

ICH: The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

Describe the analysis populations, evaluation groups (intention to treat, per protocol, etc.) and data sets to be used for analysis and methods for any additional analyses (e.g., subgroup and adjusted analyses)

11.4.2 Primary Analysis

Describe the intended primary analysis that will be done, when and how and by whom it will be done.

11.4.3 Secondary Analyses

Describe the intended secondary analysis that will be done, when and how and by whom it will be done.

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

ICH 6.9.1: ..... including timing of any planned interim analysis(ses).

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. 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 Safety analysis

Describe the analysis of the safety parameters that will be done, when and how and by whom it will be done.

11.4.6 Deviation(s) from the original statistical plan

(ICH/E6 6.9.6)
ICH: 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 protocol and/or in the final report, as appropriate).

Describe how any deviation(s) from the planned analyses will be justified and reported.

11.5 Handling of missing data and drop-outs

(ICH/E6 6.9.5; SPIRIT 20c)
ICH: Procedure for accounting for missing, unused, and spurious data.

Describe how missing data will be handled (e.g. multiple imputation, last observation carried forward, complete case analysis…) and if drop-outs are replaced. If sensitivity analyses are planned, specify them.

12. QUALITY ASSURANCE AND CONTROL

(ICH/E6 6.11, 6.13; SPIRIT #19, 23, 27)
ICH: Quality Control and Quality Assurance Procedures

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 multicentre studies. The PI is responsible for proper training of all involved study personnel.

12.1 Data handling and record keeping / archiving

(ClinO, Art. 18, 45, 57, 62; ICH/E6 6.13; SPIRIT #19, 27)
ICH: Data Handling and Record Keeping

Describe how data are handled and that all study related documents are archived (essential documents and site documents).

12.1.1 Case Report Forms

(ICH/E6 6.4.9)
ICH: The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

Describe how study data is recorded, e.g. with paper or electronic Case Report Forms (p-/e-CRF). For each enrolled study participant a CRF is maintained. CRFs must be kept current to reflect subject status at each phase during the course of study. Participants must not be identified in the CRF by name or initials and birth date. Appropriate coded identification, e.g. participant number in combination with year of birth must be used.

It should be described who is authorized for which CRF entries and it must be assured that any authorised person can be identified. If paper CRFs are used, describe how data is entered into an electronic database for analysis (e.g., double data entry).

12.1.2 Specification of source documents

(ICH/E6 6.4.9)
ICH: The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

Source data must be available at the site to document the existence of the study participants. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

Describe what is considered the source documents in the respective study (e.g., demographic data, visit dates, participation in study and Informed Consent Forms, randomisation number, SAEs, AEs and concomitant medication, results of relevant examinations. Identify data that are directly recorded in the CRF, which should also be considered being source data. Also describe where source data are found at the site.

12.1.3 Record keeping / archiving

(ICH/E6 6.13)
ICH: Data Handling and Record Keeping

All study data must be archived for a minimum of (*time according to local legislation*) years after study termination or premature termination of the clinical trial.

Specify location of storage.

IMP: Archiving for 10 years

MD: Archiving for 10 years, in the case of an implantable device 15 years

12.2 Data management

(ICH/E2; SPIRIT #19)

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 by anonymised after statistical analysis describe how they will be stored (e.g. coded, not deleted).

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

12.2.1 Data Management System

Describe what system (also software) is being used and who is responsible and how it is tested before the trial (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 (note MD: the archiving period is different for implantable devices).

12.2.4 Electronic and central data validation

Describe how data are validated.

12.3 Monitoring

(SPIRIT #23)

Describe the regular monitoring visits at the investigator's site prior to the start and during the course of the study organised by the Sponsor. Give a description of what data and documents will be monitored. Alternatively the extent and nature of monitoring activities based on the objective and design of the study can be defined in a study specific monitoring plan.

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

12.4 Audits and Inspections

(ClinO, Art. 58, 59; SPIRIT #23)

Describe the frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the Sponsor. Provide a statement that the study documentation 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 participant data strictly confidential.

12.5 Confidentiality, Data Protection

(ClinO, Art. 18, 58; SPIRIT #27, 29)

Data protection; should include the statement that direct access to source documents will be permitted for purposes of monitoring (12.3), audits and inspections (12.4) (ICHE6, 6.10) and should declare who will have access to protocol, dataset, statistical code, etc. during and after the study (publication, dissemination).

12.6 Storage of biological material and related health data

(ClinO, Art. 18; HVF Art. 28-32; SPIRIT #33)

If applicable, describe how long samples are stored, or state that they are destroyed at the end of the study.

In the event of Biobank storage, confirm that coded samples or uncoded genetic data are only stored with the participants consent independent from the study.

13. PUBLICATION AND DISSEMINATION POLICY

(ICH/E6 6.15; SPIRIT #31)
ICH: Publication policy, if not addressed in a separate agreement.

Describe plans to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions; anticipate for authorship eligibility guidelines and any intended use of professional writers and, if any plans for granting public access to the full protocol, participant-level dataset, and statistical code, and the decision to submit the report for publication, including whether who will have ultimate authority over any of the activities (Medical devices: in addition mention the protection of trade secrets).

14. FUNDING AND SUPPORT

(ClinO, Art. 25i; ICH/E6 6.14; SPIRIT #4)

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

14.1 Funding

(ClinO, Art. 25i)
ICH: Financing and insurance if not addressed in a separate agreement.

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

14.2 Other Support

(ClinO, Art. 25i)
ICH: Financing and insurance if not addressed in a separate agreement.

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

15. INSURANCE

(ClinO Art 12, 13; ICH/E6 6.14, SPIRIT #30)
ICH: ….and insurance if not addressed in a separate agreement.

Provide a statement like "Insurance will be provided by the Sponsor. A copy of the certificate is filed in each investigator site file and the trial master file."

Category A studies are exempt. Categories B and C of IMP and C of medical devices studies need to document the guarantee of liability (insurance certificate or equivalent guarantee).

It can be referred here to another place where the document is found, e.g., in Appendix or separate document.

16. REFERENCES

(ICH/E6 6.2.7)
ICH: References to literature and data that are relevant to the trial, and that provide background for the trial.

Provide a list of the references cited in the protocol.

1. Declaration of Helsinki, Version October 2013, (http://www.wma.net/en/30publications/10policies/b3/index.html)
2. International Conference on Harmonization (ICH, 1996) E6 Guideline for Good Clinical Practice. (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf)
3. International Conference on Harmonization (ICH, 1997) E8 Guideline: General Considerations for Clinical Trials http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf)
4. 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
5. Verordnung über klinische Versuche in der Humanforschung (Verordnung über klinische Versuche, KlinV) vom 20. September 2013 / Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain (Ordonnance sur les essais cliniques, OClin) du 20 septembre 2013. Ordinanza sulle sperimentazioni cliniche nella ricerca umana (Ordinanza sulle sperimentazioni cliniche, OSRUm) del 20 settembre 2013
6. Heilmittelgesetz, HMG Bundesgesetz über Arzneimittel und Medizinprodukte (Heilmittelgesetz, HMG) vom 15. Dezember 2000 / Loi fédérale sur les médicaments et les dispositifs médicaux (Loi sur les produits thérapeutiques, LPT) du 15 décembre 2000 / Legge federale sui medicamenti e i dispositivi medici (Legge sugli agenti terapeutici, LATer)
7. ISO 14155:2011 Clinical investigation of medical devices for human subjects -- Good clinical practice (www.iso.org)
8. ISO 10993 Biological evaluation of medical devices (www.iso.org)
9. MEDDEV 2.7/3 revision 3, May 2015
10. 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
11. WHO, International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
12. European regulation on medical devices 2017/745.
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. Zz
15. Yy
16. Xx

17. APPENDICES

ICH: (NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

Please consider well with adding documents here that are very frequently changing, they may be mentioned as separately provided documents and listed here.

Except for medical devices, the section headings can be renamed accordingly.

1. IMP: IB or SPC

2. Medical Devices: IB (according to ISO 14155)

3. Medical Devices: Assurance of producer

4. Medical Devices: List of norms (vollständig eingehaltene, teilweise eingehaltene)

5. Radiolabelled products: Strahlenschutzverordnung

6. e.g. List of study sites / PIs

List of countries or centres where data will be collected or reference to where list of study sites can be obtained

7. Other

e.g. Specific protocols (e.g. MRI)

e.g. Case Report Form (e.g. CRF)

e.g. Patient Information and informed consent

Model of consent form and other related documentation given to participants and authorised surrogates and additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

e.g. Other material to patients

Model of consent form and other related documentation given to participants and authorised surrogates and additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable