Clinical Protocol template for clinical trial with an investigational medicinal product (IMP)

General information and instructions

This document is the clinical protocol template for clinical trial with an investigational medicinal product[1] (IMP). swissethics strongly recommends the use of the template.

This template provides a general format for trial protocols of clinical trials with medicinal products and in particular for interventional[2] trials:

- performed in Switzerland, respectively where the sponsor-investigator is located in Switzerland
- where the Federal Act Medicinal Products and Medical Devices (TPA) applies,
- where the Federal Act on Research involving Human Beings (HRA) and the Clinical Trials Ordinance ClinO (KlinV d / OClin f / OSRUm i) apply,

[1] *Investigational medicinal product* is a product that is tested in a clinical trial or used as a comparator product, also as a placebo.

[2] *Intervention* means any action performed on the trial participant whose effect on that person shall be investigated.

The template is based on:

- the Federal Act on Research involving Human Beings (HRA) and the Clinical Trials Ordinance (ClinO) (KlinV d / OClin f / OSRUm i)
- the SPIRIT statement and
- ICH-GCP E6

Notes:

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

Instructions are indicated in *blue italics* and they need be deleted.

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 the trial protocol as provided in the template.

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

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 template to swissethics, info@swissethics.ch, phone: +41 31 306 93 95, www.swissethics.ch.

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 trial protocol in the research project application form in BASEC to avoid redundancies but not vice versa.

Change history

Version Nr	Version date	Modified without version change	Description, comments	Control
1.0	15.04.2021		Initial version.	PG
		X	Added note for gender research to chapter 11.4 and 13.	PG
		X	Added clarifications to chapter 15. *Insurance* for clinical trials category A and for trials category B and C.	PG
1.1	24.02.2022		Updated chapter 10.1.2, section on the reporting obligations for ASR/DSUR. Add reference to ICH (2010) E2F Development Safety Update Report.	PG
		X	Paragraph on reporting obligations to FOPH according to art.44 ClinO moved from chapter 10.1.2 to chapter 10.2.	PG
		X	Added instructions on sex and gender-equitable research.	PG
2.0	16.09.2024		New version adapted to the amended ClinO, status as of November 1, 2024.	PG
		X	Added reference to 'Clinicaltrials.gov' in chapter 2.1.	PG

✂ Please remove the 'General information and instructions' and the table 'Change history' ✂

Clinical Trial 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 medicinal product, 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)*
Study Categorisation:	*Risk category according to ClinO (A, B or C)*
Study Registration:	*Name of study registry (if not yet registered name the intended registry)* *Registration number (from the Swiss National Clinical trial Portal: SNCTP), other registries and numbers if applicable*
Study Identifier / Study ID:	*Study ID (e.g. institutional or Sponsor protocol identifier) [make sure this corresponds to the Study ID in the footer]*
Sponsor:	*Name of Sponsor, Institution, Address* *Contact details (full details)*
Principal Investigator, coordinating principal investigator:	*Name of Principal investigator, coordinating investigator, Address* *Contact details (full details)*
Investigational medicinal product:	*Study Drug – Generic, followed by marketed name if applicable* *Note: The investigational medicinal product is the product that is tested in the trial or used as a comparator, also as a placebo.*
Protocol Version and Date:	**(SPIRIT #3)** *Version number and version date [make sure they correspond to the version number and version date in the footer]* *Add if applicable, the Amendment number, from (date), replaces version number from (date)*

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), make sure this corresponds to the protocol version and date in the footer], and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, the ICH-GCP guidelines and the local legally applicable requirements.

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

Sponsor/Investigator:

Printed name of Sponsor and 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 and the local legally applicable requirements.

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

Site	*Name and address of site*
Principal investigator	*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	*Name of Sponsor, institution, address*
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. Note that comparator drugs and placebo are taken into account in the categorization of trials with medicinal products (ClinO Art.2 lit. g and h).*
Clinical Phase:	*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)*
Background and Rationale:	*Provide a short background and the rationale for the study, this includes the health condition studied.* *Are "sex and gender" dimensions relevant to the topic of the study (specifying genetic/biological or social mechanisms at play)? To address this question, refer to the recommendations "sex and gender in research involving humans according to the HRA" (swissethics.ch / topics / sex and gender equitable research). If it is considered that "sex and gender" dimensions are not relevant, provide a justification.*
Objective(s):	*Brief statement of primary 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.* *Are "sex and gender" dimensions relevant to the topic of the study? To address this question, refer to the recommendations "sex and gender in research involving humans according to the HRA" (swissethics.ch / topics / sex and gender equitable research).*
Measurements and procedures:	*Describe the study intervention (methodology, procedures, sampling if applicable)*
Study Product / Intervention:	*Describe the study specific intervention (product (drug, 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. Are "sex and gender" dimensions relevant to the topic of the study? To address this question, refer to the recommendations "sex and gender in research involving humans according to the HRA" (swissethics.ch / topics / sex and gender equitable research).*
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP, 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
FOPH	Federal Office of Public Health
GCP	Good Clinical Practice
IB	Investigator's Brochure
Ho	Null 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
ITT	Intention to treat
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

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

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

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		*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

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

Sponsor means a person or institution headquartered or represented in Switzerland that takes responsibility for organising a clinical trial, and in particular for the initiation, management and financing of the trial in Switzerland (Art. 2, ClinO).

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.

It is the responsibility of the Sponsor and of the investigator to ensure that role and responsibilities of the project leader and of the Sponsor are clearly defined in the project plan and understood by all.

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).

Investigator means a person responsible in Switzerland for the conduct of a clinical trial and for the protection of the participants at the trial site; an investigator who takes responsibility for organising a clinical trial in Switzerland is also a sponsor (Art. 2, ClinO)

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).

Note: Required professional qualifications of the investigator and other persons conducting the clinical performance study is given in Art. 6 ClinO.

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) and other medical and/or technical department(s) and/or institutions 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 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.

Describe here the ethical considerations relating to the study:

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

Before the 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 the Swiss National Clinical trial Portal (SNCTP) via BASEC in the national language of Switzerland in which recruitment is intended.

In addition, the study must be registered in a primary registry recognized by the WHO (International Clinical Trials Registry Platform: https://www.who.int/clinical-trials-registry-platform), or in the registry of the U.S. National Library of Medicine (https://clinicaltrials.gov), if it satisfies the definition given therein.

2.2 Categorisation of study

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

Describe the risk category and the rationale for the categorisation;

Categorisation of clinical trials of medicinal products. Note: An investigational medicinal product means a product which is being tested or used as a reference, including as a placebo, in a clinical trial on medicinal products (Art. 2, ClinO);

1 Clinical trials of medicinal products come under Category A if:

a. the investigational medicinal product is a medicinal product authorised in Switzerland;
b. the investigational medicinal product has not been modified; and
c. the use of the investigational medicinal product:
    1. is in accordance with the prescribing information,
    2. is in an indication or dosage different from that specified in the pre-scribing information, but in accordance with the following criteria:
        – the indication is within the same disease group of the International Classification of Diseases (ICD), as specified in Annex 1 number 3,
        – the disease in question is self-limiting and the dosage of the medicinal product is lower than that specified in the prescribing in-formation; or
    3. is recognised as standard in guidelines prepared in accordance with internationally accepted quality criteria.

2 They come under Category B if the investigational medicinal product:

a. is a medicinal product authorised in Switzerland, which:
   1. is not used as specified in paragraph 1 letter c, or
   2. has undergone a low-risk modification, as specified in Annex 2bis;
b. is a medicinal product authorised in a country having equivalent medicinal product control in accordance with Article 13 TPA and has either not been modified or has undergone a low-risk modification, as specified in Annex 2bis; or
c. is a placebo specifically produced for clinical trials.

3 They come under Category C if the investigational medicinal product contains an active substance and:

a. is a medicinal product authorised in Switzerland or in a country having equivalent medicinal product control in accordance with Article 13 TPA and has undergone more than a low-risk modification, as specified in Annex 2bis; or
b. is a medicinal product authorised neither in Switzerland nor in a country having equivalent medicinal product control in accordance with Article 13 TPA.

4 If a clinical trial comes under more than one category, it is assigned to the highest of these categories; the categories are arranged in ascending order from A to C.

2.3 Competent Ethics Committee (CEC)

(ClinO, Art 24-29, 38; SPIRIT #24)

The investigator *(for multicentric trials:* at each site*)* ensures that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the clinical study.

For clinical trials category B and C, the application must be submitted to the CA within two years of approval by the CEC (ClinO Art. 23).

An application for an extension beyond the two years is a substantial amendment; if this is not complied with, the approval to conduct the study lapses.

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 completion or premature study termination and the final report) and that no changes are made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate immediate hazards to study participants.

The investigator reports the premature termination, interruption or resumption of the study, including reasons thereof, to the CEC within 15 days. An interruption lasting more than two years is considered a premature termination. The investigator reports the first visit of the first participant in Switzerland and the end of the study in Switzerland to the CEC within 30 days. The investigator reports the global completion of an international trial to the CEC within 90 days. *Unless otherwise specified in this protocol, the last follow-up visit of the last study participant is defined as the completion of the trial.* The final study report will be submitted within one year after the completion of the study or premature study termination. *See CliniO Art. 38 for more details.* Amendments are reported according to chapter 2.10.

Note: The sponsor may submit the application instead of the investigator. In this case, the sponsor assumes the obligations of the investigator as specified in ClinO Art. 29 and 36a (if applicable) and also the notification and reporting obligations vis-à-vis the CEC as specified in ClinO Art. 44, if this is provided for in the protocol or in other application documents.

2.4 Competent Authorities (CA)

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

For category B and C trials:

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. The application must be submitted to the CEC within two years of approval by the CA (ClinO Art. 23). An application for an extension beyond the two years is a substantial amendment; if this is not complied with, the approval to conduct the study lapses.

Mention the reporting duties and allowed time frame to CA including the reporting duties in case of completion, premature termination or resumption of the study, including reasons thereof and the final report (see above chapter 2.3 and ClinO Art. 38 for details). Reporting duties and timelines are the same as for CEC, except of non-substantial amendments that shall be reported as soon as possible (ClinO

Art. 34).

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, and Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annually a safety report and interim reports and be informed about study stop/end in agreement with local requirements. The CEC will also be informed annually about the general progress of the clinical trial.

The safety report can be written and submitted in the format of the Development safety update report (DSUR). See chapter 10.1.2.

Add other local requirements in case of 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)

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

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

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

Explain that subjects will be informed about the study (what, how, by whom) and that consent is obtained from each subject; include the mention of compensation if any. Describe the process specific to the study (see also HRA and Art. 7-9 ClinO), including processes for vulnerable subjects (e.g. children assent) or subject lacking capacity of judgment, if applicable.

Check that the layout of the information respects the epicene language, or it is written in an inclusive format. Make sure that the information covers the study's aspect related to "sex and gender" appropriately. If applicable, ensure that the issue of contraception and pregnancy are fully and clearly presented.

The PI explains to each subject 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 subject is 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 subjects are informed that he/she can ask any question, and consult with family members, friends, their treating physicians or other experts before deciding about their participation in the study. Enough time is given to the subjects. *Important note: Enough time needs to be given to the subject to give an informed consent. The time depends on the type of intervention, the risks, and other factors (see*

the guidance document "Guideline of swissethics for the time for consideration between information and consent" published on swissethics.ch/topics/position papers, available in German *and* French*). If necessary, specify the timeframe given.*

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

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

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

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

In case prenatal and presymptomatic genetic tests are provided for in the protocol, the ICF must comply with the provisions of Art. 7b ClinO. That is, the study participants must be informed that incidental findings are to be expected as a result of the genetic tests. The following aspects should be addressed and described:

- *Describe how genetic counselling is provided to study participants, when prenatal or presymptomatic genetic testing is performed as part of the study. Describe how study participants will be informed of any incidental genetic findings that directly affect their health.*

Additionally, if applicable, in case of non-genetic incidental findings are expected in the study (e.g., radiological findings) that directly affect the study participants health care provided to the study participants, describe how they will be informed.

In case of vulnerable population the following aspects should be addressed and described:

- *Describe how the legal representative is informed regarding the procedures of the study and how his or her consent is obtained;*
- *In the event that the minor and / or subject under tutelage is capable of judgment, describe how their consent (or assent) is collected in addition to the consent of their legal representative;*
- *In the event of a subject lacking capacity of judgment, mention that signs and symptoms showing that the subject is unwilling to participate in the study will result in the subject being excluded from participation.*

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

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

2.8 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.

The investigator has appropriate knowledge and skills in the areas of data security and data protection or is able to ensure compliance by calling in appropriate expertise (Art. 6, ClinO).

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited.

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

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 Premature termination of the study

(ClinO Art. 38, 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

If the study is terminated earlier than planned, the investigator notifies the CEC according to the provisions of ClinO Article 38. *For trials of category B and C, the investigator also notifies the CA.*

2.10 Protocol amendments

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

State, who is allowed to amend the protocol. 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 once a year to the CEC with the safety report / general study progress report of the clinical trial.

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.

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

3.2 Investigational Medicinal Product (treatment) and Indication

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

This section should contain a description of the investigational medicinal product and of the placebo (if applicable), 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)

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.

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 study (published or available unpublished data that should be based on or referred to a systematic review). This shall include an analysis of adverse effects and any history of variations or recalls. If none is available, include a statement that there is no available clinical research data to date on the investigational medicinal product.

3.5 Rationale for the dosage, route, regimen

(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.

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 medicinal product).

3.7 Risks / Benefits

(ClinO, Appendix 4, 3.5; Art 25d2; ICH/E6 6.2.3; SPIRIT #6a)
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.

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 investigation population and the rationale for it. Provide information on the representativeness of the investigation population in relation to the target population.

Ensure that the criteria for selecting the persons intended to participate and the trial design allow an appropriate representation of the groups of persons who are relevant for answering the scientific question; in particular, the distribution of genders and age groups should be taken into account. The exclusion or intended underrepresentation of relevant groups of persons must be stated and justified. See also chapter 7.1, and Art. 4a ClinO.

Refer to the recommendations "sex and gender in research involving humans according to the HRA" (swissethics.ch / topics / sex and gender equitable research) to address "sex and gender" issues in this chapter. Describe how recruitment of the subjects is conducted to ensure "sex and gender" balance is achieved, or give an explanation why this would not be possible and how this imbalance would impact the scientific validity of the investigation result.

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

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

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).

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 A on diastolic blood pressure compared to Drug 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 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 the end of treatment/intervention to verify whether a given treatment was successful or not.

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

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

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

Other endpoints will be listed as secondary endpoints.

5.2 Secondary Outcomes

Provide a short description of the secondary outcome variables and the rationale for the choice of outcomes. (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 investigational medicinal product 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., double-blind – who is blinded, placebo-controlled, parallel design), allocation ratio and framework (e.g., superiority, equivalence, non-inferiority, exploratory). Provide a description of intended procedures and stages, the expected duration of 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, 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. Refer to chapter 13 for the communication of the allocation to the

participant at study end

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. Ensure that the criteria for selecting the persons intended to participate and the trial design allow an appropriate representation of the groups of persons who are relevant for answering the scientific question; in particular, the distribution of genders and age groups must be considered. The exclusion or intended underrepresentation of relevant groups of persons must be stated and justified. Refer to the recommendations "sex and gender in research involving humans according to the HRA" (swissethics.ch / topics / sex and gender equitable research) to address "sex and gender" issues in this chapter, if relevant.

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

- *Informed Consent as documented by signature,*
- *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 medicinal 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 medicinal product 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.*

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

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

7.2 Recruitment and screening

(ClinO, Art 23a, Appendix 3, 1.4 & 1.6; SPIRIT #15)

Describe how, where and by whom participants are recruited / preselected for study, also mention any advertisement; describe any screening requirements (e.g. laboratory or diagnostic tests). Refer to section 9.3. for description of screening procedures. Describe any payment or compensation given to study participants.

The first study participant must be enrolled in the trial within two years following the issuance of the last authorization, either from the CEC or from the CA. An application for an extension is a substantial amendment. If the extension is not approved, then the approval already granted lapses. If the first participant is not enrolled in the clinical trial within the deadline, then the clinical trial is interrupted. In the case of clinical trials on rare diseases, the CEC and CA may set a longer period at the request of the applicant as part of the approval procedure.

The investigator or the sponsor notifies the CEC and the CA *(for category B and C trials, delete CA, if not applicable)* of the first study participant, in accordance to Art 23a ClinO. If the first participating person is not included in the trial within two years following the issuance of the last authorization, the trial is considered interrupted. The clinical trial may not be commenced until an application for an extension of the time limit has been approved. The application for the extension is submitted to the CEC, and to CA *(for category B and C trials, delete CA, if not applicable)* as a substantial amendment.

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 medicinal product treatment/trial treatment) and procedures specifying: When and how to withdraw subjects from the trial/ investigational medicinal product treatment and whether and how subjects are to be replaced.

Describe the criteria and procedures when and how participants are withdrawn from the study / investigational medicinal product treatment and whether 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 Medicinal Products

(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

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

Describe the investigational medicinal product, the name (generic and brand name), its source, formulation/material, strength, colour etc., route and mode of administration for medication and the deviation from commercial product, if applicable.

8.1.2 Control Intervention (standard/routine/comparator treatment)

ICH: Name and description of the investigational medicinal 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 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. Describe deviation from commercial products if applicable.

8.1.4 Storage Conditions

Describe how the investigational medicinal product and those for the standard/routine/comparator therapy are stored (e.g., temperature range, exposure to light, etc.). IMP supplies must be kept in a secure, limited access storage area under the recommended storage conditions.

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 medicinal product treatment/trial treatment group/arm of the trial.

Describe the route, dose, regimen and the rationale for timing, doses of the investigational medicinal product(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.

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 medicinal product treatment/trial treatment group/arm of the trial.

Describe the route, dose, regimen and the rationale for timing, doses of the comparator(s) (e.g. standard, routine, placebo) medical product(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.

This chapter can also be merged with chapter 8.1.2.

8.3 Dose modifications

(SPIRIT #11b)

Describe criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., IMP 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 medicinal 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 Accountability

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

Provide plans of accurate and adequate records maintenance, on-site and per participant, 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

(SPIRIT 11c)

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

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. 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 not 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 not 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, pharmacokinetic parameters (describe condition of participant, e.g., fasting, x hours after treatment with the investigational medicinal product), 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.]. This should be a practical instruction, 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 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); 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., heartbeat, 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.

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, e.g. confirmation of eligibility, ...)

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., Randomisation, 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; 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.

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.

The documentation of SAEs is mandatory for all categories. Adapt the whole paragraph above according to the study category and study specificities.

Note:

For category A trials there is no legal obligation in Switzerland to document AEs (the documentation of such events should follow standard clinical practice, which is independent form the clinical trial),.

For category B trials if AEs occur during the conduct of the trial, the investigator must document them in a standardized manner if the AEs are designated in the protocol as critical for the safety assessment; or if this was requested by the CEC or CA.

For category C trials, if AEs occur during the conduct of the trial, the investigator must document them in a standardized manner. In justified exceptional cases, the sponsor can exempt the standardized documentation of AEs in trials of category C that are not designated as critical for the safety assessment from the documentation requirement. This must be stated in the protocol, see chapter 10.3 and must be approved by the CEC and CA.

Explanations: It should be emphasized that either the CEC or CA is responsible for assessing the requested exemptions from the documentation requirement, depending on the justification provided. The decisive factors here are the areas of review of the respective authority, as defined in Articles 25 and 32 ClinO. The following principle applies: Exceptions that are justified by the sponsor with pharmacological arguments, for example already known adverse effects of an active substance or known adverse interactions with other medicinal products, must be reviewed by the CA. Exemptions that are justified by the sponsor with clinical (i.e., non-pharmacological) arguments, for example in the case of adverse events that are very likely to occur due to the medical indication, are to be assessed by the CEC, as it has the necessary expertise in the medical field. (ClinO Art. 39 1bis).

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 an investigational medicinal product, whether or not related to the investigational medicinal 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 follow-up visit) will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

Both Investigator and Sponsor make a causality assessment of the event to the study investigtational medicine product, 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 evaluates the SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational medicinal product and is both serious and unexpected, it is classified as a SUSAR.

Note: In case of double-blinded studies, unblinding may be needed to determine a SUSAR. The Sponsor should not disclose the treatment allocation 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

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 (immediate safety and protective measures, pregnancies if applicable, etc.) are reported by the research site to the Sponsor. If applicable, describe the process for the multicentre trial,

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.

Reporting of SAEs or other safety relevant events to the Marketing Authorization 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 life-threatening or fatal, or within 15 days (all other events).

The reporting obligations of SUSAR also apply if the investigator or the sponsor becomes aware of a suspected case that has arisen in Switzerland after termination of the clinical trial, or if the investigator or the sponsor only becomes aware of such a suspected case after termination of the clinical trial.

Reporting of immediate safety and protective measures

All suspected new risks and relevant new aspects of known adverse reactions that require immediate safety-related measures, must be reported to the Sponsor-Investigator within 24 hours. The Sponsor-Investigator must report these measures 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 must immediately inform all participating Investigators about the immediate safety and protective measures.

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 investigational medicinal product.

Periodic reporting of safety and general progress of the clinical trial.

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).

Once a year, the investigator submits to the CEC a list of the safety events including the severity of the events, their causality to the intervention and the safety of the study participants. The investigator also informs the CEC about the general progress of the clinical trial.

The safety report can be written and submitted in the format of the Development safety update report (DSUR) in compliance to ICH Harmonised Guideline E2F for commercial and non-commercial sponsor.

The safety report and the general study progress report can be merged in one single report.

The safety report / general study progress report is submitted once a year to the CEC via Investigator and to Swissmedic in case of a category B or C study via Sponsor-Investigator.

The start date for the safety report is the date is the sponsor's first authorisation to conduct a clinical trial in any country worldwide.

The safety report / general study progress report is submitted to the CEC and to Swissmedic throughout the duration of the clinical trial in Switzerland, and the last submission of the safety report will cover the Last Patient Last Visit in Switzerland. In case of international clinical trials, after the submission of the

safety report covering Last Patient Last Visit in Switzerland, further information on safety will be captured in the final study report and submitted to the CEC within one year of the global completion of the study.

For multicentre studies the 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 via BASEC.

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 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 sponsor 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.

Notes: In the case of concomitant examinations with ionizing radiation, the radiopharmaceuticals or medical devices used for this purpose must be approved or bear a conformity mark and must also be used in accordance with the Information for healthcare professionals (Art. 2 let. c ClinO).

FOPH Radiological Protection examines all concomitant examinations with non-authorization-compliant or non-CE-compliant use, and not only those in which the effective dose exceeds 5 mSv (Art. 36a ClinO).

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 notifies Swissmedic within 7 working days of it becoming known.

Add if applicable: For each application of ionising radiation, the investigator documents all information relevant to radiation protection in the final study report, and includes a retrospective participant dose estimation. *There is no reporting obligation for radiopharmaceuticals used in conformity with the authorization and for medical devices with a conformity mark in accordance with Art. 13 Medical Devices Ordinance (Med DO) used in accordance with the instructions for use. The FOPH may also provide for exemptions from the reporting obligation or on request.*

Add if applicable: Within a year of the completion or premature termination of the clinical trial which included investigations involving radioactive sources, the investigator submits to the FOPH the final study report including all information of relevance for radiological protection. *The final study report is submitted to the FOPH if the FOPH has issued an opinion in accordance with ClinO Art. 36 or 36a.*

10.3 Exemption from the documentation requirements of AE

For category C trials only. Write N/A in this chapter and subchapters if not applicable.

Generally, if AEs occur during the conduct of the trial, the investigator must document them in a standardized manner. In justified exceptional cases, the sponsor can exempt the standardized documentation of AEs in trials of category C that are not designated as critical for the safety assessment from the documentation requirement.

The sponsor justifies the exemption from the documentation requirements of the AEs listed under chapter 10.3.1 and chapter 10.3.2 as not critical for safety evaluation. *Adapt the sentence as appropriate.*

10.3.1 Exemption from the documentation requirements of AE due to pharmacological arguments

List here AEs exempted from the documentation requirements due to pharmacological arguments and give a justification. For example, due to known adverse effects of an active substance or known adverse interactions with other medicinal products.

The exemption will be assessed by the CA, as it has the necessary expertise in the medical field (ClinO Art. 29 1bis, Art. 32).

10.3.2 Exemption from the documentation requirements of AE due to clinical arguments

List here AEs exempted from the documentation requirements due to clinical (non-pharmacological) arguments and give a justification. For example, in case of adverse events that are very likely to occur due to the medical indication, etc.

The exemption will be assessed by the CEC, as it has the necessary expertise in the medical field (ClinO Art. 29 1bis, Art. 25).

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(es).

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

11.3 Statistical criteria of termination of 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(es).

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).

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

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(es).

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

(ClinO, Art. 45, ICH/E6 6.13)
ICH: Data Handling and Record Keeping

The sponsor retains all data relating to the clinical trial until the expiry date of the last delivered batch of the medicinal product under investigation or the last manufactured product in accordance with Article 2a paragraph 2 TPA, but for at least twenty years after completion or premature termination of the clinical trial. The investigator retains all documents necessary for the identification and follow-up of the trial participants and all other original data for at least twenty years after completion or discontinuation of the clinical trial.

Specify location of storage.

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.

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; 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

(ClinO Art. 65; 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.

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

The sponsor will enter and publish a summary of the trial results in a public register in accordance with ClinO Art. 65a within one year of completion or premature termination of the trial. An interruption lasting more than two years is considered a premature termination of the trial.

For the purpose of publication in the public register the sponsor also ensures that a lay summary of the trial results is entered in BASEC within one year of completion or premature termination of the trial. The entry is made at least in the national languages of Switzerland in which the study participants were recruited.

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

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 10-14; 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." The insurance (guarantee) must cover damage occurring up to 20 years after the end of the clinical trial. Refer to ClinO Art. 10 for exemptions from

liability and to ClinO Art. 12 for exemptions from liability coverage requirements.

Category A clinical trials involving measures for sampling of biological material or collection of health-related personal data which entail only minimal risks and burden are exempt from liability coverage requirements (ClinO Art. 12).

Categories B and C studies need to document the guarantee of liability (insurance certificate or equivalent guarantee) (ClinO Art. 13). The policy value shall be set in accordance with ClinO Annex 2.

It can be referred here to another place where the insurance certificate or equivalent guarantee 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 (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)
2. International Conference on Harmonization ICH E6 Guideline for Good Clinical Practice. (https://www.ich.org/page/efficacy-guidelines)
3. International Conference on Harmonization ICH E8 Guideline: General Considerations for Clinical Trials (https://www.ich.org/page/efficacy-guidelines)
4. International Conference on Harmonization (ICH E2F Development Safety Update Report. (https://www.ich.org/page/efficacy-guidelines)
5. 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
6. 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
7. 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)
8. WHO, International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
9. Strahlenschutzverordnung (StSV) vom 26. April 2017 / Ordonnance sur la radioprotection (ORaP) du 26 avril 2017 / Ordinanza sulla radioprotezione (ORaP) del 26 aprile 2017.
10. Zz
11. Yy
12. 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.)

Documents that do frequently change during the course of the study, can be mentioned as 'documents provided separately' and listed here.

The section headings can be renamed accordingly.

1. IMP: IB or SPC

2. Monitoring Plan

3. Patients' Recruitment Plan

4. 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

5. 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 documents given to the 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