Introduction to the Clinical Study Protocol template

This page is not included as part of the Clinical Study Protocol (CSP) template, but gives a short introduction to you, who will write a CSP. This page should be removed when using this template. The CSP template is primarily directed towards interventional studies. Some sections can thus be removed if they do not apply to clinical trials of drugs. This template is not designed to address clinical trials for medical devices. For more information, please visit the websites of the Swedish Medical Products Agency (Läkemedelsverket) and the Swedish Ethical Review Authority (Etikprövningsmyndigheten). Please also refer to the Swedish Medical Product Agency's document, "Tips och råd för studieprotokoll" (in Swedish).

This CSP template aims to serve as a help document to facilitate your work. It is not required to use all sections of the template. Sections can be removed and/or new sections can be added. This applies also to sub-sections. The template should be adjusted so that it fits your study.

- On the first page of the CSP (including headings), <<Text>> should be replaced with study-specific information.
- Text written in red Italics include information about what can or should be described under that respective section. This text should be deleted from the final document.
- Examples of partial wordings that can be used for part of the text, are written in plain font/style.
- When the CSP is final, update the table of contents.

Version: 7 November 2019

Responsible for the template:
- The national QA network within the node organization connected to Clinical studies Sweden (Kliniska Studier Sverige).

The template will be reviewed regularly by the national QA network. Any suggestions for improvement of this template can be sent to any of the email addresses provided below and the designated QA contact at the respective regional node can then further lift the proposal.

Contact information for the regional nodes:
- Gothia Forum: gothiaforum@vgregion.se
- Forum Norr: forumnorr@regionvasterbotten.se
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- Forum Sydost: forumo@regionostergotland.se
- Karolinska Trial Alliance kta.karolinska@sll.se
- Forum Söder: forumsoder@skane.se
CLINICAL STUDY PROTOCOL

**<<Title>>**

*The title should preferably include the name of the investigational product, study population, keywords about the study design (e.g., phase, randomization, blinding, etc) and the primary objective.*

**<<Short title/Acronym>>**

---

Study code:  
<< Study code >>

EudraCT number:  
<< EudraCT number >>

Version number:  
<< Version number >>

Date:  
<< YYYY-MM-DD >>

Sponsor:  
<< Name >>

*It is optional whether the principal investigator should be included on the title page or not. If it is relevant for the study, keep it and otherwise the line can be removed.*

Principal Investigator  
<< Name >>
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Signature page

For single-center studies, remove the signature line of the coordinating investigator. If the sponsor and principal investigator are the same person, clarify this on the first signature line by writing “Sponsor/Principal Investigator”, then remove the other signature lines.

For multicenter studies, the Swedish Medical Products Agency only requires the signature of the coordinating investigator for approval. This assumes that an agreement/contract is written between each principal investigator and the sponsor/principal investigator. In this case, remove the text regarding the “Principal Investigator”.

Text suggestion:

**Sponsor**

I am responsible for ensuring that this protocol includes all essential information to be able to conduct this study. I will submit the protocol and all other important study-related information to the responsible investigator(s) so that they can conduct the study correctly. I am aware that it is my responsibility to hold the staff members who work with this study informed and trained.

---

**Coordinating Investigator / Principal Investigator**

I have read this protocol and agree that it includes all essential information to be able to conduct the study. By signing my name below, I agree to conduct the study in compliance with this protocol, the Declaration of Helsinki, ICH GCP (Good Clinical Practice) guidelines and the national and international regulations governing the conduct of this clinical study.

I will submit this protocol and all other important study-related information to the staff members and responsible investigators who participate in this study, so that they can conduct the study correctly. I am aware of my responsibility to continuously keep the staff members and responsible investigators who work with this study informed and trained.

I am aware that quality control of this study will be performed in the form of monitoring, possibly audit, and possibly inspection.
Coordinating Investigator / Principal Investigator's signature                         Date

Printed name

**Principal Investigator**

I have read this protocol and it contains all essential information to conduct this study. By signing my name below, I agree to conduct the study in compliance with this protocol, the Declaration of Helsinki, ICH GCP (Good Clinical Practice) guidelines and the national and international regulations governing the conduct of this clinical study.

I will submit this protocol and all other important study-related information to the staff members and responsible investigators who participate in this study, so that they can conduct the study correctly. I am aware of my responsibility to continuously keep the staff members and responsible investigators who work with this study informed and trained.

I am aware that quality control of this study will be performed in the form of monitoring, possibly audit, and possibly inspection.

Principal Investigator's signature                         Date

Printed name
Contact information

List the name, role in the study, contact address, telephone number, and email for all involved in the study (Sponsor, Coordinating Investigator/Principal Investigator, clinical monitoring organization if appointed, etc.). Add rows as needed for the study.

<table>
<thead>
<tr>
<th>Role</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>&lt;&lt;Name, title&gt;&gt;</td>
</tr>
<tr>
<td></td>
<td>&lt;&lt;Site/Institution&gt;&gt;</td>
</tr>
<tr>
<td></td>
<td>&lt;&lt;Contact address&gt;&gt;</td>
</tr>
<tr>
<td></td>
<td>&lt;&lt;Telephone number&gt;&gt;</td>
</tr>
<tr>
<td></td>
<td>&lt;&lt;Email&gt;&gt;</td>
</tr>
<tr>
<td>Coordinating Investigator / Principal Investigator</td>
<td></td>
</tr>
<tr>
<td>Clinical monitoring organization</td>
<td></td>
</tr>
</tbody>
</table>
List of used acronyms and abbreviations

List all abbreviations used in the protocol. Each term should be written out fully the first time it is used in the protocol, with the abbreviation in parentheses. Examples of common abbreviations are shown below but this list should be adapted to your study; add and/or remove rows as needed.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term/Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event = any untoward medical occurrence</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction = adverse event, that is each unfavorable and unexpected reaction to a study treatment, regardless of dose</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>DSUR</td>
<td>Development Safety Update Report = annual safety report</td>
</tr>
<tr>
<td>EPM</td>
<td>Etikprövningsmyndigheten (English: Swedish Ethical Review Authority)</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Council for Harmonization</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat = including all data from all subjects who have participated in the study</td>
</tr>
<tr>
<td>LVFS</td>
<td>Läkemedelsverkets författningssamling (English: Swedish Medical Products Agency’s statutes)</td>
</tr>
<tr>
<td>PP</td>
<td>Per Protocol analysis = including only data from subjects who have completed the study completely in accordance with the protocol, with no deviations from the protocol</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event = serious untoward medical occurrence</td>
</tr>
<tr>
<td>SPC or SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
</tbody>
</table>
1. Synopsis

Brief summary of the study, including study design, primary objective and possibly secondary objectives, investigational product, dose, route of administration, study population, number of subjects, time plan for the study. Note! Not an introduction but a summary.

<table>
<thead>
<tr>
<th>EudraCT number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title:</td>
</tr>
<tr>
<td>Study code:</td>
</tr>
<tr>
<td>Short background/Rationale/Purpose:</td>
</tr>
<tr>
<td>Study objectives:</td>
</tr>
<tr>
<td>Primary objective:</td>
</tr>
<tr>
<td>Secondary objectives:</td>
</tr>
<tr>
<td>Study design:</td>
</tr>
<tr>
<td>Study population:</td>
</tr>
<tr>
<td>Number of subjects:</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
</tr>
<tr>
<td>Investigational product(s), dosage, administration:</td>
</tr>
<tr>
<td>Study outcomes:</td>
</tr>
<tr>
<td>Primary variable:</td>
</tr>
<tr>
<td>Secondary variable(s):</td>
</tr>
<tr>
<td>Study period:</td>
</tr>
</tbody>
</table>

2. Background and rationale

Provide a summary of the background of the study, including rationale/justification for the proposed study. This should be stated in a scientific context that motivates the choice of objectives and expected outcomes of the study. Describe which disease will be studied, current treatment strategies, and background to the trial including relevant references to scientific literature. Summarize results from earlier relevant preclinical/clinical studies.
3. Risk-benefit evaluation

The benefits of the study should be weighed against the risks for the subjects. Risks can be divided in those with causal relationship with the investigational product and with causal relationship with study-specific examinations. If an investigational product is administered in a manner that is not described in the summary of product characteristics (SPC), the risks related to this must be evaluated. The sponsor should summarize if the risk-benefit assessment is positive for the study. This section is an important source of information for ethical applications and when authoring the Informed Consent Form (ICF).

Be sure to describe:

- Expected clinical benefits with the investigational product(s) used in the study.
- Other expected benefits, e.g., health economics benefits.
- Risks associated with participation in this study; study-specific examinations and/or sampling not included in routine clinical practice.
- Expected adverse drug reactions in the study.
- Possible interactions with concomitant medical treatments.
- Steps that will be taken to control or mitigate risks (i.e. close follow-up of subjects).
- Risk-benefit rationale, concluding that it is ethical to perform this study and that the benefits justify the risks.

4. Study objectives

Study objectives or purpose = describe why the study is done and what you want to accomplish with the study.

List the study’s primary and secondary objectives (e.g., to study the effect, pharmacokinetics, and/or safety of the investigational product).

Describe which variables will measure this. Be sure that each variable is clearly defined. This section can have sub-sections such as “primary objective”, “secondary objective”, “primary outcome”, and “secondary outcome”. Briefly state these, while methods and questionnaires can be referred to under section 8.1, Assessment of clinical efficacy.

4.1. Primary objective

Describe the primary objective (there should only be one).

Example of a main aim / primary objective: To study whether drug x gives a better blood-pressure-lowering effect than drug y.

Text suggestion: The primary objective of this study is to…
4.2. Secondary objective(s)

Describe possible secondary objective(s). These should be as few as possible (e.g., AE, subgroup analyses, quality of life, etc).

Text suggestion: The secondary objective of this study is to…

4.3. Primary variable

The primary variable is described in more detail in section 8.1.1, Primary variable.

Text suggestion: Primary variable: Blood pressure measured 30 hours after administration of the investigational product.

4.4. Secondary variable(s)

Describe what will be measured to be able to answer the secondary objective. Secondary variables are described in more detail in section 8.1.2, Secondary variable(s).

5. Study design and procedures

5.1. Overall study design

The scientific integrity of the study and credibility of the study data depends substantially on the study design.

A description of the study design should include:

- Type of clinical study (Phase I, human pharmacology; Phase II, therapeutic explorative; Phase III, therapeutic confirmative; Phase IV, therapeutic usage).
- The study design to be conducted, e.g., open, randomized, single/double-blinded, placebo-controlled. If randomization occurs, refer to section 7.5, Randomization, for more information.
- Parallel group or cross-over etc
- Provide rationale for the chosen study design. The rationale should be relevant for the study’s objective and should also contribute to identification of relevant study outcomes.
- It must be clear how long a subject is expected to participate in the study.
- List which investigational product(s) that is used in the study as well as possible comparative treatments. Refer to section 7, Study treatments, for more detailed information.
- A schematic diagram of the study design, procedures, and stage; see provided example (Figure X).
5.2. Procedures and flow chart

Provide a review of each visit by describing which study-related procedure(s) the study subject undergoes during each visit (examinations, ECG, AE reporting, etc). Include a table that summarizes the activities during each visit, see example in Table X.

Describe any procedure at pre-screening that is planned for the study.

Keep in mind that it must be a qualified physician who checks the inclusion/exclusion criteria and obtains the informed consent. Define the visit window, e.g., how much a return visit may vary in time.

Example table:
Table X Flow chart

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening Day/Week x Inclusion visit</th>
<th>Visit 1 Baseline</th>
<th>Visit 2 Day/Week x (±10 days)</th>
<th>Visit 3 Day/Week x (±10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incl/exclusion criteria</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history/concomitant medications</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>√*</td>
<td>√*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instruction for handling of Investigational product(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filled in EQ-5D</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>X-ray (CT)</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events (AE &amp; SAE)</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Study end</td>
<td></td>
<td></td>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>

*Randomization can be done at, e.g., the screening visit or visit 1; adjust the table for the study.

5.3. Biological sampling procedures

5.3.1. Handling, storage, and destruction of biological samples
Specify sampling, sampling volumes, analytical methods (including information about method validation) and where the analyses will be performed. Check if the lab is accredited or which quality standards should be met for the chosen analysis.
Detailed sampling and handling procedures are described in a separate document.

5.3.2. Total volume of blood per study subject

Text suggestion: The total volume of blood taken from each subject during the study is maximum <<volume>> ml.

5.3.3. Biobank

If a sample is taken within the healthcare system for research purposes, it is covered by the Swedish Biobank Act, see exemptions below.

From 1 January 2019, an exemption was introduced for samples that are taken for research and will not be saved in the biobank: The Swedish Biobank Act is not applicable to samples which are intended for research and which are analyzed within six months after sampling date and destroyed immediately after analysis. Both conditions must be met. For more information see link (in Swedish): http://biobanksverige.se/forandring-i-biobankslagen-januari-2019/.

Researchers who are uncertain about whether a sample in the study is covered by the exemption rule are advised to contact the region’s biobank coordinator or a regional biobank center for advice.

Text suggestion: All samples taken in this study are registered in a biobank at <<Name of biobank>> and handled according to the current biobank laws and regulations. The samples are coded/pseudonymized to protect the study participants’ identification. All samples and the identification/code list are stored securely and separately to prevent unauthorized persons from having access to them.

5.4. End of Study

Define criteria for the trial’s end (usually the last study participant’s last visit: Definition of end of trial – Last Subject Last Visit – LSLV).

If treatment of the study participants who completed the study differs from normal clinical practice, this should be stated. This can for example mean that the study participants should receive the investigational product after the study ends – if so, describe how this will be done.

See also section 6.4, Withdrawal criteria, and section 15, Notification of study completion, reporting, and publication.

Text suggestion:

The study ends when the last study participant has completed the last follow-up.

The study may be prematurely terminated if it appears that the treatment involved a large number of undesirable serious events or if recruitment of study participants cannot be met within reasonable time limits. If the study is prematurely terminated or suspended, the investigator should immediately inform the study participants about this and ensure
appropriate treatment and follow-up. The regulatory authority should be informed as soon as possible, but no later than within 15 days.

Decisions on premature termination are taken by the sponsor.

6. Subject selection

6.1. Inclusion criteria

Only pre-defined inclusion, exclusion, and withdrawal criteria can be used in the study. Inclusion criteria often include: signed informed consent, age, disease, symptoms, possibly requirements for negative pregnancy test, contraception use during the study. If fertile women are to be included, see document, “Antikonception - behandlingsrekommendationer” (in Swedish), on the Swedish Medical Product Agency’s website.

Note that all inclusion criteria are written so that they can be answered with a “Yes”.

Text suggestion: To be included in the study, subjects must meet the following criteria:

- The subject has given written consent to participate in the study.
- For female participants, adequate contraception should be used, specify. A negative pregnancy test can possibly be a requirement, specify requirement/type of pregnancy test. Contraceptive requirements may also apply to male participants.

6.2. Exclusion criteria

State the criteria that the subject must not meet in order to be included in the study, regarding the subject’s safety or something that may interfere with the study results.

Check that all contraindications for the investigational product in the SPC are included.

The following exclusion criteria are commonly included in studies:

- Contraindications
- Concomitant medications
- Known or suspected allergies against any product included in the study
- Pregnancy, breastfeeding, or planned pregnancy
- Mental inability, reluctance or language difficulties that result in difficulty understanding the meaning of study participation
- Treatment or disease which, according to the investigator, can affect treatment or study results.
- Participation or recent participation in a clinical study with an investigational product (specify how recently, usually 30 days). Previous participation in this study.

Text suggestion: Subjects must not be included in the study if any of the following criteria are met:

- ..
6.3. Screening

Describe the process for screening and inclusion. Also provide information about whether and when re-screening is allowed.

Text suggestion: Subject eligibility (that subjects fulfill all inclusion criteria and do not meet any exclusion criteria) is established before inclusion, treatment, or randomization.

6.4. Withdrawal criteria

Specify criteria for when and how subjects can be prematurely taken out of the study.

- The study subject may choose to discontinue the study at any time
- The principal investigator or safety committee can terminate a subject’s participation (due to, e.g., non-tolerable adverse events/adverse reaction, pregnancy, etc)
- A concerned Competent Authority can terminate the study.

Describe the care of study subjects who prematurely discontinue the study (e.g., continued treatment, examinations).

Describe how data will be handled for subjects who discontinue the study prematurely. Specify if a closing visit will be done or if other follow-up is planned (e.g., overall survival).

It should also be clarified whether a subject who has discontinued the trial will/can be replaced to achieve the desired number of included subjects and if so, in which case/how this will be done.

If an exclusion criterion applies throughout the study, this should also be stated.

See also section 5.4, End of Study, and section 15, Notification of study completion, reporting, and publication.

Example text:
Subjects can discontinue their participation in the study at any time without any consequence to his/her continued treatment. The investigator/sponsor can at any time terminate the study for a subject due to, e.g., unacceptable adverse events/adverse reactions or because the subject does not follow procedures in the study protocol. If the subject discontinues the study, follow-up of this subject will be performed according to the clinic’s routine.

7. Study treatments

7.1. Description of investigational product(s)

Describe the investigational product(s) in detail. State the name, manufacturer, formulation, restrictions, treatment time with the drug, allowable treatment interruption, etc., for the investigational product and comparative treatments.
Indicate what is used as a control (standard treatment) or placebo.

Describe how the investigational product(s) are provided for the study: Are drugs used from the clinic’s shelf, ordered from the pharmacy, provided by the manufacturer, or prescribed?

7.2. Dose and administration

Describe rationale for the basis of the chosen dose, administration route, administration instructions (e.g., with food). Describe the situations where possible change of dose may be relevant, e.g., dose reduction due to adverse events/adverse reactions, temporary treatment interruption. Describe any dose titration. If any aids are used, describe this as well as information about CE marking.

7.3. Packaging, labelling, and handling of investigational products(s)

State how investigational product(s) are packaged, labelled, delivered, and stored. Describe the packaging, amount of medication per package and where the packaging takes place. Indicate how the investigational product is labelled for the clinical trial (attach an appendix with the labeling to the application).

Describe how the Investigational product(s) will be delivered and stored. List the conditions that must be maintained during transport and storage such as refrigeration/room temperature, light sensitivity, etc. Also describe how, e.g., temperature will be controlled.

7.4. Drug accountability and treatment compliance

Describe how traceability and accountability for investigational product(s) including placebo will be reported. State whether a drug accountability log will be used to follow the pathway of the study medication(s) during the study.

Describe how a subject’s treatment compliance will be controlled and defined, facilitated and documented (for example instructions, labeling, measurement of blood levels, whether the medication(s) is taken by the subject at home or is only administered by healthcare personnel, diary, home visits, etc.). Also describe how missed doses will be handled and consequences of low compliance.

7.5. Randomization

Describe in detail how randomization will be performed and how subjects receive a randomization number. Also include information according to the example text below.

Text suggestion: Subjects are included/randomized consecutively as they are found to be eligible for inclusion in the study. If a subject discontinues their study participation, their subject code will not be reused and the subject will not be allowed to re-enter the study again.

7.6. Blinding

Describe the process for blinding. If the study is not a blinded study, this section can be removed.
7.7. Code breaking

The protocol must describe how the code is broken in emergency situations and who should be informed in connection with this. Describe how, possible, code break envelopes are stored and who will have access to this as well as how these persons can be reached in case of an emergency.

If an electronic system is used, it must be clear how to break the code if the system does not work.

If this is not relevant, remove this section.

Text suggestion: The list for breaking the code can be found...

7.8. Concomitant medications

Medications that are routinely given to subjects, but are not study treatments, should be listed. These can include medicinal products used for background treatment, challenge agents, diagnostics and other substances used to measure outcomes. List also possible “rescue medications”, that is, if the study treatment does not have a sufficient effect in the given dose, what are subjects given then?

Motivate and describe permitted and non-permitted treatments and drug use before study start, during the study, and after study end. Make an assessment if something should be stated as an exclusion criterion and added to section 6.2, Exclusion criteria.

Specify what should be documented in the CRF regarding other concomitant medications (name, dose, start and stop date, indication, etc.). The text suggestion below can be a part of the text in this section.

Text suggestion: Medications that are considered necessary for the safety and well-being of the subject can be given at the discretion of the investigator, unless otherwise specified as an exclusion criterion. Concomitant medications should be reported in the Case Report Form (CRF).

7.9. Destruction

Describe routines for how investigational product(s) shall be destroyed (if applicable).

7.10. Treatment after study end

Describe any continued treatment of subjects after the study end, e.g., advice, if the subject returns to previous treatments, if the subject receives no further treatment, if the subject continues treatment with the investigational product (note that this may require approval by the Swedish Medical Products Agency and/or the Swedish Ethical Review Authority).
8. Assessment of efficacy and safety

8.1. Assessment of clinical efficacy

This section describes measurements and variables associated with primary and secondary objectives to demonstrate the effect of treatment through, e.g., different types of analyses and measurements such as X-ray, analysis of blood samples, measurements of tumor size, and questionnaires. Describe methods as well as approaches to sample collection and when the different measurements will be performed. State where any analyses will be performed. State whether biological material will be stored in the biobank and routines for this. See also section 5.3.3, Biobank.

8.1.1. Primary variable

Describe the primary variable as precisely as possible. Include information about how the primary variable will be measured; type of sample, method used, and responsible laboratory. State whether the analysis will be performed continuously during the study or after completion of subject enrollment.

8.1.2. Secondary variable(s)

Describe the secondary variable(s) as precisely as possible. Include information about how the secondary variable(s) will be measured; type of sample, method used, and responsible laboratory. State whether the analysis will be performed continuously during the study or after completion of subject enrollment.

8.2. Assessment of clinical safety

Describe the safety variable(s) as precisely as possible. Include information about how the safety variable(s) will be measured; type of sample, method used, and responsible laboratory. State whether the analysis will be performed continuously during the study or after completion of subject enrollment.

Describe any measures for handling deviations in section 9.3, Reporting and registration of adverse events.

9. Handling of Adverse Events

Explain which adverse events (AE) and serious adverse events (SAE) will be reported during the study (compare with the Investigator’s Brochure for non-approved investigational products or SPC for approved medications). Carefully consider what shall be reported, what shall not be reported and under which time period of the study that AE/SAE shall be reported. If the disease itself causes certain symptoms, hospitalization, etc, these conditions can be given as examples of what shall not be reported as an incident (AE, SAE, or SUSAR).
AE and SAE are followed up until they are fully evaluated or no longer considered clinically non-significant by the principal investigator (described in section 9.2.1, Assessment of causal relationship, and section 9.4, Follow-up of Adverse). Note that persistent adverse events are classified as serious.

9.1. Definitions

9.1.1. Adverse Event (AE)
Adverse event (AE): Any untoward medical occurrence in a clinical investigation subject administered a medicinal product and, which does not necessarily have a causal relationship with the treatment, can be an unfavorable and unintended sign (including an abnormal laboratory discovery), symptom or disease temporally associated with the use of the medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

9.1.2. Adverse Drug Reaction (ADR)
Keep relevant selections and delete other sections.

In the pre-approval clinical experience with a new medicinal product or new use of a medicinal product, and particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to the medicinal product related to any dose should be considered adverse drug reaction (ADR). The phrase “response” to a medicinal product means that the causal relationship between the medical product and an adverse event is at least a reasonable possibility, that is the relationship cannot be ruled out.

9.1.3. Serious Adverse Event (SAE)
Serious adverse event (SAE): Any untoward medical occurrence that at any dose:
- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- results in a congenital anomaly/malformation

Medical and scientific assessment will be made to determine if an event is “serious” and whether it would prompt reporting in other situations, for example important medical events that may not be directly life-threatening or result in death or hospitalization but may compromise the study subject or may require intervention to prevent one of the other results set forth in the definitions above. These should also normally be considered as SAEs.

9.1.4. Suspected Unexpected Serious Adverse Reaction (SUSAR)
SUSAR: A reaction/event that is unexpected, serious, and suspected to be caused by the treatment, i.e. adverse events that are not included in the Investigator’s Brochure (IB) or SPC.
9.2. **Assessment of adverse events**

9.2.1. **Assessment of causal relationship**

The investigator is responsible for determining whether there is a causal relationship between the AE/SAE and use of the investigational product.

Those AEs which are suspected of having a relationship to the investigational product will be followed up until the study subject has recovered or is well taken care of and on their way to good recovery (see also section 9.4, Follow-up of Adverse).

All AE will be categorized either as likely related, possibly related, or not related, in accordance with the definitions below:

**Likely related**: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational product. It is unlikely that the event can be attributed to underlying disease or other medications, but is most likely caused by the investigational product and its emergence is reasonable in relationship with use of the investigational product.

**Possibly related**: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational product. The event could be explained by the investigational product and its emergence is reasonable in relationship with use of the investigational product, but there is insufficient information to determine the relationship. The event could be explained by an underlying disease or other medications.

**Not related**: Clinical event, including abnormal results from laboratory analyses, that is not reasonably related to the use of the intervention/investigational product. The event is unlikely related to the intervention/investigational product and can be explained by other medications or underlying disease.

9.2.2. **Assessment of severity**

*In addition to assessing the causal relationship between administration of the investigational product and side effect/AE, an assessment of the intensity (severity) of the event is required. The following classifications can be used:*

Each adverse event shall be classified by an investigator as mild, moderate or severe.

**Mild**: The adverse event is relatively tolerable and transient in nature but does not affect the study subject’s normal life.

**Moderate**: The adverse event causes deterioration of function but does not affect health. The event can be sufficiently unpleasant and interferes with normal activities but does not completely obstruct them.

**Severe**: The adverse event causes deterioration of function or work ability or poses a health risk to the study subject.
Assessment of severity is generally made by the reporting investigator.

Common Terminology Criteria for Adverse Event (CTCAE) is another way to classify severity according to a five-point scale.

9.3. Reporting and registration of adverse events

- Describe how incidents are obtained, e.g., that study subjects at each contact with the investigator/nurse will be asked about how they have been feeling since the previous visit or describe if another way is used to capture incidents in the study.
- Describe where AE/SAE are registered. Normally, they are registered primarily in the subject’s medical records. Describe how these will be included in the study’s CRF, reporting forms or worksheets, and where registrations of severity and relation is made, since it is not always done in the medical record.
- Describe also AEs which do not need to be documented and reported as AEs. If this is not indicated, all adverse medical events should be collected as AEs in, e.g., a diary or otherwise.
- Describe here during which time period incidents are intended to be followed, e.g., from study start or from start of treatment with the investigational product to XX weeks after the last dose.
- All reported incidents that have not been resolved by the end of the study should be followed up. How, when, and for how long this follow-up will last should be described, e.g., telephone contact or visit to the study site approximately XX weeks after the last visit in the study. The follow-up and the time for the follow-up visit/contact are adapted to each individual study.

- **Assessment of causal relationship (between AE/SAE and investigational product), whether the AE is considered to be an SAE or not, shall be done by a licensed physician.**

Text suggestion:

At each study visit, adverse events (AE) are registered, starting after study start/or from start of treatment with the investigational product, up to and including X weeks after the study subject has ended their treatment with the investigational product. All AE that occur during the study and which are observed by the investigator/study nurse or reported by the subject will be registered in the CRF regardless of whether they are related to the investigational product or not. Assessment of causal relationship, severity, and whether the AE is considered to be an SAE or not will be done by the investigator directly in CRF/on study-specific worksheet. At minimum, for each AE/SAE, a description of the event is recorded (diagnosis/symptom if diagnosis is missing), start and stop dates, causal relationship, severity, if the AE is considered to be an SAE or not, measures and outcome.

The following symptoms are clearly related to the process and the expected course of condition and therefore will not be reported as AE:
Example:

Expected adverse events based on knowledge of the disease in question and expected clinical course.

9.3.1. Reporting of adverse events (AE)

Text suggestion: All AE shall be registered in the CRF within <<indicate time frame>> as above (section 9.3).

9.3.2. Reporting of serious adverse events (SAE)

Text suggestion: Serious adverse events (SAE) are reported to the sponsor on a special SAE form within 24 hours of the investigator being informed of the SAE.

Follow-up information describing the outcome and handling of the SAE is reported as soon as this information is available. The original should be kept in the Investigator Site File.

Provide details about the reporting procedure for SAE. Include reporting times, what will happen upon receipt of an SAE, who will review what is reported and who will assess whether the adverse event was expected for the investigational product or not (this is done using the reference safety information). The processes for receiving, confirming, and reviewing of reported SAEs should be described. Reviewing of SAEs must occur in due time, with consideration of the reporting times for a potential SUSAR.

Add information about SAEs that should not be reported.

Text suggestion: Based on knowledge of the disease in question and expected clinical course, some events that are otherwise serious are not considered as SAEs in this study. The following is a list of SAEs that shall not be reported as SAEs:

Example:

• Expected events based on the knowledge of the disease in question and expected clinical course.
• If a study subject is hospitalized with a documented cancer-related problem, this will not be reported as an SAE.

9.3.3. Reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR)

Text suggestion: Those SAE which are assessed by sponsor to be SUSAR are reported via a CIOMS form to the European Medicines Agency (EudraVigilance database) according to the specified time frames.

In investigator-initiated studies where non-commercial sponsors lack another possibility to report directly in the EudraVigilance database, the Swedish Medical Products Agency can help with this when a SUSAR occurs in Sweden. However this must be clearly justified in the application. Reporting then takes place via the CIOMS form which is sent to the Medical Products Agency via Eudralink or mail. Since these reports contain personal data, they should not be sent to the Swedish Medical Products Agency via normal email. SUSARs
should, if possible, be reported unblinded, that is, should state to which investigational product the subject had a reaction. Placebo should only be reported if it is suspected that any component of the placebo treatment has caused the reaction.

Note that information to EPM about SUSAR and annual safety reporting are requirements according to the Swedish Medical Product Agency’s statutes (in Swedish: Läkemedelsverket författningssamling, LVFS) but not EPM.

Text suggestion: SUSAR that are fatal or life-threatening are reported as soon as possible and no later than 7 days after the incident has become known to the sponsor. Relevant follow-up information is sent thereafter within an additional 8 days. Other SUSAR are reported as soon as possible and no later than 15 days after they have come to the sponsor’s knowledge.

Multi-center studies: Information about SUSAR occurring during the study is compiled by the sponsor and sent out to the principal investigator at all participating centers. In order to preserve the integrity of the study, it is recommended that reporting of SUSAR to investigators in a blinded study is done without unblinding, that is, without specifying which investigational product the study subject received. Describe how the reporting will be done.

9.4. Follow-up of Adverse Events

Describe the follow-up of study subjects who have been affected by adverse events (until the adverse event is resolved/stable/persistent), measures in case of unacceptable adverse events (dose adjustment, treatment interruption, withdrawal of subject from the study). Describe follow-up of subjects with regards to safety after the study is completed.

9.5. Independent Data Monitoring Committee

If the clinical study involves an extended risk or when the study is performed during a long time period and is divided into different blinded treatment groups, an external independent data monitoring committee should evaluate the decoded results (independent of the sponsor and investigator).

Remove this section if not applicable.

9.6. Annual Safety Report (Development Safety Update Report, DSUR)

As long as the study is in process in Sweden, the sponsor is obliged to submit an annual safety report to the Swedish Medical Products Agency. It defines for which time period the report applies and a list of all SAE that have occurred as well as possibly SUSAR. A summary assessment of the safety situation for the study subjects and a risk/benefit evaluation for the study must also be described.

Note that information to EPM about SUSAR and annual safety reporting are requirements according to LVFS but not EPM.
9.7. Procedures in case of emergencies, overdose or pregnancy

If a study subject who participates in a clinical trial for investigational products becomes pregnant, this person must be followed up until the birth has taken place. If the fetus/child has any congenital malformation, this must be reported as a serious adverse event (SAE).

Remove this section if not applicable.

9.8. Reference Safety Information

Describe the adverse events, both type and frequency, that can be expected of the investigational product, as well as which precautions that will be taken. Specify the document (SPC, IB or Investigational Medicinal Product Dossier (IMPD)) that is to be used for Reference Safety Information regarding assessment of whether an adverse event/incident is expected or not.

10. Statistics

This statistics section provides general guidelines, i.e. everything is not applicable to all studies. It is not necessary to use all sub-sections and some sub-sections can be deleted and/or new ones added.

10.1. Analysis population

- Define the study subjects that will be included in the analyses; e.g., state if the analyses will be applicable to intention-to-treat (ITT) or per protocol (PP).
- Specify whether sensitivity analyses of the main analyses will be performed, i.e. examining the sensitivity of an ITT analysis with help of a complementary PP analysis.

10.2. Statistical analyses

10.2.1. Statistical methods

- Provide a general description of the descriptive/summary statistics.
- Describe the statistical methods that will be used to answer the primary and secondary objectives, and clarify the underlying statistical models. State which covariates (and any stratifications) will be adjusted for in the analyses. Any subgroup analyses must be specified.
- State any transformations of variables and justification for this.
- State how the study results will be reported, e.g., a relative treatment effect with associated 95% confidence interval and p-value.
- State if one- or two-sided tests of statistical significance will be used. Justify the use of one-sided tests in particular.
- If hypothesis testing is not appropriate, an alternative process for arriving at statistical conclusions should be provided.
10.2.2. Drop-outs

- Specify how drop-outs and missing values will be handled. For planned imputation of missing values, the method for this must be stated.
- State how any deviations from the original statistical analysis plan will be reported.

10.3. Adjustment of significance and confidence interval

- Indicate possible tests for multiple comparisons. Adjustment should always be considered for multiple primary outcomes. Specify details of any adjustment procedures or provide an explanation for why justification is not considered necessary.

10.4. Sample size calculations

- State the total number of subjects needed for the study. Sample size calculations should be performed for all primary outcome variables (in the case of several). In the case of multi-center studies, the number of subjects at each center should be stated.
- State and motivate the effect size (e.g., group differences, standard deviations) that the sample size calculation builds, usually the smallest clinically relevant effect.
- Specify in detail the assumptions on which the sample size is based. Specify in particular:
  - method by which the sample size is calculated
  - significance level
  - desired power
  - compensation for expected drop-outs
  - handling of any corrections for multiple comparisons

10.5. Interim analysis (if relevant)

- A description of the statistical methods to be applied.
- Time points for interim analyses.
- Criteria for study termination.
- Potential need for recalculation of sample size.

11. Quality Control and Quality Assurance

In a clinical trial for investigational products it is the sponsor’s role to be responsible for Quality Control (monitoring) and Quality Assurance (auditing). An independent review (monitoring) should be carried out for all clinical trial for investigational products. The sponsor is responsible for appointing a monitor and for the quality of a clinical trial for investigational products throughout the study; design, conduct, data collection, evaluation, reporting, and archiving. Methods used should be proportionate to the study’s risks.

11.1. Quality Assurance and Sponsor oversight

In this section, describe which quality assurance systems the study will have to ensure and control the quality as well as the sponsor’s methods for having oversight of the study’s
quality. For example, communication plan, training of study personnel, working manuals, meetings, central/local monitoring, audits, etc.

The sponsor’s quality-related work must be based on a risk analysis of the study as a whole: design, conduct, data collection, evaluation, reporting and archiving.

To enable monitoring and auditing, the protocol or other written agreement must specify that the investigators allow study-related monitoring, auditing, and regulatory inspections by providing direct access to the CRF, medical record, as well as other source data and other study-specific documentation. Similarly, this also must be apparent to the subjects in the Subject Information and Informed Consent form.

The sponsor is responsible for the study’s monitoring plan, which should be based on the identified risks, as well as follow-up of risks during the study and timeliness of the monitoring plan.

11.2. Monitoring

In order to fulfill LVFS regulations and ICH GCP, an independent monitor shall ensure the subjects’ safety and integrity as well as check that the subjects’ study data is reliable and of high quality.

Briefly describe how the independent review will be performed before, during, and after the study. Details are advantageously described in a separate monitoring plan.

Describe which levels of quality control can be applied, e.g., what is monitored centrally and what is monitored on site. Consider above.

Describe generally here how deviations from the protocol or regulations that occur at the site will be documented and handled (significant deviations should be reported in the final report to the authorities). Details shall be described in a separate monitoring plan.

The minimum for quality control is that the following can be checked:

- That subjects exist
- That informed consent has been signed prior to execution of any study-specific actions
- That the study’s main parameters and safety reporting are handled correctly

Other tasks for a monitor also include verifying that the trial’s essential documents are complete (according to chapter 8, ICH-GCP (E6(R2)).

Text suggestion: The study will be monitored by an independent monitor before the study begins, during the study conduct, and after the study has been completed, so as to ensure that the study is carried out according to the protocol and that data is collected, documented, and reported according to ICH-GCP and applicable ethical and regulatory requirements. Monitoring is performed as per the study’s monitoring plan and is intended to ensure that the subject’s rights, safety, and well-being are met as well as data in the CRF are complete, correct, and consistent with the source data.
11.3. Source data

Refer to, and indicate in the site-specific source data location list, which documents are used as source data for each variable. Also describe that the monitor has access to medical records and source data after secrecy agreements have been signed by the responsible party at the site as well as by the monitor. Subjects have provided consent by signing the Subject Information and Informed Consent form where this is specified.

Text suggestion: The investigator must keep source documents for each subject in the study. A document describing what has been classified as source data in the study should be included in the Investigator Site File (ISF). The investigator must ensure that all source documents are accessible for monitoring and other quality control activities.

Source data is defined before study start at each individual site. The CRF can be defined as source data in cases where data is not registered elsewhere, e.g., inclusion and exclusion criteria. In such cases, data is registered directly in the CRF.

11.4. Deviations or serious breaches

The protocol should also describe how deviations or serious breaches from the study protocol, GCP and other regulations, which directly affect, or with high likelihood could affect, the safety of study subjects or the study’s scientific value, shall be notified in writing as soon as possible to the Medical Products Agency (MPA, Läkemedelsverket). See also section 13, Substantial changes to the study.

Text suggestion: Serious breaches and deviations from the study protocol, GCP and other regulations that significantly and directly affects, or with high likelihood could affect, the subjects in Sweden or the scientific value of the study, shall be immediately reported within 7 days (from knowledge) to the Swedish Medical Products Agency (MPA). It is the sponsor’s responsibility to judge the consequences of deviations that have occurred, and thus also to decide whether the MPA should be informed.

Text suggestion: Minor deviations that do not affect subjects’ integrity or safety, nor significantly affect the study’s scientific value, are documented in the study documentation of the principal investigator and the sponsor.

11.5. Audits and inspections

Text suggestion: Authorized representatives for the sponsor and Competent Authorities (CA) may carry out audits or inspections at the study site, including source data verification. The investigator must ensure that all source documents are available for audits and inspections. The purpose of an audit or inspection is to systematically and independently review all study-related activities and documents, so as to determine whether these activities were performed, registered, analyzed and reported correctly according to protocol, Good Clinical Practice (GCP) and applicable regulations.
12. Ethics

12.1. Compliance to the protocol, GCP and regulations

*Text suggestion:* The study will be performed in accordance with the study protocol, ICH-GCP E6 (R2), the latest version of the Declaration of Helsinki and applicable regulatory requirements. This is to ensure the safety and integrity of the study subjects as well as the quality of the data collected.

12.2. Ethical review of the study

The final study protocol, including the final versions of the informed consent form and other information provided to subjects, must first be approved or given a written positive opinion by the Swedish Ethical Review Authority. The Swedish Ethical Review Authority must be informed of any changes in the study protocol in accordance with applicable requirements, see further information at the Swedish Ethical Review Authority’s website (in Swedish, https://etikprovning.se/for-forskare/andringsansokan).

*Text suggestion:* The final study protocol, including the final versions of the informed consent form and other information provided to subjects, must first be approved or given a written positive opinion by the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM). The EPM must be informed of any changes in the study protocol in accordance with applicable requirements. See also section 13, Substantial changes to the study.

12.3. Procedure for obtaining informed consent

Describe the procedure for how information is given to study subjects and how consent is obtained. Remember to adapt and describe the procedure based on whether the subject is a child. In studies where minors participate, the consent of both parents (legal representatives of the minor) must be obtained. See the EPM website for more information (in Swedish, https://etikprovning.se/for-forskare/vad-sager-lagen/).

The principal investigator (or the person to whom the task has been delegated) must provide both oral and written information to the intended subject regarding what participation in the study entails. Keep in mind that in a clinical trial for investigational products, informed consent must be obtained by a qualified physician.

A copy of the subject information as well as the signed informed consent form shall be provided to the subject.

If subject information changes during the study execution, the subject has the right to once again take a position on whether he/she would like to continue their participation. This by allowing the subject to sign a revised subject information and informed consent form.

*Text suggestion:* The principal investigator at each site shall ensure that the subject is given full and adequate oral and written information about the study, its purpose, any risks and benefits as well as inclusion and exclusion criteria. Subjects must also be informed that they are free to discontinue their participation in the study at any time without having to provide a
reason. Subjects should be given the opportunity to ask questions and be allowed time to consider the provided information. If the person chooses to participate, both the subject and the investigator shall sign the informed consent form. A copy of the subject information as well as the informed consent form shall be provided to the subject. The subject’s signed and dated informed consent must be obtained before performing any study-specific activity in the study. Each subject who participated in the study will be identified by a subject number on a subject identification list. The subject agrees that monitors and inspectors may have access to their medical records. If new information is added to the study, the subject has the right to reconsider whether he/she will continue their participation.

12.4. Data protection

The General Data Protection Regulation (GDPR) has strengthened the data subject’s rights and given increased responsibility to those responsible for data collection. This means that when collecting research data, it is necessary to decide whether the data collection is legal, correct, appropriate, that integrity and confidentiality are considered and that no more information than necessary is collected, as well as that no more persons than necessary have access to the data. There should be a legal basis for data collection, which for research is for general interest.

The personal data controller is obliged to take measures to ensure that the regulation is followed, describe built-in data protection features and security when processing and report personal data breaches.

Text suggestion: If any part of the data is handled by any other organization, inside or outside the EU, appropriate agreements and/or other documentation will be established, to ensure that the data processing is performed in accordance with the provisions of the General Data Protection Regulation (GDPR) and other relevant legislation, before any data transfer takes place.

The content of the informed consent form complies with relevant integrity and data protection legislation. In the subject information and the informed consent form, the subject will be given complete information about how collection, use and publication of their study data will take place. The subject information and the informed consent form will explain how study data are stored to maintain confidentiality in accordance with national data legislation (please describe how data is stored and which data security measures are taken). All information processed by the sponsor will be pseudonymized and identified with <<Study code/Study ID/Initials>>.

The informed consent form will also explain that for verification of the data, authorized representatives of the sponsor, as well as relevant authority, may require access to parts of medical records or study records that are relevant to the study, including the subject’s medical history.
12.5. Insurances

Here it should be explained how subjects are insured through Swedish patient insurance as well as whether Swedish pharmaceutical insurance is valid for the investigational product(s). Alternatively, discuss with your organization if there are existing insurance policies.

Swedish Patient Insurance (Patientskadeförsäkring): The Swedish healthcare regions have signed a patient insurance with Landstingens Ömsesidiga Försäkringsbolag, Löf. Check what applies to medical research at www.lof.se.

Swedish Pharmaceutical Insurance (Läkemedelsförsäkring): All marketed investigational products do not automatically have a Swedish Pharmaceutical Insurance. It is easiest to check by looking up the investigational product in FASS, where it is shown whether an insurance is in place.

13. Substantial changes to the study

This section describes how to handle substantial changes in the study. Substantial changes in the study protocol must be approved by the Swedish Medical Products Agency (Läkemedelsverket) and/or the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM) before they are implemented. Use the form that is common throughout the EU (Substantial Amendment Notification Form). Mark the changed section with the “tracked changes” function so that is clear what is old and new text. What is meant by substantial changes is stated on a high level in LVFS 2011:19, chapter 7, 2 § (in Swedish). More detailed guidance on which types of changes are considered substantial can be found in Chapter 3 of the EU Commission’s guidelines (CT-1).

Text suggestion: Substantial changes to the signed study protocol are only possible through approved protocol amendments and by agreement from all responsible persons. Information on non-substantial changes should be clearly noted in the amended protocol.

In the event that substantial changes to the protocol (e.g., changing of the main objective, primary or secondary variables, method to measure the primary variable, changing of the investigational product or dosage) will be made during the course of the study, approval from the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM) as well as the Swedish Medical Products Agency (Läkemedelsverket) shall be obtained before any changes are implemented. A change that concerns a new site, new investigator or a new study patient information sheet shall only be approved by EPM.

Non-substantial changes will be recorded and later entered in documentation that is submitted, for example in any subsequent notifications of a substantial change or in connection with End of Trial reporting.

The investigator must not make any deviation from or change of the protocol, except which necessary to eliminate an immediate risk to the study subjects, or where the changes only include logistical or administrative aspects of the study (e.g., change of telephone number). Other deviations/changes besides the above mentioned required agreement with the
sponsor and documented approval/favorable opinion regarding the amendment from relevant authorities. See also section 11.4, Deviations and serious breaches.

14. Collection, handling, and archiving data

It must be clear from the protocol in what way the source data will be collected. Describe which other types of data collection documents, in addition to the CRF, are used, e.g.: diaries, quality of life questionnaires, health economics, different patient-reported outcomes scales, etc. Describe how corrections will occur and by whom, that there will be an independent copy of the CRF with the investigator when the study is completed, how other study source documentation is stored and who has access to it. Documents must be stored for at least 10 years after study has been completed according to current Swedish law (chapter 10 in LVFS 2011:19) (note that after implementation of the new EU regulation 536/2014, this period will be increased to 25 years). If the clinical study is included in a marketing application, documents must be archived for longer than 10 years. The sponsor and investigator can also agree that the documents shall be archived for longer than 10 years. The Swedish Archives Act (Arkivlagen) applies to archiving of research material.

The sponsor shall have a Trial Master File with documentation for the whole study. The principal investigator shall have an Investigator Site File with all study documentation for the study site. The files should have relevant content according to the study and follow ICH-GCP chapter 8 “Essential documents”. The principal investigator will store the study site’s study data, subject identification list, original of study patient information sheet and obtained study consent inaccessible to unauthorized persons, but such that study subjects can be identified by those responsible for the study. This information may not be provided to the sponsor.

For information about data protection see section 12.4, Data protection.

Text suggestion:

Subjects who participate in the study are coded with a specific study identification number. All subjects are registered in a subject identification list (subject enrolment and identification list) that connects the subject’s name and personal number with a study identification number.

All data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification. The complete Trial Master File, as well as source documents, will be archived for at least xx years after the study is completed. Source data in the medical records system is stored and archived in accordance with the respective hospital regulations.

14.1. Case Report Form (Forskningspersonsformulär)

Text suggestion:

A Case Report Form (CRF) is used for data collection. Describe which type of CRF will be used (eCRF or paper CRF). The investigator must ensure that data is registered and any corrections in the CRF are made as stated in the study protocol and in accordance with the
instructions. The investigator must ensure that the registered data is correct, complete, and that reporting takes place according to the timelines that have been predefined and agreed. The investigator signs the completed CRF. A copy of the completed CRF will be archived at the study site.

If an examination/test is not performed and data does not exist, ND (Not done) or NK (Not known) is marked. If the question is irrelevant NA (Not applicable) is written. Corrections in the paper CRF are done by striking out the incorrect information, and adding the correct information next to the incorrect information, signing, and dating the correction.

15. Notification of study completion, reporting, and publication

The study results regarding both efficacy and safety shall be reported to the EudraCT database by the sponsor at latest 12 months after study completion (6 months if children participate in the study). A complete report with individual data shall be available from the sponsor on request or for any inspections by the Swedish Medical Products Agency throughout the entire retention period. A published article is not to be equated with a summary of a report. The report must contain sufficient information so that the Swedish Medical Products Agency can make an evaluation.

The sponsor is responsible for the compilation of statistical analyses and their presentation to involved investigators. These analyses form a part of the final report and may be the basis for a manuscript for publication.

If the results are summarized in a manuscript with the purpose to publish in a scientific journal, it is recommended that the study’s EudraCT number is stated in the abstract. This clearly documents that the study has been published in advance and meets the requirements from ICMJE (International Committee for Medical Journal Editors) that are set for publications in medical science journals.

See also section 5.4, End of Study, as well as section 6.4, Withdrawal criteria.

If the study is prematurely terminated, the form “Declaration of End of Trial Notification” should only be used if the reason concerns the study’s safety. In other cases, it is sufficient that the authorities are informed. If the sponsor terminates an ongoing study, the concerned authorities must be informed as soon as possible, but no later than within 15 days.

Text suggestion:
The Swedish Medical Products Agency shall be informed of the study’s completion at latest 90 days after study end, through submission of a “Declaration of End of Trial Notification” form.

Within one year (6 months for studies involving children) after the study is completed, the results shall be analyzed, a clinical study report with individual data shall be prepared, and the study results shall also be reported in the EudraCT database.
16. References

Literature referenced in the text is listed here. The list should be built up in the order in which it is referred to in the protocol. For example, the Vancouver system can be used.

17. Attachments

For example, validated self-report scales, questionnaires, diaries, etc. All attachments should have a version number and be dated.