**

**Mall Prövningsprotokoll engelska**

Klinisk läkemedelsprövning CTR

**Detta dokument är framtaget och kvalitetssäkrat av Kliniska Studier Sverige.**

Vi utvecklar och erbjuder stöd för kliniska studier i hälso- och sjukvården.

Stödet vi erbjuder ger goda förutsättningar för kliniska studier av hög kvalitet.

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## About the Clinical Trial Protocol template for medicinal products

Clinical trial protocol template was first published 2022-02-03. This is CTR version 2, 2023-03-08 of this document.

This template is adapted to meet the requirements of the new EU Regulation on clinical trials of medicinal products for human use (EU 536/2014) when the application is made via the EU common portal CTIS (Clinical Trials Information System).

The EU Regulation on clinical trials of medicinal products for human use (EU 536/2014) is also called CTR (Clinical Trials Regulation) in this template.

This version is updated in accordance with comments from Medical Product Agency and a section on radiation dose information has also been added to the template.

## Responsible for the template

Clinical Studies Sweden (Kliniska Studier Sverige) is responsible for the template. Suggestions for improvement of this template can be sent to any of the email addresses provided below.

* Gothia Forum: gothiaforum@vgregion.se
* Forum Norr: forumnorr@regionvasterbotten.se
* Forum Mellansverige: forummellansverige-ucr@uu.se
* Forum Sydost: forumo@regionostergotland.se
* Forum Stockholm-Gotland: feasibility.karolinska@sll.se
* Forum Söder: forumsoder@skane.se

## Instruction for the author of the protocol

The two first pages are not included in the Clinical Trial Protocol (CTP) template but gives a short introduction to you who will write a CTP. These pages should be removed when using this template. The CTP template is primarily directed towards intervention studies (clinical trials) and is based on the requirements of the EU- common Regulation 536/2014 and ICH-GCP. Visit the website of the Swedish Medical Products Agency (Läkemedelsverket) for more [information about the EU-common Regulation 536/2014](https://www.lakemedelsverket.se/sv/tillstand-godkannande-och-kontroll/klinisk-provning/lakemedel-for-manniskor%22%20%5Cl%20%22hmainbody1).

This template is not adapted to address clinical trials for medical devices. Visit the website of the Swedish Medical Products Agency (Läkemedelsverket) ([Link](https://www.lakemedelsverket.se/sv/medicinteknik/tillverka/regelverk)). There is a separate template ([Clinical Investigation Plan](https://www.kliniskastudier.se/forskningsstod-och-radgivning/mallar-och-stoddokument/kliniska-provningar-medicintekniska-produkter)).

For a clinical trial to receive the necessary approval to be conducted, the benefits of the trial must outweigh the risks, the safety of the subjects must take precedence over all other interests, and the trial must be designed to generate reliable and robust data. This must be clearly described in the protocol.

This CTP template is a supportive document to facilitate your work. It is not always required to use all sections of this template. Sections can be removed and/or new sections can be added. This applies also to subsections. The template should be adjusted so that it fits your trial. Note that if headings are removed, you must ensure that the requirements for what should be included in a CTP according to CTR and ICH-GCP are still met.

* On the first page of the CTP (including headings), <<Text>> should be replaced with trial-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 text suggestions that can be used are written in plain font/style.
* When the CTP is complete, update the table of contents.

The CTR defines certain clinical trials as so-called low-intervention clinical trials. These trials may be subject to less stringent rules, as described in the instruction text of the template under the relevant section.

A low-intervention clinical trial is a clinical trial where:

1. The investigational medicinal product, excluding placebo preparation, is approved,
2. It is clear from the clinical trial protocol that,
	1. the investigational medicinal product is used according to the terms in its marketing authorization, or
	2. use of the investigational medicinal product is evidence-based and supported by published scientific evidence of the safety and efficacy of this product (i.e. an established off-label praxis available) in one of the involved EU member states, and
3. the complementary diagnostic or monitoring procedures do not contribute more than minimally to the risk or burden to subject safety compared to normal clinical practice in any of the member states involved.

If you consider your clinical trial to be a low-intervention clinical trial, this should be stated and justified in the appropriate place in CTIS and clearly described and justified in the CTP and in the cover letter sent via CTIS when applying for authorisation of a clinical trial of a medicinal product.

The term co-ordinating investigator does not exist in CTR and is therefore not a requirement but the term appears in ICH-GCP and can be used.

Information about radiation doses may be described in the trial protocol if relevant.

The protocol should, if possible, be written in a searchable format rather than scanned images. The protocol can be written in Swedish or English. The protocol should describe the objectives, design, methodology, statistical considerations, aim and organisation of the trial.

## CLINICAL TRIAL PROTOCOL

**<<Title>>**

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

<<Short title/and if applicable Acronym>>

|  |  |
| --- | --- |
|  |  |
| Trial ID:  | << Trial code >>  |
| EU Trial number:  | << XXXX-XXXXXX-XX-XX >>  |
| Version number:  | << Version number *to be updated in case of changes* >>  |
| Date:  | << YYYY-MM-DD *to be updated in case of changes*>>  |
| Sponsor:  | << Name >>  |
| Co-sponsor: | << Name >> |
|  |  |
|  |  |

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## Description of changes in the trial protocol

|  |  |
| --- | --- |
| **Protocol version** | **Summary of changes***Describe all changes since the first final protocol.* |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

## Signature page

*If the sponsor and principal investigator are the same person, write ”Sponsor/Principal Investigator” on the first signature line then remove the other signature lines.*

*If the clinical trial has more than one sponsor, all sponsors should agree, for example, on the signing of the protocol by means of a written agreement setting out their respective obligations. For example, the sponsor responsible for the design of the protocol may be deemed as the most appropriate to sign the protocol. Protocol signatures are not required for clinical trial applications, but these should be in place for both the sponsor and principal investigators before the start of the trial in accordance with ICH-GCP E6(R2).*

*Text suggestion:*

**Sponsor**

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

Sponsor’s signature Date

Printed name

**Principal Investigator**

I have read this protocol and agree that it includes all essential information to be able to conduct the trial. By signing my name below, I agree to conduct the trial in compliance with this clinical trial protocol, the EU Regulation on clinical trials of medicinal products for human use (EU 536/2014), the Declaration of Helsinki, ICH-GCP (Good Clinical Practice) guidelines and the current national regulations governing the conduct of this clinical trial.

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

I am aware that quality control of this trial will be performed in the form of monitoring and eventual audit and inspection.

Principal Investigator’s signature Date

Printed name

## Contact information

*List the name, role in the trial, clinic/department, contact address, telephone number, and email for all involved in the trial (Sponsor, if applicable Co-sponsor, principal Investigators, clinical monitoring organization if appointed, etc.). Add rows if needed for the trial. Describe where the contact list for principal investigators is kept, if separately from the protocol If the information is not provided in the protocol.*

*Contact details must be provided for the sponsor; name and address and the name and responsibilities of the sponsor's representative and any co-sponsors authorised to sign the clinical trial protocol or any eventual amendments of this.*

*In order to avoid liability issues in clinical trials with multiple sponsors, all sponsors shall be subject to the liability of one sponsor (i.e. all sponsors have the same responsibility for the clinical trial) unless they otherwise agree in a written agreement.*

|  |  |
| --- | --- |
| **Responsibility in the clinical trial** |  |
| SponsorResponsibility:* X
* Y
 | <<Name, title>><<Site/Institution>><<Contact address>><<Telephone number>><<Email>> |
| Co-sponsorResponsibility:* X
* Y
 |  |
|  *Principal Investigators* |  |
| *Specify others involved:Clinical monitoring organization, laboratories, project management, statistics or data management.* |  |

## 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 trial; add and/or remove rows as needed.*

|  |  |
| --- | --- |
| **Abbreviation** | **Term/Explanation** |
| Adverse Event (AE) | Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment. |
| Serious Adverse Event (SAE) | Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death |
| AR | Adverse Reaction = any unfavorable and unexpected reaction to an investigational medicinal product, regardless of dose |
| ASR | Annual Safety Report = the annual safety report for reporting to authorities. In Sweden this is the Swedish Medical Products Agency via CTIS. |
| CRF | Case Report Form  |
| CTIS | Clinical Trials Information System = Centralized EU database/portal for application and communication with authorities concerning clinical trials. In Sweden this includes the Swedish Medical Products Agency and the Swedish Ethical Review Authority. |
| CTR | EU Regulation 536/2014, also called CTR, Clinical Trials Regulation |
| DSUR | Development Safety Update Report = the standard which should be used for annual safety reporting to authorities |
| GCP | Good Clinical Practice |
| IB | Investigator’s Brochure |
| ICH | International Council for Harmonization  |
| ITT | Intention-to-treat = including all data from all subjects who have participated in the trial |
| Läkemedelsverket | Swedish Medical Products Agency – the national authority responsible for regulation and surveillance of the development, manufacturing and sale of medicinal products.  |
| PP | Per Protocol analysis = including only data from subjects who have completed the trial completely in accordance with the protocol, with no deviations from the protocol  |
| RSI  | Reference safety information. A list of all known serious adverse reactions for the investigational medicinal product, including severity and frequency of the adverse reaction. The RSI is contained in the Summary of Product Characteristics or IB and is used to determine which adverse reactions should be reported as suspected unexpected serious adverse reactions (SUSARs). |
| SPC or SmPC | Summary of Product Characteristics |
| SUSAR | Suspected Unexpected Serious Adverse Reaction. This is an event that is likely related to the investigational medicinal product but with unexpected occurrence. An adverse reaction is unexpected if its nature or seriousness is not consistent with the information on the product in the RSI.  |

## Synopsis

*Brief summary of the trial including aim, primary and secondary objectives, trial design, investigational medicinal product, dose, route of administration, trial population, number of subjects, time plan for the trial.*

*Note: This is a summary, not an introduction.*

*The synopsis should be understandable to a layman, in Swedish or applicable local language and should be a maximum of two pages. The synopsis can be part of the protocol or a separate document (e.g. when different language versions are submitted) in CTIS. In case of different language versions, such as when the protocol is written in English, the synopsis in Swedish/local language should always be uploaded as a separate document in CTIS together with the protocol.*

*For more details on what is recommended to be included in the synopsis, see the European Commission's CTR Questions and Answers document (*[link](https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-10_en%22%20%5Cl%20%22set-of-documents-applicable-to-clinical-trials-that-will-be-authorised-under-regulation-eu-no-5362014-once-it-becomes-applicable)*), Chapter V, EudraLex - Volume 10 - Clinical trials guidelines), question 5.8.*

|  |  |
| --- | --- |
| EU Trial number: |  |
| Title: |  |
| Trial ID: |  |
| Short background/ Rationale/Aim: |  |
| Primary objective: |  |
| Secondary objectives: |  |
| Primary outcome:*Also describe time of the assessment* |  |
| Secondary outcome:*Also describe time of the assessment* |  |
| Trial design:*Describe the design and how long the subjects participate in the trial. E.g. double-blind placebo-controlled trial where subjects participate for x weeks* |  |
| Trial population:*E.g. patients with asthma 18-55 years old* |  |
| Number of subjects: |  |
| Inclusion criteria: |  |
| Exclusion criteria: |  |
| Intervention:*Describe interventions and length of treatment, including background treatment. Describe also trial-related diagnostic and monitoring procedures used* |  |
| Investigational medicinal product(s), dosage, administration: |  |
| Ethical considerations, benefit/risk: |  |
| Trial period: | *E.g. Q1 20XX – Q1 20XX* |

## Background and rationale

*Provide a summary of the background of the trial, including justification for why the proposed trial is relevant and/or necessary to perform. This should be stated in a scientific context that motivates the choice of objectives and expected outcomes of the trial. Describe which disease will be studied, current treatment strategies, and background to the trial including relevant references to scientific literature. Summarize results from previous relevant preclinical/clinical studies. Provide references to literature and data that are relevant to the clinical trial and provide background information to the clinical trial.*

*Also describe whether patients/ patient organisations were involved in the design of the clinical trial, and if so, describe their involvement.*

## Benefit-risk evaluation

*The benefits of the trial must be weighed against the risks to the subjects. A clinical trial may be conducted only if the anticipated benefit to the subject or to public health justifies the foreseeable risks and inconveniences, and compliance with this requirement is continuously monitored during the trial. This needs to be described in detail and is essential for the assessment of the application for approval of a clinical trial by the authorities.*

*Risks can be divided into those with causal relationship with the investigational medicinal products and those with causal relationship with trial-specific examinations. It could be an advantage to do a list/table of all expected and potential risks with a description of how each of the risks will be managed.*

*If an investigational medicinal 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 benefit-risk evaluation is positive for the trial. This section is an important source of information when authoring the Informed Consent Form (ICF).*

*Summarize the expected therapeutic benefit in terms of:*

* *the investigational medicinal product’s characteristics and knowledge about it*
* *for the subject as an individual*
* *for the group represented by the subject or public health benefit*

*Summarize the risks and inconveniences to subjects regarding:*

* *the investigational and auxiliary medicinal product’s characteristics and knowledge about them*
* *the characteristics of the intervention in relation to normal clinical practice, the safety measures, including provisions for risk minimisation measures, monitoring, safety reporting and safety plan, and the risk to subjects' health that the medical condition for which the investigational medicinal product is being investigated may pose*
* *subjects participating in clinical trials in an emergency situation - scientific justification is required such that participation in the clinical trial provides a direct clinically relevant benefit to the subject.*

*Check also that you describe:*

* *The measures taken to minimise sources of error, including, where appropriate, randomisation and blinding.*
* *Other expected benefits, e.g., health economics benefits.*
* *Risks that are associated with participation in this trial; trial-specific examinations and/or sampling not included in routine clinical practice. The risk of possible deterioration of the subjects' disease state in, e.g., placebo treatment should also be included.*
* *Expected adverse reactions. This includes both the investigational medicinal product and the comparator product.*
* *Possible interactions with concomitant medical treatments.*
* *Steps that will be taken to control or mitigate risks (i.e. close follow-up of subjects).*
* *Benefit-risk rationale, concluding that it is ethical to perform the trial and that the benefits justify the risks.*

## Trial objectives

*Objectives or purpose = describe why the trial is done and what you want to accomplish with the trial. Note that the connection should be clear between the objective, endpoint and method description for measurement of the outcome.*

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

*Describe which endpoint will measure these. Be sure that each endpoint is clearly defined. Use neutral words to describe the objectives. This section can have sub-sections such as “primary objective”, “secondary objective”, “primary endpoint”, and “secondary endpoints”. Briefly state these, while methods and questionnaires can be referred to under section 8.1, Methods for measurement of endpoints for clinical efficacy.*

### Primary objective

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

*Example of a primary objective: Is the antihypertensive effect of drug x better/worse/equivalent to the antihypertensive effect of drug y.*

*Text suggestion:* The primary objective of this trial is to…

### Secondary objective(s)

*Describe eventual 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 trial is to…

### Primary endpoint

*The method by which the primary endpoint is measured. The primary endpoint is described in more detail in section 8.1.1, Primary endpoint*

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

### Secondary endpoint

*Describe what will be measured for the secondary endpoints. Secondary endpoints are described in more detail in section 8.1.2, Secondary endpoints .*

## Trial design and procedures

### Overall trial design

*The trial should be designed so that the data obtained can answer the scientific questions.*

*A description of the trial design should include:*

* *Type of clinical trial (Phase I, human pharmacology; Phase II, therapeutic explorative; Phase III, therapeutic confirmative; Phase IV, therapeutic usage).*
* *The trial 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 a rationale for the chosen trial design. The rationale should be relevant for the trial’s objective and should also contribute to identification of relevant trial endpoint (variables).*
* *Describe how long a subject will participate in the trial. Also describe* *the sequence and duration of all periods in the clinical trial, including follow-up, if applicable.*
* *List which investigational medicinal product(s) is used in the trial as well as possible comparative treatments. Refer to section 7, Trial treatments, for more detailed information.*
* *A schematic diagram of the trial design, procedures, and steps; see provided example (Figure X).*
* *If the trial involves a decentralised process, this should be described in the protocol. More information about decentralised clinical trials is available on the website of the Swedish Medical Product Agency (Läkemedelsverket) ([link](https://www.lakemedelsverket.se/sv/tillstand-godkannande-och-kontroll/klinisk-provning/lakemedel-for-manniskor/decentraliserade-och-virtuella-kliniska-lakemedelsprovningar)).*



### Procedures and flow chart

*Describe all trial-related procedure(s) (e.g. ECG, sampling, examinations, AE reporting, etc) the subject undergoes during each visit. Include a table that summarizes the activities during each visit, see example in Table X.*

*Describe any pre-screening procedures planned for the trial.*

*Keep in mind that it must be a physician who checks the inclusion/exclusion criteria and obtains the informed consent.*

*Also define the visit window, i.e., how much a follow-up visit may vary in time.*

*Example table:*

*Table X* Flow chart

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Procedure | *Screening* *Day/Week x Inclusion visit* | *Visit 1**Baseline* | *Visit 2**Day/Week x (±10 days)* | *Visit 3**Day/Week x (±10 days)* |
| *Incl/exclusion criteria* | √ |  |  |  |
| *Informed consent*  | √ |  |  |  |
| *Medical history/ concomitant medications* | √ |  |  |  |
| *Randomization* | √\* | √\* |  |  |
| *Instructions for handling the medicinal product(s)* |  | √ |  |  |
| *Fill out EQ-5D* |  | √ | √ | √ |
| *X-ray (CT)* |  |  | √ | √ |
| *Adverse Events (AE & SAE)* |  | √ | √ | √ |
|  *End of Trial* |  |  |  | √ |
|  |  |  |  |  |

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

### Biological sampling procedures

*A description of the procedures to comply with the applicable rules for the collection, storage and future use of biological samples from subjects, if applicable, unless specified in a separate document.*

#### 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.*

#### Total volume of blood per subject

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

#### Biobank

*For information about the Swedish Biobank Act see [www.biobanksverige.se](http://www.biobanksverige.se).*

*Researchers may contact the region’s biobank coordinator or a regional biobank center for further advice.*

*According to CTR, a biobank application must be submitted to kliniskaprovningar@biobanksverige.se in parallel with the clinical trial application in CTIS. For more information see <https://biobanksverige.se/forskning/klinisk-provning/>*

*Text suggestion:* All samples taken in this trial 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 subject´s identity. All samples and the identification/code list are stored securely and separately to prevent access by unauthorized persons.

### End of Trial

*Provide a clear and unambiguous indication of what constitutes the end of the trial and, if it is not the date of the last visit of the last subject, a specification of the estimated end date of the trial.*

*If treatment of the subjects who completed the trial differs from normal clinical practice, this should be stated. This can, for example, mean that the trial subjects should receive the investigational medicinal product after the trial ends – if so, describe how this will be done (see section 7.10, Treatment after trial end).*

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

*If a clinical trial is suspended or terminated prematurely due to a change in the benefit/risk balance, for reasons of subject safety, this should be notified to the concerned Member States via CTIS. The notification should be made as soon as possible, but no later than 15 days after the clinical trial was suspended or terminated prematurely. The reasons for such action and follow-up measures should be provided. The resumption of a clinical trial after it has been temporarily suspended due to a change in the benefit/risk balance is considered to be a substantial modification.*

*Text suggestion:*

The trial ends when the last subject has completed the last follow-up (or if this is not relevant give the estimate completion date instead).

The trial may be prematurely terminated if it this is necessary for safety reasons affecting the risk-benefit balance or if the recruitment of subjects cannot be met within reasonable time limits. If the trial is prematurely terminated or suspended, the investigator should immediately inform the subjects about this and ensure appropriate treatment and follow-up. The Swedish Medical Products Agency should be informed as soon as possible via CTIS, but no later than 15 days after trial suspension.

Decisions on premature termination are taken by the sponsor.

## Subject selection

*A description of the groups and subgroups of subjects to be enrolled in the clinical trial, including, where applicable, groups of subjects with special needs (e.g. age, gender, healthy volunteers, subjects with rare diseases). A justification for the possible inclusion of subjects who are unable to give informed consent. A justification of the gender and age distribution of the subjects if a certain gender or age group is not enrolled or is underrepresented in the clinical trial, an explanation of the reasons and a justification of these exclusion criteria.*

### Inclusion criteria

*Only pre-defined inclusion, exclusion, and withdrawal criteria can be used in the trial. Inclusion criteria often include signed informed consent, age, disease, symptoms, possibly requirements for negative pregnancy test, contraception use during the trial. If fertile women are to be included, see information about,“[Antikonceptionsrekommendationer](https://www.lakemedelsverket.se/sv/tillstand-godkannande-och-kontroll/klinisk-provning/lakemedel-for-manniskor/antikonception-preventivmetoder)” (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 trial, subjects must meet all of the following criteria:

1. The subject has given their written consent to participate in the trial.
2. *For female subjects of fertile age, adequate contraception should be used, specify which methods. A negative pregnancy test can eventually be a requirement, specify requirement/type of pregnancy test. Contraceptive requirements may also apply to male subjects.*

### Exclusion criteria

*State the criteria that the subject cannot meet in order to be included in the trial, with respect to the subject’s safety or something that may interfere with the trial results.*

*Check that all contraindications for the investigational medicinal product in the SPC/IB are included.*

*The following exclusion criteria are commonly included in trials:*

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

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

1. ..
2. ..
3. ..

### Screening

*Describe the process for screening and inclusion. Indicate when the determination for the specific trial should be made (e.g. "before randomisation or treatment decision"), adapted to the inclusion criteria that need to be assessed (e.g. lab samples). 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 ...

### Withdrawal criteria

*Specify criteria for when and how subjects can/must be prematurely taken out of part of the trial or the complete trial.*

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

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

*Describe how data will be handled for subjects who discontinue the trial prematurely. Specify if a closing visit will be performed 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 trial, this should also be stated.*

*See also section 5.4, End of Trial, and section 15, Notification of trial completion, reporting, and publication.*

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

## Trial treatments

*The term investigational medicinal product includes medicinal products used as comparators (placebo or active medicinal product). The same requirements apply to comparator medicinal products as to the medicinal products under investigation. Comparator medicinal products should therefore be described in a similar way in this section, i.e. when the instruction text below states investigational medicinal products, the corresponding information also needs to be provided for any comparator medicinal products.*

### Description of investigational medicinal product(s)

*Describe all investigational medicinal product(s) in detail. State the name, manufacturer, formulation, restrictions, treatment time with the drug, allowable treatment interruption, etc.*

*Describe whether investigational medicinal products are authorised for sale and whether they are to be used in accordance with the terms of the marketing authorisation. If the investigational medicinal product is authorised but not used in accordance with the terms of the marketing authorisation (different indication, dose, duration of treatment, etc.), the protocol should include additional pre-clinical and clinical data relevant to the use of the investigational medicinal product in the trial.*

*In multicentre trials involving several EU countries and where the trade name of the medicinal product varies within the EU, only the active substance or ATC code should be provided.*

*Indicate what is used as a control/comparator (standard treatment) or placebo.*

*Describe how the investigational medicinal product(s) are provided and the responsibilities associated with it: Are drugs used from the clinic’s shelf, ordered from the pharmacy, provided by the manufacturer, or prescribed? Describe also the responsibilities associated with administration.*

### Dose and administration

*Describe rationale for the basis of the chosen dose, dosing regimen, administration route and method, administration instructions (e.g., with food) and the treatment period. 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 will be used, describe this as well as information about CE marking if this is a medical device.*

###  Packaging, labeling, and handling of investigational medicinal products(s)

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

*Describe how the investigational medicinal 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.*

*Labelling of investigational medicinal products and auxiliary medicinal products shall be in accordance with Chapter X, Articles 66 to 67, Annex VI, Sections A to D of the [CTR](https://eur-lex.europa.eu/legal-content/sv/ALL/?uri=CELEX:32014R0536).*

### Drug accountability and treatment compliance

*Describe how traceability for investigational medicinal product(s) including comparator medicinal products will be documented in e.g. medication log, etc.*

*There is a possibility of less stringent rules in terms of documentation of traceability for low-intervention clinical trials.*

*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.*

### 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 trial. If a subject discontinues their participation, the subject’s trial-specific code will not be reused and the subject will not be allowed to re-enter the trial again.

### Blinding

*Describe the process for blinding.*

### Code breaking

*The protocol must describe how the code is broken in emergency situations and who should be informed in connection with this. A clear definition of situations where the code may need to be broken helps prevent unnecessary unblinding. It is important that the code in emergency situations can be broken by the investigator, or by the treating physician, without the involvement of the sponsor. 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.*

*Text suggestion:* The list for breaking the code can be found at…

### Auxiliary medicinal products

*Medicinal products are given to subjects that are not investigational medicinal products should be listed. These are called auxiliary medicinal products and include medicinal products used for background treatment, challenge agents, rescue medications and other substances used to measure endpoints. Provide justification for the selected dose, dosing regimen, route of administration, method of administration, and treatment period for all auxiliary medicinal products. Also indicate whether the auxiliary medicinal product has marketing authorization and if within the trial it will be used according to the terms in its approval. If this are not approved, a justification must be given for using this auxiliary medicinal product.*

*Safety reporting for auxiliary medicinal products, which are already on the market, shall be carried out in accordance with Chapter 3 of Title IX of [Directive 2001/83/EG](https://eur-lex.europa.eu/legal-content/sv/ALL/?uri=CELEX%3A32001L0083).*

*See also recommendations of the EMA expert group available on the Commission's website EudraLex ([link](https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-10_en%22%20%5Cl%20%22set-of-documents-applicable-to-clinical-trials-that-will-be-authorised-under-regulation-eu-no-5362014-once-it-becomes-applicable)). EudraLex - Volume 10 - Clinical trials guidelines Chapter III, Auxiliary Medicinal Products in Clinical Trials.*

*Describe how traceability and compliance of non-market approved auxiliary medicinal products will be documented e.g. medication log etc and how these will be labelled.*

### Concomitant use of other medicinal products and treatments

*For other concomitant medications (non-investigational medicinal products or auxiliary medicinal products and other treatments), justify and describe permitted and unauthorised treatments and medicinal product use before starting the trial, during the trial and after the end of the trial. Assess whether anything should be listed as an exclusion criterion and add this to section 6.2, Exclusion criteria.*

*Indicate what should be documented in the CRF regarding other concomitant medications (name, dose, start and stop dates, indication, etc.) The following text suggestion can be a part of the text under this heading.*

*Text suggestion:* Medications considered necessary for the safety and well-being of the subject may be provided at the discretion of the investigators, unless otherwise specified in the exclusion criteria. Concomitant medication should be recorded in the Case Report Form (CRF).

### Destruction

*Describe routines for how investigational medicinal product(s) shall be destroyed (if applicable). This also includes auxiliary medicinal products that do not have marketing authorization.*

### Treatment after trial end

*Describe any continued treatment of subjects after the trial end, e.g., if the subject returns to previous treatments, if the subject receives no further treatment, if the subject continues treatment with the investigational medicinal product (note that this may require approval by the Swedish Medical Products Agency).*

## Methods for measurement of endpoints for clinical efficacy and safety

### Methods for measurement of endpoints for clinical efficacy

*This section describes measurements and endpoints 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.*

#### Primary endpoint

*Describe the primary endpoint as precisely as possible. Include information about how the primary variable will be measured: e.g. type of sample, method used and eventual responsible laboratory. State whether the analysis will be performed continuously during the trial or after completion of subject enrollment.*

#### Secondary endpoints

*Describe the secondary endpoints as precisely as possible. Include information about how the secondary endpoints will be measured: e.g. type of sample, method used and eventual responsible laboratory. State whether the analysis will be performed continuously during the trial or after completion of subject enrollment.*

### Methods for measurement of endpoints for clinical safety

*This paragraph may be included as part of the other paragraphs under 8.1. Describe the endpoint(s) for clinical safety as precisely as possible. Include information about how the endpoint(s) will be measured: e.g. type of sample, method used and eventual responsible laboratory. State whether the analysis will be performed continuously during the trial or after completion of subject enrollment.*

*Describe any measures for handling deviations in section 9.3, Reporting and registration of Adverse Events.*

## Handling of Adverse Events

*Explain which adverse events (AE) and serious adverse events (SAE) will be reported during the trial (compare with the Investigator’s Brochure for non-approved investigational medicinal products or SPC for approved medications used according to the approved indication). Carefully consider what should and should not be reported, and under which time period of the trial that AE/SAE shall be reported. If the disease itself causes certain symptoms, hospitalization, etc., these conditions can be given as exceptions for what shall* ***not*** *be reported as an 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 Events). Note that persistent adverse events are classified as serious.*

### Definitions

#### Adverse Event (AE)

*Text suggestion:* Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

#### Adverse Reaction (AR)

*Keep relevant selections and delete other sections.*

*Text suggestion:* 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 reactions to the medicinal product related to any dose should be considered an adverse reaction (AR). The phrase “reaction” 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.

#### Serious Adverse Event (SAE)

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

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 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.

#### 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 reactions that are not included in the Investigator’s Brochure (IB) or SPC.

### Assessment of Adverse Events (AE)

#### Assessment of causal relationship

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

Consideration should be given to whether there is a reasonable possibility of establishing a causal relationship between the adverse event and the investigational medicinal product based on the analysis of the available evidence.

All AE can be categorized as either likely related, possibly related, unlikely 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 medicinal product. It is unlikely that the event can be attributed to underlying disease or other medications but is most likely caused by the investigational medicinal product and its emergence is reasonable in relationship with use of the investigational medicinal product.

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

**Unlikely related**: Clinical event, including abnormal responses from laboratory tests, unlikely to be related to the intervention/investigational medicinal product and can be reasonably explained by other medication or underlying disease.

**Not related**: Clinical event, including abnormal results from laboratory analyses, that is not reasonably related to the use of the intervention/investigational medicinal product.

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

If the reporting investigator does not provide any information on causality, the sponsor should consult with the reporting investigator and encourage the expression of a position on this issue. The sponsor must take into account the assessment of causality provided by the investigator. If the sponsor disagrees with the investigator's assessment of causality, both the investigator's and the sponsor's views should be included in the report.

#### Assessment of intensity

*In addition to assessing the causal relationship between administration of the investigational medicinal product and AE, an assessment of the intensity 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 its nature but does not affect the 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 subject.

*Assessment of intensity is generally made by the reporting investigator.*

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

#### Assessment of seriousness

The investigator is responsible for assessing the seriousness (serious or non-serious). If the adverse event is considered serious, this should be reported as a serious adverse event (SAE) by the investigator to the sponsor. See also section 9.3.2, Reporting of Serious Adverse Events (SAE).

### Reporting and registration of Adverse Events

* *The investigator should register, and document adverse event or abnormal laboratory responses identified in the protocol as critical for safety assessment and report them to the sponsor according to the reporting requirements and within the time periods specified in the protocol.*
* *Less stringent rules from registration and reporting requirements may be granted in low-intervention clinical trials (for definition see cover page) after a thorough risk analysis.*
* *The sponsor should maintain a detailed register of all adverse event reported by the investigator.*
* *Describe how AE/SAE are captured, e.g., that trial 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 adverse event in the trial.*
* *Describe where AE/SAE are registered. Describe how these will be registered in the trial’s CRF, reporting forms or worksheets, and where registrations of severity and causality are made, since this is not always done in the medical record.*
* *Also describe 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 adverse events are intended to be followed, e.g., from trial start or from start of treatment with the investigational medicinal product to XX weeks after the last dose.*
* *All reported adverse events that have not been resolved by the end of the trial 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 site approximately XX weeks after the last visit in the trial. The follow-up and the time for the follow-up visit/contact are adapted to each individual trial.*
* ***Assessment of causal relationship (between AE/SAE and investigational medicinal product), whether the AE is considered to be an SAE or not, shall be made by a licensed physician.***

*Text suggestion:* At each trial visit, adverse events (AE) are registered, starting after *trial start/or from start of treatment with the investigational medicinal product,* up to and including *X* *weeks* after the subject has ended their treatment with the investigational medicinal product. All AE that occurs during the trial and which are observed by the investigator/trial nurse or reported by the subject will be registered in the CRF regardless of whether they are assessed as related to the investigational medicinal product or not. Assessment of causal relationship, severity, and whether the AE is considered to be an SAE will be made by the investigator directly in the *CRF/on a trial-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, measures and outcome.

The following symptoms are clearly related to the process and the expected course of the 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.*

#### Reporting of Adverse Events (AE)

*Text suggestion:* All AE shall be registered in the CRF within *<<indicate time frame>> as indicated above (section 9.3, Reporting and registration of Adverse Events)*.

#### 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, how reporting will be done (e.g. in CRF), 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 medicinal 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 trial. 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 trial subject is hospitalized with a documented cancer-related problem, this will not be reported as an SAE.*

#### Reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR)

*In investigator-initiated trials where non-commercial sponsors lack the possibility to report SUSAR 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 cover letter to the application. Reporting then takes place via the [CIOMS form](https://cioms.ch/wp-content/uploads/2017/05/cioms-form1.pdf) which is sent to the Swedish Medical Products Agency via Eudralink. Since these reports contain personal data, they should not be sent to the Swedish Medical Products Agency via normal email.*

*The reference safety information provides the basis for assessing whether the adverse reaction is unexpected or not.*

*SUSARs should, if possible, be reported unblinded, that is, should state to which trial medicinal product the subject had a reaction. The investigator should only unblind the treatment allocation for a subject if unblinding is relevant to the subject's safety. Unblinded data should only be available to persons who need to participate in safety reporting to the regulatory authority and Data Safety Monitoring Boards (DSMBs) or to persons performing ongoing safety evaluations during the clinical trial. Placebo should only be reported if it is suspected that any component of the placebo treatment has caused the reaction.*

*Text suggestion:* Those SAE which are assessed by sponsor to be SUSAR are reported via a [CIOMS form](https://cioms.ch/wp-content/uploads/2017/05/cioms-form1.pdf) to the EudraVigilance database / Swedish Medical Products Agency according to the specified time frames.

SUSAR that are fatal or life-threatening are reported as soon as possible and no later than 7 days after the serious adverse event 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.

*Multicentre trials:* Information about SUSAR occurring during the trial is compiled by the sponsor and sent to the principal investigators at all participating sites. *In order to preserve the integrity of the trial, it is recommended that reporting of SUSAR to investigators in a blinded trial is made without unblinding, that is, without specifying which investigational medicinal product the subject received. Describe how the reporting will be done.*

### Follow-up of Adverse Events

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

### Independent Data Monitoring Committee

*If the clinical trial involves an extended risk or if the trial is performed over a longer time period and is divided into different blinded treatment groups, an external independent (of the sponsor and investigator) data monitoring committee should evaluate the decoded results. Further information visit EMA webpage (*[*link*](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf)*).*

### Annual Safety Report (ASR)

*For investigational medicinal products other than placebo, the sponsor must submit an annual report on the safety of each investigational medicinal product used in a clinical trial. This is done in the CTIS. The safety report should be written according to the format Development Safety Update Report, (DSUR).*

*The safety report defines for which time period the report applies and a list of all SAE that have occurred, as well as possible SUSAR. A summary assessment of the safety situation for the subjects and a benefit/risk evaluation for the trial must also be included. The ASR should also be accompanied by the RSI in force at the start date of the report. If significant changes in the RSI have occurred during the reporting period, these should be listed in the ASR.*

*The annual report should contain only aggregated and anonymised data.*

*If a clinical trial involves the use of more than one investigational medicinal product, the sponsor may, if specified in the protocol, submit a single annual safety report for all investigational medicinal products used in the clinical trial.*

*The obligation to submit a safety report starts when a clinical trial is authorised and ends when the last clinical trial conducted by the sponsor with the investigational medicinal product is completed.*

### Procedures in case of emergencies, overdose or pregnancy

*Medication errors, pregnancy and uses other than those specified in the CTP, including misuse and abuse of the investigational medicinal product, shall be subject to the same reporting obligations as adverse reactions.*

*If an unforeseen event is likely to have a serious impact on the benefit/risk relationship, the sponsor and investigator should take appropriate Urgent Safety Measures (USM) necessary to protect the subjects. Examples of such measures are to temporarily suspend the clinical trial or to introduce supplementary monitoring measures. The sponsor should, via CTIS, inform the concerned Member States about the event and the measures taken. Notification must be made as soon as possible, but no later than seven days after the measures have been taken.*

*If a subject who participates in a clinical trial 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).*

*Information about pregnancy does not need to be included in the trial if it is not applicable for the included subjects.*

## Statistics

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

### Analysis population

* *Define the subjects that will be included in the analyses, e.g., state if the analyses will apply 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.*

### Statistical analyses

#### 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 trial 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.*

#### 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.*

### 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 adjustment is not considered necessary.*

### Sample size calculations

* *State the total number of subjects needed for the trial. Sample size calculations should be performed for all primary outcome variables (in the case of several). In the case of multicentre trials, the number of subjects at each site should be stated.*
* *State and motivate the effect size (e.g., group differences, standard deviations) that sample size calculation builds upon, 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*

### Interim analysis (if relevant)

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

## Quality Control and Quality Assurance

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

*There may be less stringent rules for low-intervention clinical trials (see cover page), e.g. limited monitoring requirements.*

### Quality Assurance and Sponsor oversight

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

*The sponsor’s quality-related work must be based on a risk analysis of the trial 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 trial-related monitoring, auditing, and regulatory inspections by providing access to the CRF, subject’s medical record and other source data and other trial-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 trial’s monitoring plan, which should be based on the identified risks, follow-up of risks during the trial and timeliness of the monitoring plan.*

### Monitoring

*In order to fulfill the EU regulation on clinical trials on medicinal products for human use, 536/2014 and ICH-GCP, an independent monitor should be appointed to, via monitoring, ensure the subjects’ safety and integrity are satisfied and check that reported personal data is reliable and of high quality.*

*Briefly describe how the independent review (monitoring) will be performed before, during, and after the trial. 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. See 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. See also section* [11.4](file:///C%3A%5C%5CUsers%5C%5C227130%5C%5CAppData%5C%5CLocal%5C%5CMicrosoft%5C%5CWindows%5C%5CINetCache%5C%5CContent.Outlook%5C%5CJTXL2UYR%5C%5CPr%C3%B6vningsprotokoll%20med%20hj%C3%A4lptext%20-%20Mall-eng_v.%202022-10-12_.docx%22%20%5Cl%20%22_Deviations%2C_serious_breaches)*.*

*The minimum level for quality control is that the following can be verified:*

* *that subjects exist*
* *that informed consent has been signed prior to execution of any trial-specific actions*
* *that subjects are included according to the protocol’s inclusion and exclusion criteria*
* *that the trial’s main parameters and safety reporting are handled correctly*

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

*Text suggestion:* The trial will be monitored by an independent monitor before the trial begins, during conducting the trial, and after the trial has been completed. This is to ensure that the trial 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 trial’s monitoring plan and is intended to ensure that the subject’s rights, safety, and well-being are met and that data in the CRF are complete, correct, and consistent with the source data.

### Source data

*Refer to, and indicate in the site-specific source data reference document of the trial site, the location of the source data for each variable. The CRF may in specific cases be defined as the source data for specific endpoints (variables) that are not recorded elsewhere, in which case the data are recorded directly in the CRF.*

*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 and 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 trial. A document describing what has been classified as source data in the trial (source data reference document) 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 trial start at each individual site and can, in cases where source data is not registered in another document, consist of the CRF. This should be decided in consultation with the monitor and clearly stated in the source data reference document.

Access to trial-related documentation, such as subjects' medical records, CRFs, other source data and other trial documentation will be provided for monitoring and auditing purposes. Access to subjects' medical records will require a confidentiality agreement to be signed by the person in charge of the medical records at the trial site and by the monitor and auditor, if applicable. Access will also be granted in the context of regulatory inspections.

### Deviations, serious breaches and other reporting obligations

*The protocol should describe how deviations or serious breaches from Clinical Trials Regulation, the approved trial protocol, ICH-GCP and other regulations, directly affect, or with high likelihood could affect, the safety of subjects and their rights or the reliability and robustness of the data generated in the trial. In addition, the protocol needs to describe how the investigators should report suspected serious breaches to the sponsor.*

*Serious breaches should be assessed by the sponsor and without undue delay but at the latest within 7 days be reported by the sponsor to the Swedish Medical Products Agency via CTIS. See also section 13, Substantial changes to the trial.*

*Link to Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol (includes ICH-GCP and other relevant regulations): <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-notification-serious-breaches-regulation-eu-no-536/2014-clinical-trial-protocol_en.pdf>*

*The sponsor should notify the relevant Member States, via CTIS, of any unexpected events that may affect the benefit/risk relationship of a trial but are not suspected unexpected serious adverse reactions. This should be done without undue delay, but no later than 15 days after the sponsor becomes aware of the event.*

*Text suggestion*: The responsible investigator shall, without delay, report to the sponsor any serious breaches and deviations from the trial protocol, ICH-GCP and other regulations that significantly and directly affect, or with high likelihood could affect, the subjects’ safety and integrity or the reliability and robustness of the data generated in the trial. The sponsor should assess the suspected serious breach and the consequences of deviations that have occurred, and, without undue delay but no later than 7 days (from knowledge) report these to the Swedish Medical Products Agency via CTIS.

Other unexpected events that may affect the benefit/risk relationship must be reported via CTIS without undue delay, but no later than 15 days after the sponsor becomes aware of the event.

Minor deviations that do not affect subjects’ integrity or safety, nor significantly affect the trial’s scientific value, are documented in the trial documentation of the principal investigator and the sponsor and appropriate measures shall be taken. The deviations must be recorded in the clinical trial report.

### Audits and inspections

*Text suggestion:* Authorized representatives for the sponsor and Competent Authorities (CA) may carry out audits or inspections at the trial 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 trial-related activities and documents, to determine whether these activities were performed, registered, analyzed and reported correctly according to protocol, ICH- GCP and applicable regulations.

## Ethics

### Compliance to the protocol, ICH-GCP and regulations

*Text suggestion*: The trial will be performed in compliance with this clinical trial protocol, the EU regulation on clinical trials on medicinal products for human use (536/2014), the Declaration of Helsinki, ICH-GCP (Good Clinical Practice), and current national regulations governing this clinical trial. This is to ensure the safety and integrity of the trial subjects as well as the quality of the data collected.

### Ethical review of the trial

*Describe the procedure for approval of the final clinical trial protocol, informed consent form and other documents that is provided to the subject.* *Application for permission for a clinical trial on medicinal products from the Swedish Medical Products Agency and the Swedish Ethical Review Authority is made via CTIS. The Swedish Medical Products Agency has an obligation to forward the application documents to the Swedish Ethical Review Authority. The Swedish Ethical Review Authority submits its opinion on the application back to the Swedish Medical Products Agency.*

*Text suggestion*: The final protocol for clinical trials on medicinal products must be approved, as a part of the application for a permit for clinical trials via CTIS, by both the Swedish Ethical Review Authority and the Swedish Medical Products Agency before the trial can be conducted. The authority must be informed via CTIS of any changes in the trial protocol in accordance with current requirements. *See also section 13, Substantial changes to the trial.*

### Procedure for obtaining informed consent

*Describe the procedure for recruitment, how information is given to trial subjects and how consent is obtained. For vulnerable groups see information on the Swedish Medical Products Agency website ([link](https://www.lakemedelsverket.se/sv/tillstand-godkannande-och-kontroll/klinisk-provning/lakemedel-for-manniskor/provningsforordning-536-2014/forsokspersoner-och-informerat-samtycke-enligt-forordning-536-2014)) and Chapter V of the [CTR](https://eur-lex.europa.eu/legal-content/sv/ALL/?uri=CELEX:32014R0536).*

*Remember to adapt and describe the procedure based on whether the subject is a child. In trials where minors participate, the consent of both parents (legal representatives of the minor) must be obtained. In Sweden, a minor means a person younger than 18 years of age. According to the Medicines Act, a minor who has reached the age of 15 must also give his or her informed consent to participate in the clinical trial of a medicinal product, provided that the minor understands the implications of the trial for him or her.*

*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 trial entails. Keep in mind that in a clinical trial for investigational medicinal products, informed consent must be obtained by a licensed physician.*

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

*If the subject information changes during the trial execution, the subject has the right to once again decide whether he/she would like to continue their participation. This occurs 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 trial, 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 trial 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 any trial-specific activity is performed. Each subject who participates in the trial will be identified by a subject number on a subject identification list. The subject agrees that monitors, auditors, and inspectors may have access to their medical records and other source data. If new information is added to the trial, the subject has the right to reconsider whether he/she will continue their participation.

### 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 necessarily have access to the data. There should be a lawful ground for data collection, which for research is for public interest.*

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

*Appropriate technical and organisational measures shall be taken to protect the personal data and processed information from unauthorised access, disclosure, dissemination, alteration or destruction and from accidental loss, in particular where the processing involves the transmission of data over a network.*

*Text suggestion:* If any part of the data is processed by another organization, inside or outside the EU, appropriate agreements and/or other appropriate protective measures are taken 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.

In the information provided to subjects, subjects will be fully informed about how their trial data will be collected, used and disclosed. The content of the informed consent form complies with relevant integrity and data protection legislation. The subject information and the informed consent form will explain how trial 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 <<Trial code/Trial ID/Initials>>*.

The informed consent form will also explain that for verification of the data, representatives delegated by the sponsor, as well as relevant authorities, may require access to parts of medical records or trial records that are relevant to the trial, including the subject’s medical history.

### Insurances

*Here it should be explained how subjects are insured throughout the trial. Check if subjects are insured through the Swedish patient insurance and whether Swedish pharmaceutical insurance is valid for the investigational medicinal 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](http://www.lof.se/).*

*Swedish Pharmaceutical Insurance (Läkemedelsförsäkring): All marketed investigational medicinal products do not automatically have a Swedish Pharmaceutical Insurance. Check if the product is covered by the drug insurance at [lff.se](https://lff.se/) and that the insurance also covers clinical trials.*

## Substantial changes to the trial

*This section describes how to handle substantial changes in the trial. Substantial changes include changes that:*

* *may affect the safety or rights of the subjects,*
* *can change the reliability and robustness of the data generated in the clinical trial, or*
* *are significant for any other reason, such as the addition of a trial site or a change of the principal investigator*

*Substantial changes to the clinical trial protocol may not be implemented before authorisation has been granted by the relevant authority via CTIS. It is the responsibility of the sponsor to assess whether a change is substantial or not. For examples of what are considered substantial and non-substantial amendments, see the European Commission's CTR Questions and Answers document ([link](https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-10_en%22%20%5Cl%20%22set-of-documents-applicable-to-clinical-trials-that-will-be-authorised-under-regulation-eu-no-5362014-once-it-becomes-applicable), Chapter V, EudraLex - Volume 10 - Clinical trials guidelines).*

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

*Text suggestion:* Substantial changes to the signed clinical trial protocol are only possible through approved protocol amendments.

In the event that substantial changes to the protocol which may affect the safety, rights of subjects or the reliability and robustness of data generated need to be implemented during the course of the trial, permission from the relevant authority via application in CTIS should be obtained before implementing the change. This includes the addition of a new trial site or a change of the principal investigator at the trial site.

Non-substantial amendments are entered into the CTIS in the next substantial amendment application concerning the same part. If the non-substantial change is relevant to the Authority's oversight (e.g. contact details), the CTIS should be updated on an ongoing basis.

## Collection, handling, and archiving of data

*From the protocol it must be clear how the 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 measures, etc. Describe how corrections will occur and by whom, that there will be an independent copy of the CRF with the investigator when the trial is completed, and how other trial documentation is stored and who has access to it. The sponsor and investigator must archive the information in the Trial Master File for at least 25 years after the end of the clinical trial, providing that a longer archiving period follows from other parts of the law. The sponsor and investigator can also agree that the documents shall be archived for a longer period. The Swedish Archives Act (Arkivlagen) applies to archiving of research material. For clinical trials in ATMP (Advanced Therapy Medicinal Product), the archiving period is 30 years according to GCP specific for ATMP.*

*The sponsor and the investigator shall keep a Clinical trial master file. The clinical trial master file shall at all times contain the essential documents relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated, taking into account all characteristics of the clinical trial, including in particular whether the clinical trial is a low-intervention clinical trial. It shall be* *readily available, and directly accessible upon request, to the Member States.*

*The clinical trial master file kept by the investigator and that kept by the sponsor may have a different content if this is justified by the different nature of the responsibilities of the investigator and the sponsor. The sponsor has the documentation for the entire trial. The principal investigator shall keep an Investigator Site File (part of the Clinical Trial Master File) with all trial documentation for the site. The files should have relevant content according to the trial and follow ICH-GCP chapter 8 “Essential documents”. The principal investigator will store the trial site’s data, subject identification list, original of the subject information sheet and obtained trial consent inaccessible to unauthorized persons, but such that trial subjects can be identified by those responsible for the trial. This information must not be stored at the sponsor.*

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

*Text suggestion:*

Subjects who participate in the trial are coded with a trial-specific 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 subject number/trial 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 with essential documents will be archived for at least 25 years. Source data in the medical records system are stored and archived in accordance with national regulations.

### Case Report Form

*All information related to the clinical trial should be recorded, processed, handled and stored by the sponsor or investigator, as appropriate, so that it can be accurately reported, interpreted and controlled, while protecting the subjects' medical records and personal data in accordance with applicable personal data protection law.*

*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 clinical trial 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 principal investigator signs the completed CRF. A copy of the completed CRF will be archived at the site.

## Notification of trial completion, reporting, and publication

*The sponsor must notify, via CTIS, each concerned Member State that a clinical trial involving that Member State has been terminated. Notification must also be made when a trial has been terminated in all participating EU countries and also when termination has occurred in all participating third countries. The notification must be made within 15 days.*

*Within one year of the completion of the clinical trial in all Member States, the sponsor must submit a summary of the results of the clinical trial to CTIS, regardless of the outcome of the trial.*

*Guidance on content can be found in the CTR (*[*Link*](https://eur-lex.europa.eu/legal-content/SV/TXT/?uri=CELEX%3A32014R0536)*), Annex IV. It should be accompanied by a summary written in a way that is understandable to lay people. The content of the summary is given in CTR (*[*Link*](https://eur-lex.europa.eu/legal-content/SV/TXT/?uri=CELEX%3A32014R0536)*), Annex V.*

*For clinical trials involving children, the above summaries must be submitted within six months of the end of the trial. This shortened deadline of six months applies to sponsors who are marketing authorisation holders for the medicinal product.*

*If the trial is submitted for marketing authorization of an investigational medicinal product, the applicant for marketing authorisation must also, in addition to the summary of results, submit the full clinical trial report to CTIS within 30 days of the decision being taken.*

*In addition to submitting a summary of the results to CTIS 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.*

*In addition to submitting a summary of the results to CTIS, a full clinical trial report with individual data shall be completed by the sponsor and provided to Principal investigators. The clinical trial report shall be archived in the Trial Master File by the sponsor and by the principal investigator at each site, in their Investigator Site Files, throughout the entire retention period, and available on request for inspections by the authorities. The clinical trial report must contain sufficient information so that the Swedish Medical Products Agency or other authorities can make a complete evaluation of the trial conduct and the results. A published article is not to be equated with the summary report to CTIS or the full clinical trial report.*

*The sponsor is responsible for the compilation of statistical analyses and their presentation to involved principal investigators. These analyses 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 EU trial number is stated at the end of the abstract. This clearly documents that the trial 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.*

*If a clinical trial is suspended or prematurely terminated due to a change in the risk-benefit balance, for reasons of subject safety, this must be notified to the Member States concerned through CTIS. The notification should be made as soon as possible, but not later than 15 days after the clinical trial was suspended or terminated prematurely. The reasons for such action and follow-up measures must be provided. The resumption of a clinical trial after its temporary interruption due to a change in the benefit/risk balance is considered a substantial modification.*

*Interruptions that do not affect the benefit/risk relationship must be notified, via CTIS, within 15 days, stating the reason for the interruption. Notification of restart shall be made, via CTIS, within 15 days. See also section 5.4, End of Trial, as well as section 6.4, Withdrawal criteria.*

*Text suggestion:*End of the trial is reported in CTIS at the latest 15 days after completion.

Within one year of trial completion, a clinical study report is completed, and a summary of the clinical trial results must be reported in CTIS, including a summary for lay people.

## References

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

## Attachments

*These could include, for example, validated self-report scales, questionnaires, diaries, etc. All attachments should have a version number and be dated.*