Clinical Trial Protocol Template (model)

1. information on clinical trial protocol template

This protocol template has been designed mainly for non-commercial clinical trials which are subject to the European Communities (Clinical trials on Medicinal Products for Human Use) Regulations, Directive 2001/20/EC. The template is available for use by all investigators who are carrying out clinical trials if they so wish, however there is no requirement to use it.

All advisory text and quotations from GCP are in parentheses i.e. < >. All of these should be deleted before finalising the document.

All sample text is in ‘basic text’ style. This text should be altered or deleted as required while the draft is being developed.

1. study title

<Insert the title of the study>

<Insert the title of the study in Finnish/Swedish>

1. study sponsor

<Insert the name of the sponsor (=coordinating or principal investigator in non-commercial studies>

1. application details

|  |
| --- |
| * 1. Study title   <Insert full title including brief reference to the design, disease or condition being studied and the primary objective.> |
| * 1. Reference numbers   Protocol identification (code or reference number):  EudraCT number:  Date and version number: |
| * 1. Applicant details   Chief investigator/ Co-ordinating investigator  Name/title:  Contact details:  Principal Investigators  Name(s)/ titles:  Contact details:  Sponsor  Name:  Contact details:  Funder(s) :  Name:  Contact details: |
| * 1. Signatures   <The protocol should be signed by the sponsor and:   * the overall coordinating investigator for a multi-centre (incl. multinational) trial or/and * the principal investigator in a single-site trial.>   <The sponsor and the coordinating/principal investigator who is responsible for conducting the trial should sign the protocol, to confirm this protocol. Site-specific information may be provided on separate protocol page(s).>    <Name and title and position in the company of the person(s) authorised to sign the protocol and the protocol amendment(s) for the sponsor should be included.>  Date: |
| * 1. Other relevant information   <Include other important information as necessary (e.g. name, title, address, and telephone and fax number(s) of the sponsor's medical expert for the trial; name, contact details of contract research organisation/study monitor; name and contact details of medical/safety monitor if other than the sponsor; name and contact details of central laboratories and/or technical departments, statistical and data management etc.)> |

1. confidentiality statement

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the study team, regulatory authorities, and members of the Ethics Committee.

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1. document history

<Details of all protocol amendments should be included in this section whenever a new version of the protocol is created.>

|  |  |  |
| --- | --- | --- |
| **Document** | **Date of Issue** | **Summary of Change** |
|  |  |  |
|  |  |  |
| Protocol version no. | <Insert date> | <Describe changes> |
| Original protocol | <Insert date> | Not applicable |

1. synopsis

<A brief synopsis (usually limited to 3 pages) that summarises the study should be provided. An example is presented below. >

|  |  |
| --- | --- |
| Title of study |  |
| Name of sponsor/company |  |
| Phase of development |  |
| Objectives |  |
| Trial design |  |
| Key inclusion criteria |  |
| Key exclusion criteria |  |
| Number of subjects |  |
| Test product, dose and mode of administration |  |
| Duration of treatment |  |
| Statistical methods |  |
| Sample size |  |

1. abbreviations

<A list of the abbreviations, should be provided. Examples of abbreviations are listed below, amend as appropriate.>

AE Adverse event

AR Adverse reaction

CA Competent authority

CI Coordinating investigator

CRA Clinical research associate

CRF Case report form

CRO Contract research organisation

CT Clinical trial

CTA Clinical trial authorisation

CXR Chest x-ray

EC Ethics committee

ECG Electrocardiogram

EU European Union

e-CRF Electronic case report form

GCP Good Clinical Practice

GP General Practitioner

IB Investigators brochure

ICF Informed consent form

ICH International Conference on Harmonisation

IMP Investigational medicinal product(s)

IMPD Investigational medicinal product dossier

PI Principal investigator

PIL Patient information leaflet

RSI Reference Safety Information

SAE Serious adverse event

SAR Serious adverse reaction

SI Subject information leaflet

SmPC Summary of product characteristics

SOP Standard operating procedure

SUSAR Suspected unexpected serious adverse reaction

1. introduction
   1. Background information

<Describe briefly the main characteristics of the disease being studied and currently available treatment.>

<Include a summary of results from nonclinical studies that have potential clinical significance.>

<Include a summary from relevant clinical trials.>

<Describe the population to be studied.>

<Provide discussion of important literature and data that are relevant to the trial and that provide background for the trial (reference list to be inserted later).>

* 1. Rational for the study

<Include a name, description and characteristics of the investigational medical product(s) to be studied in this clinical trial.>

<Include a discussion of known risks and benefits, if any, to human subjects.>

<Description of and justification for the route of administration, dose, dosage regimen, and treatment period(s)>

1. study objective

<Include a description of the objectives and the purpose of the trial.>

<The objectives of the study are the questions that the study is intended to answer and are based on the hypothesis formulated.>

<Usually there is only one primary objective and a few secondary objectives.>

* 1. Primary objective

<The primary objective is the main question to be answered by the study.>

<Example: to investigate the efficacy of X compared to placebo in subjects with < insert condition>>

* 1. Secondary objective

<Secondary objectives are additional questions to be addressed.>

<Example: to investigate the safety of treatment X compared to placebo in subjects with < insert condition>>

* 1. Exploratory objectives

< Include exploratory objectives, if needed>

* 1. Primary and secondary/exploratory endpoints/outcome measures

<Give a general description the end-points/outcome measures and how/when they will be measured during the trial. Examples:

- the change of blood pressure (mmHg) measured from upper extremity from baseline to month X

* time (days) from the start of treatment to first <event>
* >

<Primary endpoints should be capable of measuring the primary objective of the study. Choice of primary endpoint must be justified. Primary endpoint is used in calculation of sample size and will be used to decide the overall results or ‘success’ of the trial. Secondary endpoints provide supportive data only.>

<Assessments of endpoints/outcome measures (for example efficacy and safety assessment) should be described in detail in section 10.3.2>

1. trial design
   1. General considerations

<The overall study plan and design of the study e.g., multicentre, randomised, double-blind, placebo-controlled, parallel design or cross-over, open labelled, phase I, II, III, IV etc should be included. List the countries in which the trial will take place.>

<It is usually helpful to display the design of the study graphically. This can be included here or in an appendix.>

Figure 1: Study Schema

**Follow up**

**Investigational Arm**

RANDOMISATION

EN

ROLLMENT

**Follow up**

**Control Arm**

<Include a description of the sequence and duration of all trial periods e.g. screening period, treatment period, post-treatment follow-up period and provide the expected duration of subjects’ participation and the number of visits. Describe the dose and mode of administration of investigational medicinal products and comparator/placebo.>

* 1. Selection of study population
     1. Overall description of trial subjects

<Give an overall description of the trial subjects. Describe demographic characteristics (e.g. gender, age) and the presence or absence of a medical condition/disease of subjects.>

* + 1. Inclusion criteria

<List as many criteria as necessary to clearly define your study population.>

<If men and women of reproductive capability will be enrolled, indicate whether contraception is required. If yes, include details of allowable contraception methods for the trial.>

<Include a statement that subjects meeting all of the criteria below may be included in the study.

Example>

To be eligible for inclusion, each subject must meet each of the following criteria at Screening (Visit 1) and must continue to fulfil these criteria at Baseline (Visit 2).

<Example criteria, amend as appropriate:

* Subjects must be able and willing to give written informed consent and to comply with the requirements of this study protocol
* Subjects must be male or female, aged 18 years or above at Baseline
* Diagnosed with < disease of a particular severity or duration> or, <if healthy volunteers> Subjects who are judged to be in generally good health by the investigator based upon the results of the medical history, laboratory tests, physical examination, CXR, 12-lead ECG performed during Screening <amend as appropriate>
* Female subjects must be not of child-bearing potential, defined as postmenopausal for at least 1 year or surgically sterile <or/and, amend as appropriate> Female subjects of child bearing potential and male subjects whose partner is of child bearing potential must be willing to ensure that they or their partner use effective contraception during the study and for xx months/weeks thereafter.
* Female subjects' serum pregnancy test performed at the screening visit and urine pregnancy test performed at the baseline visit must be negative.
* Subjects have clinically acceptable laboratory and ECG/CXR findings <specify other assessments> within xx months/weeks prior to enrolment.>

<Add additional study specific criteria as required.>

* + 1. Exclusion criteria

<Include a statement that all candidates meeting any of the exclusion criteria at screening/ baseline will be excluded from study participation and then list each criterion.

Sample text:>

Subjects are excluded from the study if any of the following criteria are met at Screening (Visit 1) or at Baseline (Visit 2):

<Example criteria, amend as appropriate:

* Allergy/sensitivity to study medications or their ingredients
* Female subjects who are pregnant or breast-feeding or considering becoming pregnant during the study.
* Subjects who have participated in another study and received any other investigational agent within < include time frame>
* Subjects unable to provide written informed consent
* Subjects who have any other significant disease or disorder (including uncontrolled diabetes, unstable ischemic heart disease, moderate to severe congestive heart failure, recent cerebrovascular accident) which, in the opinion of the investigator, may either put the subject at risk by participation in the study, or may influence the result of the study.
* Subjects who have a history of drug or alcohol use that, in the opinion of the investigator, would interfere with adherence to study requirements.
* Known history of, or documented positive hepatitis B or C or HIV infection
* Prior or concurrent malignancy
* aspartite transaminase (AST) or alanine transaminase (ALT) ≥ 3 x upper-limit of reference range
* Creatinine clearance (CrCl) < 60 mL/min measured by 24-hour urine collection or estimated by the Cockcroft and Gault formula
* Subjects who have clinically significant ECG findings as judged by the investigator
* Subject who are scheduled for procedures requiring general anaesthesia during the study>

<Add additional study specific criteria as required.>

* 1. Study assessments and procedures

<Describe all study assessments and procedures in detail. Include detailed schedule of assessments. Provide an outline of all the study visits, procedures to be done during the study, follow-up after the study and discontinuation visit.>

Figure 2: Schedule of events

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Procedures | Visit 1  Screen | Visit 2  Baseline  Day 0 | Visit 3  Week x  ±x Days | Visit 4  Week x  ±x Days | Visit 5  Week x  ±x Days | Visit 6  Week x  ±x Days | Visit 7  End Treatment  Week x  ±x Days | Visit 8  Follow up |
| Inclusion/Exclusion  Criteria |  |  |  |  |  |  |  |  |
| Informed consent |  |  |  |  |  |  |  |  |
| Medical history |  |  |  |  |  |  |  |  |
| Physical  examination and  weight/height |  |  |  |  |  |  |  |  |
| Vital signs |  |  |  |  |  |  |  |  |
| Laboratory tests |  |  |  |  |  |  |  |  |
| Pregnancy test |  |  |  |  |  |  |  |  |
| Randomisation |  |  |  |  |  |  |  |  |
| Dispensing of study medications |  |  |  |  |  |  |  |  |
| Concomitant  medications |  |  |  |  |  |  |  |  |
| <Assessment (describe)> |  |  |  |  |  |  |  |  |
| <Assessment (describe)> |  |  |  |  |  |  |  |  |
| <Assessment (describe)> |  |  |  |  |  |  |  |  |
| <Assessment (describe)> |  |  |  |  |  |  |  |  |
| Adverse event assessments |  |  |  |  |  |  |  |  |
| Medication  compliance check |  |  |  |  |  |  |  |  |

<In the study procedures and assessments, if applicable, windows should be defined outside of which the occurrence of the procedure/assessment would constitute a protocol violation.>

<Include a statement that informed consent will be obtained prior to any study-related procedures being undertaken>

* + 1. Description of Study Assessments

Medical and Surgical History

<Provide details as appropriate.>

Demographics

The date of birth, gender and race will be recorded.

Physical Examination

The complete physical examination will include the evaluation of the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, neurological systems. Height, weight and oral temperature will also be recorded.

Vital Signs

<Sampletext:

Vital signs will be recorded for all subjects and will include: blood pressure (BP), temperature (°C), pulse, and respiratory rate.

Vital signs will be obtained at Baseline, at each study visit and at the end of study. Resting pulse and blood pressure (BP) measurements will be measured after the subject has sat for at least five minutes.

ECG Test

< Sample text:>

One ECG including a 12-lead examination will be performed at Screening/Baseline.

Abnormal findings will be noted for clinical significance. The report will be signed by the investigator.

Clinical Laboratory Tests

<Describe any laboratory tests e.g. biochemistry, urinalysis and pregnancy tests>

<Sample text:

* haematology: haemoglobin, white blood cells (WBC), red blood cells (RBC), platelet count < add additional tests>
* biochemistry: glucose, urea, creatinine or creatinine-clearance, sodium, potassium, ALT < add additional tests>

All laboratory results will be reviewed and the reports signed by the investigator who will record in the CRF whether they are normal, abnormal but not clinically significant, or abnormal and clinically significant.

Pregnancy Tests

Serum pregnancy test and urine pregnancy test in women of child-bearing potential will be performed.

Concomitant Medication

<Describe what information will be recorded. All over-the-counter or prescription medication, vitamins, and/or herbal supplements will be recorded on CRFs. The indication for treatments will be recorded. >

* + 1. Endpoints assessments

<Describe the end-points assessments briefly.>

Efficacy Assessment

<Describe how the efficacy assessments/outcome measures are measured, in detail. Examples:

- Take blood pressure (mmHg) twice with at least 3 minutes apart after at least 10 min rest from non-dominant upper extremity in a subject in supine position

* Ask if the subject has had <event> since last visit and document details <describe which details> and time (date), duration

>

Safety Assessment

<Describe of the safety parameters/assessments>

<Sample text:>

The following safety evaluations will be performed during the study: adverse event monitoring, vital signs, physical examination, and laboratory assessments.

Tähän väliotsikko Procedures during visits?

* + 1. Screening procedure

<Describe the method for identifying and recruiting candidates for the trial.>

<Describe pre-screening procedures. Include only those evaluations necessary to assess whether a subject meets recruitment criteria. Discuss the sequence of events that should occur during Screening and the decision points regarding eligibility. List the framework prior to recruitment within which screening tests and visits must be done; e.g. What is the maximum duration allowed between screening and randomisation? Describe all procedures that must be completed before the subject can be included into the study.>

<Consider including that during the screening period, subjects will be evaluated for eligibility. Date of screening, subject age, gender and reason for ineligibility (if subject is not eligible) will be recorded. The results of the screening evaluation must meet the inclusion/exclusion criteria for the subject to continue in the study.>

<Include a statement that informed consent will be obtained prior to any study related procedures being undertaken>

* + 1. Baseline assessments

<Specify and describe all baseline assessments to be taken at baseline visit>

<Sample text:>

The following pre-treatment Baseline assessments will be performed prior to randomisation:

* confirmation of eligibility (review inclusion/exclusion criteria)
* recording of demographics, medical history and concomitant medications
* physical examination
* ECG
* blood collection for biochemistry and haematology
* for women of child-bearing potential a negative pregnancy test must be documented
  + 1. Subsequent study visits and procedures

<Describe all the visits and procedures that must be performed during the study treatment phase. Specify if they are clinic visits or telephone assessments. Add visit numbers and window periods if applicable.>

<For each visit, consider:

* eligibility check
* assessment of efficacy outcome measures
* assessments of safety (adverse event monitoring, vital signs, physical examination, and laboratory assessments)
* dispensing of study medications
* recording of concomitant medications
* assessment of compliance with study medications

A detailed description of each of the assessments, if not covered anywhere else in the protocol should be included here.>

* + 1. Method of assigning Subjects to treatment groups

<Describe the specific methods used to assign subjects to treatment groups.>

Randomisation

<Include a detailed description of the randomisation method to be used in the study, how randomisation is going to be carried out, and who will provide the randomisation codes.>

Blinding

<Describe the specific procedures used to carry out blinding.>

< Include a statement that the study will be conducted in a double-blind fashion. Study treatment assignment will be blinded for both the investigators and the subject.>

<Include the circumstances in which the blind would be broken for an individual or for all subjects, e.g., for serious adverse events>

<Include a statement that in the case of an emergency, when knowledge of the subject’s study treatment assignment is essential for the clinical management of the subject, an investigator may unblind a subject. Any intentional or unintentional breaking of the blind will be recorded and reported to the sponsor as soon as possible.>

<Describe the procedures used for unblinding and who has access to subject codes>

* 1. Definition of end-of-trial

<The definition of end-of-trial must be provided. In most cases the end of trial will be the date of the last visit of the last subject. Any exceptions should be justified.>

<The Sponsors and/or the trial steering committee have the right at any time to terminate the study for clinical or administrative reasons.>

<The end of the study will be reported to the EC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The investigators will inform subjects and ensure that the appropriate follow-up is arranged for all involved.>

<A summary report of the study will be provided to the EC and Regulatory Authority within 1 year of the end of the study and within 6 months for paediatric studies. This is a legal requirement.>

<Include all procedures/assessments related to the end-of-study visit.

Example:

The end-of-trial is the date of the last visit/telephone follow-up/ home visit of the last subject. The end of study visit form should include:

* assessment of endpoints/outcome measures
* assessments of safety including general (e.g. physical examination), specific safety assessments (e.g. specific laboratory tests according to the applicable product information and/or population) and adverse event collection
* assessment of compliance with study treatment(s)
* recording of concomitant medications>
  + 1. Premature termination of the study

<Describe the criteria for terminating the study prematurely and the procedures that will take place if the study is terminated prematurely.>

<Include a statement of the reasons that the study or a part of the study may be stopped e.g. new information about safety or efficacy, unsatisfactory progress of the study or other (specify).>

* 1. Discontinuation/withdrawal of subjects from study protocol

Subjects have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason without any consequences. The investigator has the right to discontinue a subject from study treatment or withdraw a subject from the study at any time if it is in the best interest of the subject.

Subjects must discontinue the investigational medicinal product(s) and be withdrawn from the study for any of the following reasons <amend as required>:

* withdrawal of consent by the subject
* any medical condition that the investigator or sponsor determines may jeopardize the subject’s safety if she or he continues receiving the study treatment
* pregnancy
* ineligibility (either arising during the study or retrospectively having been overlooked at screening)
* an adverse event which requires discontinuation of the study medication
* treatment failure and disease progression
* lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits).
* lost to follow-up<include a statement that at least 3 documented attempts must be made to contact any subject lost to follow-up.>

<Specify any procedures that will continue to be required until the end of the study even if the treatment has been withdrawn.>

<Include a statement that all subjects who discontinue should comply with protocol specified follow-up procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures.>

If a subject is withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

If a subject is withdrawn due to an adverse event, the investigator will arrange for follow-up visits until the adverse event has resolved or stabilised.

<Describe if withdrawn subjects will be replaced and how.>

1. treatment of trial subjects
   1. Description of study treatment(s)

<Describe the study treatment(s) including placebo/comparator if used.>

<Detail the full name, generic name and trade name of the study treatments if appropriate and the form e.g. tablet, capsule etc.>

<Describe the dosage and administration of study medications. Include the rationale for the dosage selection.>

* 1. Formulation, packaging and handling

<Describe the dosage form, packaging, and labelling of the study treatment(s).>

<Detail the name and address of the company that will supply the study treatment(s).>

<Detail the name and address of the company or pharmacy performing any additional packaging that may be necessary and study labelling (if appropriate).>

<For labelling requirements, refer to Annex 13 (EU Guidelines to Good Manufacturing Practice, Investigational Medicinal Products).>

* 1. Storage and disposition of study treatment(s)

<Describe the storage conditions of the study treatment.>

<Storage conditions prior to and, if necessary, after product preparation or reconstitution must be precise. The time to administration after preparation/reconstitution must be specified>

<Describe the storage arrangement for the of the study treatment. Where the study treatment will be stored? Under whose responsibility? >

< Describe the procedures for checking that appropriate temperatures are maintained.>

<Sample text:>

The refrigerator temperature must be recorded on a temperature log on a daily basis to record proper function.

<Include a statement that the study treatment(s) must be stored and locked in a secure place until they are dispensed for subject use or are returned to the sponsor>

<Include that investigational products are for investigational use only and are to be used only within the context of this study>

* 1. Accountability of the study treatment(s)

<Describe how medication, including the placebo/comparator will be accounted for. Usually, a table of distributed and returned number of e.g. tablets, with dates and package identification number, per each subject is sufficient for documenting the accountability.>

<Describe the procedures for the shipment, receipt, disposition, return and destruction of the investigational medicinal products.>

<<Sample text:)>

The study medication will be supplied to pharmacy by <provide details of the company> and retrieved at the end of the study.

The investigator is responsible for the control of the treatment(s) under investigation. Adequate records for the receipt and disposition of the IMP must be maintained.

The investigator will use a standard prescription manner of the institution and the investigator/research nurse will collect the medication from the pharmacy <specify when and how long before dosing>

<Describe how study treatment accountability/compliance will be monitored.>

<Sample text>

Accountability and subject compliance with study treatments will be assessed by maintaining dispensing and return records. Describe how discrepancies will be handled.

* 1. Assessment of compliance

<Describe how compliance is assessed. Will the subjects be asked to bring all unused or part-used medication/vials and packaging from used medication at each visit? >

<Define significant non-compliance and what procedures will be taken if there is significant non-compliance.>

<Sample text:>

The investigator is responsible for ensuring that the study treatment is administered in compliance with the protocol. Subject compliance will be assessed by maintaining dispensing records.

* 1. Overdose of study treatment

<Describe how the overdose of a study treatment will be handled.>

* 1. Prior and concomitant therapy

<Sample text:

Any medication, other than the study medication taken during the study will be recorded in the CRF.>

<Describe the timelines for documenting medications (e.g. from the date the subject signs informed consent to the last visit).>

* + 1. Permitted medications/non- investigational or auxiliary medicinal products

<Describe other medications which will be allowed before and during the study.>

<Note, if non-investigational medicinal products will be used outside the authorisation the relevant justification for the use of these products should be provided here. Refer to the guidance documents applying to clinical trials guidance on investigational medicinal products (IMPs) and 'non investigational medicinal products (NIMPs as in Directive 2001/20/EC) or auxiliary medicinal products (AxMPs as in Regulation (EU) No 536/2014) >

* + 1. Prohibited medications

<List any contraindicated medications and check that they correspond with the exclusion and withdrawal criteria. Comment on what will happen if a prohibited medication is taken during the study. Can subjects participate in any investigational treatment studies while participating in this study?>

1. safety reporting

<Include a statement that the safety and tolerability will be evaluated throughout the study e.g. by AEs, laboratory values, vital signs and physical exam findings etc.>

<Refer to the detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’) or an updated guidance while preparing this section. >

* 1. Definitions
     1. Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

* + 1. Adverse reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose.

The phrase ‘responses to a medicinal product’ means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

* + 1. Serious adverse event (SAE)

Any untoward medical occurrence or affect that at any dose:

* results in death,
* is life-threatening\*,
* requires hospitalisation or prolongation of existing hospitalisation,
* results in persistent or significant disability or incapacity,
* is a congenital anomaly or birth defect
* important medical events\*\*

\*Regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

\*\*Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events (hereinafter referred to as ‘important medical events’) should also be considered as ‘serious’ in accordance with the definition

* + 1. Severe adverse events

The term ‘severity’ is used here to describe the intensity of a specific event. This has to be distinguished from the term ‘serious (that serves as a guide for regulatory purposes). Severity refers to the intensity of the event/reaction.

* + 1. Suspected unexpected serious adverse reactions (SUSARs)

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator’s brochure for an unauthorised investigational medicinal product or summary of product characteristics for an authorised medicinal product.

* 1. Evaluation of AEs and SAEs

<Seriousness, causality, severity and expectedness should be evaluated>.

* + 1. Assessment of seriousness

The investigator should make an assessment of seriousness as defined in section 12.1.4>.

* + 1. Assessment of causality

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions.

The causality assessment given by the investigator should not be downgraded by the sponsor.

The investigator/sponsor must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

All AEs/SAEs judged as having a reasonable suspected causal relationship to the study medication will be considered as ARs/SARs.

All AEs/SAEs judged as being related to an interaction between the study medication and another medication will also be considered to be ARs/SAR.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

* + 1. Assessment of severity

The investigator will make an assessment of severity for each AE/SAE and record this on the CRF according to one of the following categories:

Mild

An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with every day activities.

Moderate

An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe

An event that prevents normal everyday activities.

<Note: the term ‘severe’, should not be confused with ‘serious’ which is a regulatory definition based on subject/event outcome or action criteria>

* + 1. Assessment of expectedness

<The expectedness of an adverse reaction will be determined by the sponsor according to the reference safety information e.g. a dedicated chapter in investigator's brochure for a non-authorised investigational medicinal product, or the summary of product characteristics, chapter 4.8 for an authorised medicinal product which is used according to the terms and conditions of the marketing authorisation.>

* + 1. Emergency unblinding procedures

<If the study is blinded, detail the procedures for the breaking of the study blind, who can perform this, where details of contacts for unblinding can be found etc.>

* 1. Reporting procedures for all adverse events

All AEs occurring during the study observed by the investigator or reported by the subject, whether or not attributed to the study medication, will be recorded on the CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to the study medication, other suspect medication or device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study medication as judged by an investigator or the sponsor will be followed until resolution or until the event is considered stable. All related AEs that result in a subject’s withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

It will be left to the investigator’s clinical judgment whether or not an AE is of sufficient severity to require the subject’s removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

Any pregnancy occurring during the clinical study and the outcome (e.g., delivery of healthy child at term, spontaneous abortion at week X) of the pregnancy should be recorded and followed-up.

* 1. Reporting procedures for serious adverse events

The investigator will report all serious adverse events immediately to the sponsor except for those that the protocol or investigator’s brochure identifies as not requiring immediate reporting. The immediate report will be followed by detailed, written reports. The immediate and follow-up reports will identify subjects by unique code numbers assigned to the latter.

The immediate report will be made by the investigator to the sponsor within a very short period of time and under no circumstances should this exceed **24 hours** following knowledge of the serious adverse event.

All SAE information must be recorded on an SAE forms and sent expeditiously to the sponsor. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form and sent expeditiously to the sponsor.

The sponsor will keep detailed records of all adverse events which are reported to him by the investigator or investigators.

In cases where reporting is not required immediately the investigator will report within the appropriate time frame, taking account of the specificities of the trial and of the serious adverse event, as well as possible guidance in the protocol or the IB.

The academic (non-commercial) sponsors will report all SUSARs to the competent authorities concerned (according to Directive 2001/20/EC) i.e. to Fimea using CIOMS-I template. Commercial sponsors report SUSARs directly to EudraVigilance database. Fatal or life-threatening SUSARs must be reported within **7 days**. SUSARs which are not fatal and not life-threatening are to be reported within **15 days**. The sponsor will also inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

If the initial report is incomplete, e.g. if the sponsor has not provided all the information/assessment within seven days, the sponsor will submit a completed report based on the initial information within an additional eight days.

If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information will be reported as a follow-up report within **15 days.**

<For further information regarding reporting requirements refer to detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’).>

In addition to the expedited reporting above, the sponsor shall submit once a year throughout the clinical trial or on request, a safety report to the competent authority and ethics committees. The annual safety report will be presented in the DSUR format as per ICH guideline E2F - Note for guidance on development safety update reports. This is a legal requirement.

<If a study specific safety monitoring committee is to be used, describe arrangements for SAE reporting here. Include emergency reporting contact details.>

* 1. Data safety monitoring board (DSMB)

<Where a DSMB is established to perform ongoing safety surveillance and to perform interim analyses on the safety data, this committee should be an independent committee.>

<The composition of the DSMB should be described and it should be clear that each member has no conflict of interest with the sponsor or company involved in the study.>

<Criteria on which the DSMB may decide to terminate the trial prematurely should be clearly defined before the trial has started.>

<The advice(s) of the DSMB will be notified upon receipt by the sponsor to the EC and CA that approved the protocol. With this notification a statement will be included indicating whether the advice will be followed.>

<See the [EMA Guideline on Data Monitoring Committees](http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf) (EMEA/CHMP/EWP/5872/03) for assessing the need for a DSMB and for information on the establishment of a DSMB and their working procedures.>

<If other committees, for example, Steering Committees or Endpoint Adjudication Committees are established describe the role, composition and responsibilities of these committees.>

* 1. Pregnancy

<Pregnancy is not considered an AE or SAE however the investigator must collect pregnancy information for female trial subjects or female partners of male trial subjects who become pregnant while participating in a study.>

<The investigator should record the information on a Pregnancy Notification Form and submit this to the sponsor.>

<Any pregnancy that occurs in a trial subject or a trial subject’s partner during a trial should be followed to outcome. In some circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post delivery.>

1. statistics

<Where possible the statistician should write this section.>

<The sub-headings given below are suggestions. Amend as required>

< Refer to the ICH E9 guidelines - Statistical principles for clinical trials >

* 1. Description of statistical methods

<Describe the statistical methods to be employed, including timing of any planned interim analysis(es).>

* 1. Determination of sample size subjects

<State the approximate number of subjects required to complete. The number of subjects required for the study should be justified. >

<The number of subjects should always be large enough to provide a reliable answer to questions addressed and is usually determined by the primary objective of the trial.>

<If the sample size is determined on some other basis, then this should be made clear and justified.>

<There are many formulae to calculate the size of the study population. It should be clear which method is used and the reasons why this method has been chosen. Also, the calculation itself should be given with a predefined p-value (usually 5%) and power.>

* 1. Analysis sets

< The set of subjects whose data are to be included in the analyses should be defined in the statistical section of the protocol.>

* 1. Demographic and baseline disease characteristics

<Describe>

<For example> demographic and baseline disease characteristic data will be summarized for each treatment group by presenting frequency distributions and/or descriptive statistics.>

* 1. Efficacy analysis

< Include information regarding an interim analysis, when necessary>

* + 1. Primary efficacy endpoint

<Describe>

* + 1. Secondary efficacy endpoints

<Describe>

* 1. Safety analysis

<Include for example: AEs, vital signs, physical examination, clinical lab analysis.>

* 1. The level of statistical significance

<State the level of significance to be used.>

<Describe, including how potential multiplicity issues are handled>

* 1. Criteria for the termination of the trial

<Describe>

* 1. Procedure for accounting for missing, unused and spurious data

<Describe>

* 1. Procedure for reporting any deviation(s) from the original statistical plan

<Procedures for reporting any deviation(s) from the original statistical plan should be described and justified

1. direct access to source data/documents

<Consider/alter following text>

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

1. data handling and record keeping

<Briefly discuss where data will be entered stored and handled>.

* 1. Data collection, source documents and case report forms (CRF)

<Define what will comprise source documents. >

<Sample text:

Source documents for this study will include hospital records and procedure reports and data collection forms. These documents will be used to enter data on the CRFs. All data entered on CRFs must be entered legibly. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialled and dated by the investigator.

Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification

number/code.>

* 1. Data reporting

<Describe method of data entry/management. Identify any data that is recorded directly on the CRF, i.e., there is no prior written or electronic record of data that would be considered ‘source data’.>

<Include that the subjects will be identified by a study specific subjects number and/or code in the database. The name and any other identifying detail will not be included in any study data electronic file.>

1. retention of essential documents

<Essential documents should be retained for at least 15 years from study end.

The investigator/institution should agree to retain the trial-related essential documents as required by the applicable regulatory requirements and until the sponsor informs the investigator/institution these documents are no longer necessary>.

1. quality control and quality assurance procedures

<Discuss the measures undertaken to ensure that the data obtained from this research is accurate, complete and reliable.>

<Include that the study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.>

<Describe arrangements for GCP monitoring.>

1. audits and inspections

This trial may be subject to internal or external auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents will be given at that time.

1. ethics

<Note: local ethics committee requirements should be considered in preparing this section>

* 1. Declaration of Helsinki

The sponsor will ensure that this study is conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

* 1. Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and 2005/28/EC (or Regulation (EU) No 536/2014).

* 1. Approvals

<Sample text:

Required documents including the protocol, informed consent form, subject information leaflet, investigational medicinal product dossier, investigators brochure and any other required documents will be submitted to < a recognised research ethics committee> and the competent authority for written approval.

The sponsor will submit and obtain approval from the above parties for substantial amendments to the original approved documents.

Describe any organisational approval procedures of study sites for studies.>

* 1. Informed consent

<Specify who will take informed consent, how and when it will be taken. Informed consent should be obtained prior to any study related procedures being undertaken.>

<Include a statement that the investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent form.>

<A representative subject information leaflet and a sample subject consent form can be attached as a separate document.>

* 1. Benefits and risks assessment

<Give a justification of the proposed study.>

<For studies with capacitated adults and therapeutic research with minors and incapacitated subjects, it should be explained why the risk to and burden for the subject will be in proportion to the potential value of the research and, if applicable, it should be stated to what extent the research may be beneficial to the subject.>

<In case of non-therapeutic research with minors and incapacitated subjects it should be stated why the risks associated with participation can be considered negligible and the burden can be considered minimal.>

* 1. Subject confidentiality

The trial staff will ensure that the subjects’ anonymity is maintained. The subjects will be identified only by initials and a subject’s identification number on the CRF and any database. All documents will be stored securely. The study will comply with the EU General Data Protection Regulation 2016/679.

* 1. Other ethical considerations

<Include any other ethical considerations specific to the study.>

1. financing and insurance/indemnity

<Describe financing and insurance arrangements. >

<Sample text:

X <name of institution> holds an insurance (‘potilasvahinkovakuutus’) and the (commercial) sponsor has taken a specific Clinical Trial insurance which apply to this trial.>

<Y is funding this trial.>

1. clinical study report and publication policy

<Include who will sign the study report. Describe the publication policy.>

1. references

<Insert references used in text.>