**Instruction Page**

 **Protocol Template for Interventional Clinical Trials with Medicinal Products**

**(version xx)**

This protocol template, developed jointly by the Danish Medicines Agency (DKMA) and the Danish Medical Research Ethics Committees (MREC), is intended for clinical trials with medicinal products subject to the [EU Clinical Trial Regulation (CTR) No. 536/2014](http://ec.europa.eu/health/human-use/clinical-trials/regulation_en%C2%A8). It is based on the protocol template developed by the CCMO in The Netherlands. Please note that use of this template is optional.

It is strongly recommended to carefully read the [guidance given on the DKMA website](https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/how-to-apply-for-clinical-trials-with-medicinal-products-in-denmark-and-europe-/) and for [non-commercial sponsors](https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/guidance-for-non-commercial-clinical-trials-/) to consult with the [GCP-units and their guidance’s](https://gcp-enhed.dk/forsoegsdokumenter/anmeldelse-til-myndigheder/ansoegning-forordning/).

The protocol shall, when possible, be written in an easily accessible and searchable format. Specific data specified in the structured data should not appear in the protocol (e.g. time indications, names of PIs, etc.). The level/extent of requirements for the protocol/trial can be adjusted according to the risk assessment that the sponsor has prepared, but that the justification/explanation must appear in the protocol.

After completion of the research protocol, the instruction page should be deleted. For privacy protection it is recommended to ensure that all personal information (e.g. author of the document) is removed from the final version of the document.

Format requirements when submitting substantial modifications:

* The protocol must be submitted in both track-changes and clean versions It should be clear from the updated protocol which changes are considered substantial and applied for together with a justification of each change.
* The new version of the document shall be identified by the date and an updated version number.

**Regarding aspects covered by Part II of the application:**

We advise not to state or describe part II aspects of the clinical trial in the protocol, as this can lead to an unnecessary number of updates to the protocol through substantial modifications (SM). Instead, a reference to the part II document or CTIS, where the information is to be provided, should be made, and/or added to the structured data under Part II in CTIS. Otherwise, sponsor must update both Part I and Part II of the trial, when there are changes to part II aspects of the trial that are described in the protocol. It is strongly recommended to carefully read the [guidance given on the MREC website](https://videnskabsetik.dk/ansoegning-til-etisk-komite/kliniske-forsoeg-med-laegemidler-under-ctr/vejledning-til-accelereret-ansoegningsproces-for-fase-i-og-iii-forsoeg).

**The following texts are used in the template:**

- <*italic text*> = explanatory text

- <straight text> = example text

- Comments with remarks = explanatory note

For convenience, references to the applicable articles/sections in Clinical Trial Regulation No 536/2014 (CTR) are stated in grey (e.g. see CTR: Annex I D15). When finalising the research protocol these references to the applicable CTR articles/sections can be deleted.

**CLINICAL TRIAL TITLE**

<*Give full title of the clinical trial*>

|  |  |
| --- | --- |
| **Protocol ID** | ***<code or reference number>*** |
| **Short title** | ***<short title>*** |
| **EU trial number**  | ***<number>*** |
| **Protocol version** | ***<version number>*** |
| **Protocol date** | ***<date>*** |
| **Sponsor**  | ***<please include name and contact details>*** |
| **Person delegated by sponsor:** | ***<if applicable, please include name, function and contact data***  |
|  |  |
|  |  |
|  |  |
| **Funding party** |  |
| **Laboratory sites <*if applicable*>** | ***<please include name and contact details>*** |
|  |  |
| **Pharmacy**  | ***<please include name and contact details>*** |

**PROTOCOL SIGNATURE SHEET**

|  |  |  |
| --- | --- | --- |
| **Name** | **Signature** | **Date** |
| **Sponsor or Legal representative:***<please include name and function>**<For non-commercial research only>***Head of Department:***<include name and function>* |  |  |
|  |  |  |
|  |  |  |

**DOCUMENT HISTORY**

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

|  |  |  |
| --- | --- | --- |
| **Document** | **Date of version** | **Summary of Changes** |
|  |  |  |
|  |  |  |
| **Protocol version no.** | *<Insert date>* | *<Only include the most important changes>* |
| **Original protocol** | *<Insert date>* | Not applicable |

**CONFIDENTIALITY STATEMENT**

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

Furthermore, a statement that the clinical trial shall be conducted in compliance with the protocol, with the Clinical Trials Regulation and with the principles of good clinical practice

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1. ABBREVIATIONS

AE Adverse Event

AR Adverse Reaction
ATMP Advanced Therapy Medicinal Product

AxMP Auxiliary Medicinal Product

CA Competent Authority

CRA Clinical Research Associate

CRF Case Report Form

CRO Contract Research Organisation

CT Clinical Trial

DSMB Data Safety Monitoring Board

EC Ethics Committee

e-CRF Electronic Case Report Form

EU European Union

EMA European Medicines Agency

GCP Good Clinical Practice

GDPR General Data Protection Regulation

IB Investigator’s Brochure

IC Informed Consent

ICF Informed Consent Form (please also se PIS)

ICH International Conference on Harmonisation

IMP Investigational Medicinal Product

IMPD Investigational Medicinal Product Dossier

MS Member State

PI Principal Investigator

PIS Participant information sheet

RSI Reference Safety Information

SAE Serious Adverse Event

SAR Serious Adverse Reaction

SmPC Summary of Product Characteristics

SOP Standard Operating Procedure

SUSAR Suspected Unexpected Serious Adverse Reaction

1. SYNOPSIS

*<EU trial number and Full trial title.>*

**Rationale**

*<Specify background and hypothesis of the trial inclusive justification for unmet medical need.>*

**Objective**

*<Specify the primary and secondary objectives of the trial.>*

**Primary endpoint**

*<Describe the primary endpoint(s) how it is measured and when it is assessed, e.g. the primary endpoint is the percent change in the number of events from baseline to a specified time or the total number of adverse reactions at a particular time after baseline. Justify the chosen endpoint>*

**Secondary endpoints**

*<Describe the secondary endpoints, how they are measured and when they are assessed e.g. number of adverse events until 30 days post end of treatment.>*

**Trial design**

*<Describe the design and the expected duration of the trial for the individual participants, e.g. double-blind placebo controlled clinical trial where participants are participating for X weeks.>*

**Trial population**

*<Describe the trial population, indicating the main inclusion criteria including age and disease/healthy volunteer and the main exclusion criteria to protect the participant, e.g. patients with moderate asthma 18-55 years with normal kidney and liver function and without gastrointestinal ulcer or risk factors for a cardiac arrhythmia; healthy volunteers 18-60 years not exposed to X-Ray examinations during the last 12 months.>*

**Interventions**

*<Describe interventions and treatment duration, also including background treatment if any, e.g. one group receives a 10 mg tablet of product X twice daily for Z weeks while also receiving product Y as background treatment and the other group receives a placebo tablet twice daily as well as product Y. Briefly explain the difference from standard of care / standard treatment*.

*Also describe trial-related diagnostic and monitoring procedures used.>*

**Ethical considerations relating to the clinical trial including the expected benefit to the individual participant or group of patients represented by the trial participants as well as the nature and extent of burden and risks**

*<A benefit-risk analysis should be done for the trial-specific treatments and interventions, clearly explaining if the trial involves an expected individual benefit (e.g. as required in emergency situations) or a group benefit. When a trial is placebo-controlled, a brief justification should be given**. If a non-therapeutic trial is carried out in vulnerable groups, e.g. in minors, incapacitated persons, pregnant or breastfeeding women, their inclusion has to be justified and it should be explained why the risks and burden are considered minimal and why the trial can only be performed in this particular patient group. The trial-specific risks and burdens for participants and caregivers (if applicable) related to diagnostic, therapeutic and monitoring procedures should be justified, e.g. the amount and number of blood samples, the number of site visits, physical examinations or other tests, as well as physical and physiological discomfort associated with trial participation.>*

1. INTRODUCTION AND RATIONALE
	1. Therapeutic condition and current treatment status

*<Describe the main characteristics of the disease being studied and the currently available treatment options including standard of care. >*

* 1. Clinical trial rationale

*<Describe what is new in this trial, which medical need the trial addresses and the clinical relevance of this clinical trial, including whether the results of the trial will potentially have a real impact on the population and if so, how.>*

* 1. Mechanism of action, rationale for the treatment, Drug class

*<Describe the mechanism of action of the IMP(s) and rationale related to the intended indication/population. If necessary, include pharmacokinetic considerations (e.g. metabolism, drug interactions, excretion).>*

* 1. Rationale for Dose Regimen/Dose Justification

< *Describe and justify the dosage regimen of the IMP(s).>*

1. STRUCTURED RISK ANALYSIS

*<Identified risks and their mitigations should mentioned here. Not only for the products but also consent, inclusion of participant, primary effects etc.*

*<In case more than one product is concerned, make separate sections per product.>*

* 1. Potential issues of concern

*<The protocol has to contain a structured risk analysis. This analysis consists of a number of steps and should result in chapter 4.3 in a comprehensive overall synthesis of the direct risks for the research participants in this study.*

*The risk considerations on the various issues listed below should be supported by up-to-date information and should be clearly described. For details one may refer to the other chapters in the protocol, the Investigator’s Brochure (IB) or a similar document (if applicable), peer reviewed papers in (biomedical/scientific) journals.*

*The issues below are provided to structure your considerations.*

*Should issues not be applicable, please indicate so. For registered products to be used within the indication and* ***not*** *in combination with other products, chapter 4.1 can be skipped; explain in chapter 4.3 why 4.1 is skipped. Chapter 4.3 cannot be skipped.>*

* + 1. Level of knowledge about mechanism of action

*<Is there a plausible mechanism that may imply a risk? Is there adequate clinical and patho-physiological knowledge about the mechanism? Particularly consider potential activation of self-amplifying mechanisms (immunologic, psychiatric, coagulatory).>*

* + 1. Previous exposure of human beings

< *Early phase result in humans with the investigational medicinal product (IMP) and/or products with a similar biological mechanism. >*

* + 1. Induction of the mechanism in animals and/or *ex-vivo*

*<Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material?* *Consider receptor homology. Is the post-receptor mechanism similar? Measurement system applicable? Are human ex-vivo tests available?>*

* + 1. Selectivity of the mechanism

*<Selectivity of the mechanism to target tissue in animals and/or human beings. Consider receptor distribution in tissues, general pharmacological studies, toxicology studies.>*

* + 1. Analysis of potential adverse effects/events

*<Describe predictions of safety window (anticipated drug levels for beneficial vs potentially harmful effects), the dose- or concentration –effect relation, the nature and seriousness of potential adverse effects (vital organ systems affected).>*

* + 1. Pharmacokinetic considerations

*<Consider the half-life in relevant effect compartment, pharmacokinetic dynamic relations, active or toxic metabolites.>*

* + 1. Predictability of effect

*<Describe e.g. biomarkers for effect in animal and man, precision and accuracy of measurement, the relation of marker to clinical effect.>*

* + 1. Interaction with other products

*<For studies where a combination of products is given, or participants are allowed to use certain products/medicines: Systematically consider potential pharmacokinetic interactions (CYP450, P-gp) and pharmacodynamic interactions (pharmacological/physiological).>*

* + 1. Managing of negative effects

*<Can negative effects be managed? How? Consider antidotes or antagonists, and other countermeasures; for instance, assurance of access to adequate medical support in case of emergencies (also considering the number of concomitant participants and the risk of the intervention).>*

* + 1. Study population

*<For instance, are research participants healthy volunteers or patients suffering from a life-threatening disease? Are the research participants patients at an Intensive Care? Is the condition of the patients that participate in this study stable? Are women with childbearing potential included in the study?>*

* 1. Potential issues of concern not related to the IMP

*Besides the issues of concern related to the IMP, issues of concern related to other aspects must be considered. Other aspects might be risk of non-compliance with essential procedures such as obtaining informed consent, performing randomization and blinding, conducting analysis/examinations related to the primary endpoint or safety reporting.*

* 1. Summary of risks and risk management

*<Describe all known and potential risks related to the IMP including uncertainties/unknown risk, and risks related to procedure (e.g. lumbar puncture).*

|  |  |  |
| --- | --- | --- |
| **Possible or known risks of** **relevance for the trial** | **Rationale** | **Mitigation strategy** |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

*Make clear what measures have been taken to reduce what risks.* *Examples (not limited to these): type of study population, certain in- or exclusion criteria, additional safety measurements such as blood tests, dose modifications, supervision of participants, hospitalization and observation of participants, establishing a DSMB or safety committee.*

*Make clear why in your opinion neither the risks themselves nor the balance between benefits and risks are unacceptable and the remaining risks are acceptable for the participants participating in the study.>*

1. OBJECTIVES AND ENDPOINTS

*<Specification and justification of the primary endpoint and other effect parameters>*

|  |  |
| --- | --- |
| **Objective(s)** | **Endpoint(s)** |
| **Primary objective(s)** | **Endpoint for the primary objective(s)** |
| * <*Please include primary objective*>
 | * <*Please describe the primary endpoint (e.g. number of events/relapses, blood hormone levels, etc.)*>
 |
| **Secondary objective(s), if applicable** | **Endpoint(s) for secondary objective(s), if applicable** |
| * <*Please include secondary objective*>
 | * <*Please describe the secondary endpoint (e.g. number of AE and SAE, Quality of Life parameters, etc.)*>
 |
| * Etc.
 | * Etc.
 |
| **Exploratory objective(s), if applicable** | **Endpoint(s) for exploratory objective(s), if applicable** |
| * <*Please include exploratory objective* >
 | * <*Please describe exploratory endpoint>*
 |
| * Etc.
 | * Etc.
 |

1. STUDY PLAN AND DESIGN
	1. Trial Design

*<Provide a description and justification of the trial design (e.g. open, single-blind, double-blind, placebo-controlled, cross-over, parallel design). Include where possible a diagram/flow chart to give an overview of the study design and the main procedures that participants will undergo during the course of research (CTR: Annex I D17k).>*

* 1. Number of Participants

*<Give the number of participants planned to be enrolled in the trial and per cohort.>*

* 1. Overall study duration and follow-up

*<Describe the expected duration of participation per participant of the study, including follow-up (CTR: Annex I D17n).>*

* 1. Patient participation

*<If patients were involved in the design of the clinical trial, a description of their involvements should be provided (CTR: Annex I D17e).>*

1. STUDY POPULATION
	1. Population

*<Provide a description of the groups and subgroups of the participants participating in the clinical trial, including, where relevant, groups of participants with specific needs, for example. age, gender, participation of healthy volunteers, participants with rare and ultra-rare diseases (CTR: Annex I D17h).* *Describe how the planned trial population is representative of the patient population that is expected to benefit from the intervention in the future (target population). Provide an explanation of the gender distribution in the trial and if a gender is excluded or underrepresented in the trial, the reason must be described and justified (CTR: Annex I D17y). Provide an explanation of the age distribution in the trial and if an age group is excluded or underrepresented in the trial, the reason must be described and justified (CTR: Annex I D17y).>*

* 1. Inclusion criteria

*<Sample text:>*

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

* 1. Exclusion criteria

*<Sample text:>*

A potential participant who meets any of the following criteria will be excluded from participation in this study:

* 1. Vulnerable populations and clinical trials in emergency situations

*<If applicable, specify which vulnerable populations are included in the study and provide the relevant justification for the inclusion of the vulnerable population to the trial and (if applicable) for deferred consent (CTR: Annex I D17x).>*

1. STUDY TREATMENTS

* 1. Investigational Medicinal Product(s) (IMP(s))
		1. Name and description of the IMP

*<Describe the full name, generic name and trade name of the IMP and the formulation (e.g. tablet, capsule, etc.)>*

* + 1. Status of development of the IMP

*<Give a brief overview of clinical pharmacokinetic, efficacy and safety data from previous clinical studies and previously investigated indications(s) for the IMP.>*

* + 1. Description and justification of dosage and route of administration

*<Describe and justify the dose(s)/dose steps, dose rationale, the route and mode of administration, schedule, treatment duration and dose modifications of the IMP (CTR: Annex I D17f).>*

* 1. Comparator IMP(s)

*<If applicable describe and justify the dose(s)/dose steps, dose rationale, the route and mode of administration, schedule, treatment duration and dose modifications of the comparator IMP (CTR: Annex I D17f).*

*Refer to the SmPC, international guidelines, scientific publications if the comparator is standard therapy.>*

* 1. Placebo

*<If applicable.>*

* 1. Auxiliary Medicinal Product(s) (AxMP(s))
		1. Name and description of the AxMP

*<Describe the full name, generic name and trade name of the AxMP and the formulation (e.g. tablet, capsule, etc.)>*

* + 1. Statement on authorisation and justification unauthorised AxMP (if applicable)

*<If the AxMP is authorised, describe whether it will be used in the clinical trial in accordance with the terms of its marketing authorisation. If the AxMP is not authorised a justification for the use of the non-authorised AxMP in the clinical trial has to be provided (CTR: Annex I D17g).>*

* + 1. Description and justification of dosage and route of administration

*<Describe and justify the dose(s)/dose steps, dose rationale, the route and mode of administration, schedule, treatment duration and dose modifications of AxMP (CTR: Annex I D17f).>*

* 1. Additional considerations for trials involving a medical device

*<If applicable.>*

* 1. Additional considerations for trials involving an in-vitro diagnostic or companion diagnostic

* 1. Preparation and labelling of study treatment(s)
1. OTHER TREATMENTS AND RESTRICTIONS
	1. Concomitant therapy
		1. Permitted medication(s)

*<Describe medications that will be permitted before and during the study (CTR: Annex I D17aa).>*

* + 1. Prohibited medication(s)

*<Describe medications that are not permitted before and during the study (CTR: Annex I D17).>*

* 1. Lifestyle restrictions
		1. Contraceptive measures

*<Describe and justify contraceptive measures proposed for women with childbearing potential (WOCBP) participated in the trial and if relevant for male participants with WOCBP partner.>*

* + 1. Other requirements

*<If applicable, describe and justify other measures (e.g. diet restrictions or required periods of fasting during the study, or restriction on blood or tissue donation). If applicable, include a rationale for dietary or habitual requirements for study participants >*

1. TRACEABLILITY, STORAGE, ACCOUNTABLILITY AND COMPLIANCE
	1. Traceability and storage of the study treatment(s)?

*<Describe the procedures for tracing, storing, destroying and returning the IMP and unauthorised AxMP (CTR: Annex I D17t).>*

* 1. Accountability of the study treatment(s) and compliance

*<Describe the accountability procedures for the supply and administration of medicinal products to participants including the maintenance of blinding, if applicable (CTR: Annex I D17ab).*

*If applicable, describe procedures for monitoring participant compliance (CTR: Annex I D17ac).>*

1. STUDY ASSESSMENTS AND PROCEDURES
	1. Screening procedure

 *<Describe the screening procedure that is part of the trial.*

*If pre-screening (i.e. examinations/procedures before consent to participate in the trial is obtained) is included in the trial, participant information and consent form for this pre-screening, as well as a description of how to obtain consent for this, must be described and submitted under Part II.>*

* 1. Randomisation, blinding and treatment allocation

*<Describe the specific methods used to assign participants to treatment groups and to minimise bias. If applicable, provide information about the procedures for randomisation and blinding (CTR: Annex I D17m).* Describe whether double-blinding may pose a risk to participants, and how that risk is mitigated.*>*

* 1. Study procedures and assessments

*<Describe administration of study medication and all study assessments, procedures and techniques in detail. A detailed schedule of visits and assessments can be helpful. Include information on sample volumes. Provide an outline of all the study visits, procedures to be done during the study, follow-up after the end of IMP administrations/intervention and discontinuation visit. Describe which measures will be used to limit impact of procedures and assessments for participants (e.g. limiting visits, archival samples etc.)>*

* + 1. Efficacy assessments

*<Describe all efficacy assessments/outcome measures. Specify the methods and timing for assessing, recording, and analysing these parameters (CTR: Annex I D17af).>*

* + 1. Safety assessments

*<Describe the safety parameters/assessments (e.g.* adverse event monitoring, vital signs, physical examination, and laboratory assessments). *Specify the methods and timing for assessing, recording, and analysing these parameters. (CTR: Annex I D17af).*

*Discuss follow-up of participants after adverse reactions including the type and duration of follow-up. (CTR: Annex I D20d).>*

* 1. Decentralised trial procedures

*<If applicable, describe whether elements of the trial/any trial procedures are performed in a decentralised manner i.e. performed outside the trial site/hospital department. For example, monitoring of physiological parameters, answering questionnaires and blood sampling. >*

1. STUDY DISCONTINUATION AND COMPLETION
	1. Definition End of Trial

*<Give a clear and unambiguous definition of the end of the clinical trial in question, and if it is not the date of the last visit of the last participant, provide another definition of End of trial* *and a justification thereof (CTR: Annex I D17o).>*

Criteria for temporary halt and early termination of the clinical trial

*<Describe the criteria for discontinuing parts of the clinical trial or the entire clinical trial (CTR: Annex I D17p). Give information about the procedures that will take place if the trial is terminated prematurely. Also describe this in case of early termination for reasons of participant safety.>*

* 1. Discontinuation/withdrawal of individual participants

*<Describe criteria for withdrawing individual participants from treatment or from the clinical trial (CTR: Annex I D17v). Describe the procedure relating to the withdrawal of participants from treatment or from the clinical trial (CTR: Annex I D17w).>*

* 1. Arrangements for participants after their participation in the clinical trial ended

*<If applicable*, *describe the arrangements for taking care of the participants after their participation in the clinical trial has ended, where such additional care is necessary because of the participants’ participation in the clinical trial. Include information about how the arrangements differ from that normally expected for the medical condition in question (CTR: Annex I D17ae).>*

1. SAFETY REPORTING
	1. Definitions
		1. Adverse events (AEs)

Adverse events are defined as any untoward medical occurrence in a participant to whom a medicinal product is administered 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. Serious adverse events (SAEs)

Serious adverse event is any untoward medical occurrence in a patient or trial participant that at any dose:

* results in death,
* is life-threatening,
* requires inpatient hospitalization or prolongation of existing hospitalization,
* results in persistent or significant disability/incapacity,
* is a congenital anomaly/birth defect
	+ 1. Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. The event must be serious;
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the reference safety information (RSI).
	1. Recording of AEs/SAEs/SUSARS

*<Describe the procedure for eliciting and recording adverse events by the investigator (CTR: Annex I D20a).>*

* 1. Reporting of AEs and SAEs
		1. Reporting of SAEs by the investigator to the sponsor

*<Provide the list adverse events or laboratory anomalies that are critical to safety evaluations and must be reported by the investigator to the sponsor (CTR: Annex I D19a and Article 41 (1)).>*

* + 1. List of SAEs which do not require immediate reporting and procedure for reporting

*<Provide the list of SAEs which do not require immediate reporting by the investigator to the sponsor together with the relevant justification (CTR: Annex I D20b). Describe the procedure for reporting of by the investigator to the sponsor of those SAEs (CTR: Annex I D19b).>*

* 1. Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

* 1. Reporting of SUSARs by the sponsor to EudraVigilance

The sponsor will keep detailed records of all AEs which are reported to him/her by the investigator or investigators (CTR: Article 41(3)).

The sponsor will report electronically and without delay to EudraVigilance all relevant information about any SUSAR (CTR: Article 42).

The period for the reporting of SUSARs by the sponsor to EudraVigilance will take account of the seriousness of the reaction and will be as follows:

* In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction (CTR: Article 42(2(a)));
* In the case of non-fatal or non-life-threatening SUSARs, not later than **15 days** after the sponsor became aware of the reaction (CTR: Article 42(2(b)));
* In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction being fatal or life-threatening (CTR: Article 42(2(c))).

Where necessary to ensure timely reporting, the sponsor may, in accordance with section 2.4 of Annex III, submit an initial incomplete report followed up by a complete report (CTR: Article 42(2)).

* 1. Annual safety report

Regarding investigational medicinal products other than placebo, the sponsor shall submit annually through CTIS to all Member States concerned a report on the safety of each investigational medicinal product used in a clinical trial (CTR: Article 43).

* 1. Unblinding procedures for safety reporting

*<If the study is blinded, add the trial specific information regarding unblinding procedure for safety reporting (CTR: Annex I D22).>*

The investigator will only unblind the treatment allocation of a participant in the course of a clinical trial if unblinding is relevant to the safety of the participant (CTR: Annex III 2.5(17)).

When reporting a SUSAR to the EudraVigilance, the sponsor will only unblind the treatment allocation of the affected participant to whom the SUSAR relates (CTR: Annex III 2.5(18)).

In case of unblinding, describe procedure to maintain blind for persons responsible for the ongoing conduct of the clinical trial such as the management, monitors, investigators) and those persons responsible for data analysis and interpretation of results at the conclusion of the clinical trial, such as biometrics personnel (CTR: Annex III 2.5(19)).

Unblinded information will be accessible only to persons who need to be involved in the safety reporting to the EMA, to Data Safety Monitoring Boards (DSMB), or to persons performing ongoing safety evaluations during the clinical trial (CTR: Annex III 2.5(20)).

* 1. Temporary halt for reasons of participant safety

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise participant health or safety. The sponsor will submit the notification through CTIS without undue delay of a temporary halt but not later than in 15 days of the date of the temporary halt. It shall include the reasons for such action and specify follow-up measures. The study will be suspended pending a further positive decision by the concerned member state (CTR: Article 38). The investigator will take care that all participants are kept informed.

* 1. Urgent safety measures and other relevant safety reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator will take appropriate urgent safety measures to protect the participants. In addition, the sponsor will notify the Member States concerned, through CTIS, of the event and the measures taken. That notification will be made without undue delay but no later than **7 days** from the date the measures have been taken (CTR: Article 54).

* 1. Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

<*In case a DSMB/DMC is established to perform ongoing surveillance and to perform interim analyses, this committee should be an independent committee.*

*In case a DSMB/DMC is not needed, but some safety review is deemed appropriate, information on this safety committee should be given here. Information should be provided on the composition of the committee and (in)dependence of the members, the reason to establish this committee, type of data that will be reviewed and moment of review, possible measures to be taken>*

1. STATISTICAL ANALYSIS
	1. Description of statistical methods

*<Describe the statistical methods to be employed. If applicable, describe planned interim analysis in section* Interim analysis *(CTR: Annex I D17u).>*

* 1. Analysis sets

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

* 1. Participant demographics and other baseline 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. Randomisation and blinding

*<Describe the randomisation and blinding procedure, if applicable. For example allocation ratio, stratification, blocking, adaptive randomisation, measure(s) to achieve masking of treatments; matching placebo/double-dummy.>*

* 1. Sample size, trial power and level of significance used

*<Describe the number of participants planned to be enrolled and provide reason for choice of sample size. State the level of significance and power of the trial to be used (CTR: Annex I D17u. Justify the clinical relevance of the size of detectable difference of the primary endpoint. >*

* 1. Planned analysis
		1. Analysis primary endpoint

<*Describe in detail how the primary analysis (i.e. the analysis on which the main conclusion will be based) will be done for the primary outcome parameter(s) in order to avoid subjective choices to be made during the analysis (e.g. choice of time points). Discuss how the type I error will be controlled in case of multiplicities (e.g. due to multiple primary endpoints, multiple treatment arms or multiple time points of evaluation) and what the impact is of the multiplicity corrected alpha if needed, with regard to the power of the study. Any other analyses of the primary study parameter(s) (e.g. exploratory analyses) should be labelled as such and must be separated in the text from the description of the main analysis above. If multivariable methods are used, the list of covariates needs to be specified.*>

*<Describe the selection of participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, evaluable participants) (CTR: Annex I D17u).>*

* + 1. Analysis secondary endpoint(s)

*<Describe, if applicable>*

* + 1. Analysis other study parameters/endpoints

*<Describe, if applicable>*

* 1. Interim analysis

*<Describe, if applicable (CTR: Annex I D17u).>*

* 1. (Statistical) criteria for termination of the trial

*<Describe the criteria and statistical analysis used for discontinuing parts of the clinical trial or the entire clinical trial (CTR: Annex I D17u).>*

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

<Describe the procedures (CTR: Annex I D17u).If applicable, describe how re-enrollment of participants is carried out >

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

*<Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate) (CTR: Annex I D17u).>*

1. ETHICAL CONSIDERATIONS
	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*](#_top)*.>*

* 1. Recruitment and informed consent procedures

<*Provide a detailed description of the recruitment and informed consent procedure, especially when participants are incapable of giving informed consent (CTR: Annex I D17z). If applicable, please consider the important additional requirements with regard to the recruitment and informed consent procedures for trials on incapacitated participants and on minors and for trials involving emergency situations, including any additional national measures. (CTR: Articles 31, 32, 34, and 35).*

*Please indicate in this section if the aspect is described in Part II instead.>*

* 1. Benefits and risks assessment, group relatedness

<*Give a justification of the proposed study. This should include a summary of the known and potential benefits and risks as well as an evaluation of the anticipated benefits and risks (CTR: Annex I D17d)*.

*Describe why the risks, neither in themselves nor in relation to the benefits of the trial, are unjustifiable and why the therapeutic benefit for the trial participants and/or future patients justifies the trial. This means that the individual ethical issues (e.g. justification of placebo or comparator, or inclusion of incapacitated trial participants) and the overall risk/benefit associated with the trial must be considered.*

*Describe the balance of the expected therapeutic benefit to trial participants and future patients, as well as the risks and harms to individuals participating in the trial. This should include the nature of the potential benefit - is it temporary or permanent, does it decrease over time, etc.>*

* 1. Insurance cover and indemnification for trial participants

*<Some description of insurance arrangements could be included here but the proof of insurance covers should be provided with Part II of the clinical trial application.*

*For clinical trials in Denmark the Danish national requirements for describing proof of insurance cover or indemnification can be found on our website (www.researchethics.dk) and should be seen as a supplement to the requirements listed in CTR, Annex I O68. The information must appear in the protocol or in a separate Part II document.*

*The description must be specified in accordance with the trial activities conducted at trial sites in Denmark, including compliance with applicable national requirements.*

*Please indicate in this section if the aspect is described in Part II instead.>*

* 1. Compensation for trial participants

<*Please shortly describe any special incentives, compensation or treatment that participants will receive through participation in the clinical trial. For clinical trials in Denmark it is recommended, although not required, to use the EU Commission's template on compensation for trial participants on EudraLex: EudraLex - Volume 10 - European Commission. If the template is not used, all the information indicated in the template must appear in the protocol or in a separate Part II document.*

*The description must be specified in accordance with the trial activities conducted at trial sites in Denmark, including compliance with applicable national requirements.*

*Please indicate in this section if the aspect is described in Part II instead*.>

* 1. Financing and compensation for investigators and trial sites

<*Please shortly describe the compensation investigators will receive for performing the clinical trial. For clinical trials in Denmark please refer to the requirements listed in CTR, Annex I P.69-71. The information must appear in the protocol or in a separate Part II document.*

*The description must be specified in accordance with the trial activities conducted at trial sites in Denmark, including compliance with applicable national requirements.*

*Please indicate in this section if the aspect is described in Part II instead.*>

* 1. Other ethical considerations

*<Provide a description of ethical considerations relating to the clinical trial if those have not been described elsewhere (CTR: Annex I D17ag).>*

1. ADMINISTRATIVE ASPECTS, MONITORING AND CONFIDENTIALITY

*<Include a statement that the study will be conducted in compliance with the protocol, with Clinical Trials Regulation No 536/2014 and with the principles of good clinical practice (CTR: Annex I D17a). A statement concerning sponsor oversight could be included>*

* 1. Approval initial application and substantial modifications

*<Sample text:>*

The trial protocol, informed consent form, participant information sheet, investigational medicinal product dossier, investigators brochure and any other documents required by the Regulation will be submitted for the regulatory approval before the clinical trial is started via CTIS.

The sponsor will also submit and obtain approval for substantial modifications to the original approved documents via CTIS.

A ‘substantial modification’ is defined in the CTR as any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety or rights of the participants or on the reliability and robustness of the data generated in the clinical trial.

* 1. Monitoring

*<Describe the planned monitoring of the conduct of the clinical trial. The extent and nature of the monitoring shall be determined by the sponsor based on an assessment that takes into consideration all characteristics of the clinical trial. One can refer to a monitoring plan for details CTR: Annex I D17ad).>*

* 1. Recording, handling and storage of information

*<Briefly discuss the procedure for recording, processing, handling and storage of information in the trial:>*

* + 1. Handling of data and data protection

*<Include a statement by the sponsor or their representative that data will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR) and the Danish Data Protection Act.*

*Please indicate in this section if the aspect is described in Part II instead.>*

<*Provide a description of the arrangements for the protection of personal data and measures that will be implemented to ensure confidentiality of personal data of participants. Describe organisational and technical arrangements to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data (CTR: Annex I D17ak).*

*Pay particular attention to the general procedures for handling data, how data are coded, by whom the key to the code is safeguarded, who has access to the data and where it will be stored, which steps are taken to ensure data security (CTR: Annex I D17al), and which measures will be implemented in case of a data security breach (CTR: Annex I D17am).*

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

*<When personal data are transferred from the EU to countries outside the EU (‘third countries’) the level of protection ensured in the EU by the General Data Protection Regulation should not be undermined. In any event, transfers to third countries may only be carried out in full compliance with the GDPR. In case data (including any biological samples) will be transferred outside the EU, describe which measures are taken to ensure maintenance of the same level of protection as within the EU.>*

* + 1. Source documents and case report forms (CRF)

*<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. 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 participant will be referred to by the study participant identification code.

*<In case there are no source documents, describe the procedures for the identification of data to be recorded directly on the CRFs considered as source data (CTR: Annex I D17r)>.*

* + 1. Clinical trial master file and data archiving

*<Sample text:>*

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 the clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated (CTR: Article 57).

The sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial, unless other EU law requires archiving for a longer period. The medical files of participants shall be archived in accordance with national law (CTR: Article 58).

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request (CTR: Article 57).

*<Include information where and how long the clinical trial master file will be stored.>*

* + 1. Collection and storage of biological samples

<*If applicable, describe the arrangements to comply with the applicable rules for the collection, storage and future use of biological samples (CTR: Annex I D17s).*

*For clinical trials in Denmark it is recommended, although not required, to use the EU Commission's template on biological material on EudraLex: EudraLex - Volume 10 - European Commission. If the template is not used, all the information indicated in the template must appear in the protocol or in a separate Part II document.*

*The Danish national requirements for describing compliance with biological material can be found in our guideline on our website (www.researchethics.dk) and should be seen as a supplement to the requirements listed in the EU Commission's template on biological material on EudraLex.*

*The description must be specified in accordance with the trial activities conducted at trial sites in Denmark, including compliance with applicable national requirements.*

*Please indicate in this section if the aspect is described in Part II instead*.>

* 1. Audits and inspections and direct access to source data/documents

<*Include a statement confirming that the investigators and institutions involved in the clinical trial are to permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents (CTR: Annex I D17ah).>*

*<Sample text:>*

This trial may be participant to internal or external monitoring, auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents including direct access to source data will be given at that time.

* 1. Reporting of serious breaches

*<Sample text:>*

The sponsor will notify the Member States concerned about a serious breach of the Regulation or of the version of the protocol applicable at the time of the breach through CTIS without undue delay but not later than **7 days** of becoming aware of that breach (CTR: Article 52).

* 1. Notification of the start and the end of the recruitment

*<Sample text:>*

The sponsor will notify within 15 days each Member State concerned of the start of a clinical trial in relation to that Member State through CTIS (CTR: Article 36(1)).

The sponsor will notify within 15 days each Member State concerned of the first visit of the first participant in relation to that Member State through CTIS (CTR: Article 36(2)).

The sponsor will notify within 15 days each Member State concerned of the end of the recruitment of participants for a clinical trial in that Member State through the EU (CTR: Article 36(3)).

* 1. Temporary halt/(early) termination

*<Sample text:>*

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in relation to that Member State through CTIS (CTR: Article 37(1)).

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in all Member States concerned and in all third countries in which the clinical trial has been conducted through CTIS (CTR: Article 37(3)).

* + 1. Temporary halt/early termination for reasons not affecting the benefit-risk balance

*<Include information about the reporting procedures:>*

*<Sample text:>*

The sponsor will notify with 15 days each Member State concerned of a temporary halt of a clinical trial in all Member States concerned for reasons not affecting the benefit-risk balance through CTIS (CTR: Article 37(5)).

When a temporarily halted clinical trial for reasons not affecting the benefit-risk balance is resumed the sponsor will notify each Member State concerned through CTIS (CTR: Article 37(6)).

The sponsor will notify to the EU portal CTIS of early termination of the clinical trial for reasons not affecting the benefit-risk balance through CTIS. The reasons for such action and, when appropriate, follow-up measures for the participants will be provided as well (CTR: Article 37(7)).

* + 1. Temporary halt/early termination for reasons of participant safety

*<Include information about the reporting procedures:>*

*<Sample text:>*

In accordance to article 38 of the CTR, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise participant health or safety. The temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance will be notified to the Member States concerned through the EU portal CTIS without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures. The restart of the clinical trial following a temporary halt as referred to in paragraph 1 shall be deemed to be a substantial modification participant to the authorisation procedure laid down in Chapter III of the CTR (CTR: Article 38).

* 1. Summary of the results

<Sample text:>

Within one year from the end of a clinical trial in all Member States concerned, the sponsor will submit to the EU portal CTIS a summary of the results of the clinical trial. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary is set out in CTR Annex V (CTR: Article 37(4)).

*<Note: if for scientific reasons it is not possible to submit a summary of the results within one year, specify when the results are going to be submitted, together with a justification (CTR: Annex I D17aj).>*

*<Note: where the clinical trial was intended to be used for obtaining a marketing authorisation for the investigational medicinal product, the applicant for the marketing authorisation shall submit to the EU portal CTIS the clinical study report within 30 days after the day the marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, or the applicant for the marketing authorisation has withdrawn the application (CTR: Article 37(4)).*

* 1. Public disclosure and publication policy

*<Please describe the arrangements made between the sponsor and the investigator concerning the public disclosure and publication of the research data (CTR: Annex I D17ai).>*

*<Data from a clinical trial should only be submitted in support of a clinical trial application if that clinical trial has been recorded in a publicly accessible and free of charge database which is a primary or partner registry of, or a data provider to, the international clinical trials registry platform of the World Health Organization (WHO ICTRP). Submission to the EU portal CTIS fulfils this requirement. Specific provision should be made for data from clinical trials started before the date of application of this Regulation (CTR: (25)).>*

1. REFERENCES

<*Include all key references published in peer reviews journals that are relevant for the study and are discussed in the protocol. Make sure that the references are up to date (CTR: Annex I D17i).*>

|  |  |  |
| --- | --- | --- |
| **Date** | **Version** | **Update** |
| 14 Oct. 25 | 3.0 | Section 4 Updated Risk and mitigations and inserted table and added a section “Potential issues of concern not related to the IMP”. Section 6 added schedule of events. Section 11.2 added sentence on double blinding. Section 13.2 Investigator to assess causality. Section 15.2 Added sentence on part II. Section 16 to include key components of sponsor oversight. Section 16.3.1 update to include reference to ICH E6 (R3), section 4. |