This protocol template has been designed for clinical trials with medicinal products that are subject to the EU Clinical Trial Regulation No 536/2014 (CTR). Please note that the use of the template is not obligatory.

Instructions page

- 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.
- This template offers a starting document for your trial protocol. All sections can be adjusted or completed, according to the specificities of your trial. For convenience in the template, references to the applicable articles/sections in Clinical Trial Regulation No 536/2014 (CTR) are stated in grey (e.g. see CTR: Annex I D17i). When finalising the research protocol these references to the applicable CTR articles/sections can be deleted.
- All text in blue is sample text. It can be adjusted or completed according to the specificities of your trial.
- All text in the frame is explanatory text. After completion, these frames should be deleted.

Study Protocol

Clinical Trial Title:
Study Acronym:
Protocol Version and Date:
Investigational Product:

PROTOCOL SIGNATURE PAGE

Regarding disclosure rules of the CTR, please note that in CTIS only an unsigned version of the protocol should be provided.

Name	Signature	Date
Sponsor or Legal representative: *<please include name and function>* *<For non-commercial research only>* **Head of Department:** *<include name and function>*		
Coordinating Investigator: *<if applicable, please include name and function>*		
Principal Investigator: *<please include name of site, name and function>*		

I agree:

- to assume responsibility for the proper conduct of this study
- to conduct the study in compliance with this protocol and any future amendments
- not to implement any deviations from or changes to the protocol without prior review and written approval from the Ethics Committee, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements)

- that I am thoroughly familiar with the appropriate use of the investigational drug, as described in this protocol
- to ensure that all persons assisting me with the study are adequately informed about the investigational drug and their study-related duties and functions as described in the protocol
- that I am aware of and will comply with the current good clinical practice (GCP) guidelines and ethical principles outlined in the Declaration of Helsinki
- to conduct the study in accordance with all applicable laws and regulations

Table of Contents

1 Sponsor/Coordinating Investigator Information

Sponsor:

Sponsor means an individual, company, institution or organisation which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial

Principal Investigator:

Principal investigator means an investigator who is the responsible leader of a team of investigators who conduct a clinical trial at a clinical trial site.

Subinvestigator(s):
Coordinating Investigator *if applicable*:

A coordinating investigator is an investigator who bears the responsibility for the coordination of investigators operating in the various centers participating in multicenter research. Not all multicenter research will have a coordinating investigator. There is no requirement to appoint one. A project leader has the responsibility to develop a research protocol and to complete the study within the predefined goals

Statistician:
Study site(s) and co-investigator(s) *if applicable*:

2 List of Abbreviations

Please delete abbreviations that are not applicable and provide additional abbreviations used in this protocol.

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
CTA	Clinical Trial Authorisation
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation
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
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MS	Member State
PI	Principal Investigator

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

3 Protocol Version History

Version N°	Version Date	Summary of changes

4 Synopsis

A protocol synopsis should be available in at least 3 languages: Dutch, French and German.
It should be limited to 2 pages and should be understandable to a layperson.
The English version is shown here in the protocol.
It can be submitted as a separate document.

4.1 Rationale

Specify background and hypothesis of the trial.

4.2 Objective

Specify the main and secondary objectives of the trial.

4.3 Main trial endpoints

Describe the main trial endpoints and when they are assessed, e.g. the main trial 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.

4.4 Secondary trial endpoints

Describe the secondary trial endpoints, and when they are assessed e.g. number of adverse events until 30 days post end of treatment.

4.5 Trial design

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

4.6 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 subject, 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.

4.7 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. Also describe trial-related diagnostic and monitoring procedures used.

4.8 Ethical considerations relating to the clinical trial including the expected benefit to the individual subject or group of patients represented by the trial subjects 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 subjects 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.

5 Structured risk analysis

In case more than one product is concerned, make separate sections per product

5.1 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 5.2 in a comprehensive overall synthesis of the direct risks for the research subjects 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 to allow a thorough review by the ethics committee. 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 and allows an efficient communication with the ethics committee when questions arise as a result of the review of your research protocol. The remarks per item are provided as a guidance for describing 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 5.1 can be skipped; explain in chapter 5.2 why 5.1 is skipped

a. Level of knowledge about mechanism of action

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

b. Previous exposure of human beings

Concerns exposure to the test product(s) and/or products with a similar biological mechanism. Investigate direct mechanism, assess related mechanisms and analogue disease states, investigate primary and secondary pharmacology.

c. 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?.

d. 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.

e. Analysis of potential effect

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).

f. Pharmacokinetic considerations

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

g. 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.

h. 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).

i. Managing of effects

Can negative effects be managed? How? Consider antidotes or antagonists, and other counter-measures; 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).

j. Study population

For instance, are research subjects healthy volunteers or patients suffering from a life-threatening disease? Are the research subjects 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?

5.2 Overall synthesis of the direct risks for the research subjects

This should include uncertainties and the unknown and the overall risk.

Make clear what measures have been taken to reduce what risks. Examples can be: type of study population, certain in- or exclusion criteria, additional safety measurements, prolonged supervision of participants, establishing a DSMB or safety committee.

Make clear why in your opinion the remaining risks are acceptable for the subjects participating in the study.

6 Background and Rationale

6.1 Overview of Disease Pathogenesis with Relevant Literature

6.2 Epidemiology

6.3 Therapeutic conditions and current Treatments

Describe the main characteristics of the disease being studied and the currently available treatment

options.

6.4 Study Rationale

Describe what is new in this trial, which medical need the trial addresses and the clinical relevance of this clinical trial.
Summarize the findings from non-clinical studies that potentially have clinical significance and from other clinical trials that are relevant to the clinical trial (CTR: Annex I D17c).
References to literature and data that are relevant to the clinical trial, and that provide background for the clinical trial can be included (CTR: Annex I D17i).
If the trial is classified by the sponsor as low-interventional in line with CTR Article 2(3), briefly describe the justification.

6.5 Mechanism of action, Drug class

Describe the mechanism of action of the IMP(s). If necessary, include pharmacokinetic considerations (e.g. metabolism, drug interactions, excretion).

6.6 Rationale for Study Design

6.7 Rationale for Dose and Regimen

7 Study Objectives and Endpoints

Describe the primary and (if any) the secondary and exploratory endpoints and how/when they will be measured during the trial (CTR: Annex I D17l).

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.

Exploratory endpoints may include clinically important events that are expected to occur to infrequently to show a treatment effect but are included tot explore new hypotheses.

7.1 Primary Objectives

7.2 Secondary Objectives

7.3 Exploratory Objectives

7.4 Endpoints

8 Research Methods

8.1 Study 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 subjects will undergo during the course of research (CTR: Annex I D17k).

8.2 Number of Patients

Give the number of subjects planned to be enrolled in the trial and per cohort.

8.3 Patient participation

If applicable, if patients were involved in the design of the clinical trial, a description of their involvements should be provided (CTR: Annex I D17e).
Describe how patients were or will be involved during the different phases of the trial, e.g. involvement in determining the objectives, assessing the burden or distributing the results. If no patients were involved, justification should be provided.

8.4 Study Population

8.4.1 Population

Provide a description of the groups and subgroups of the subjects participating in the clinical trial, including, where relevant, groups of subjects with specific needs, for example. age, gender, participation of healthy volunteers, subjects with rare and ultra-rare diseases (CTR: Annex I D17h).

8.4.2 Inclusion Criteria

8.4.3 Exclusion Criteria

Describe all exclusion criteria for the trial (CTR: Annex I D17v).

If a specific group is excluded/underrepresented in the clinical trial, justification should be provided (CTR: Annex I D17y).

For authorised products consider contraindications included in the SmPC (for IMP(s), comparator and auxiliary medicinal products).

8.4.4 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).

Vulnerable population(s) include: incapacitated subjects without decision-making capacity, minors, pregnant or breastfeeding women, incapacitated subjects without decision-making capacity in emergency situations (CTR: Articles 31, 32, 33, 34 and 35).

Discuss the benefit/risk profile. The inclusion of a vulnerable population can be justifiable only on the basis that this information could not be obtained from non-vulnerable populations.

For incapacitated or minor subjects the trial should offer some direct benefit to the subject, or some direct benefit to the population represented. See CTR Article 33 for requirements specific to pregnant/breastfeeding subjects.

For emergency clinical trials refer to CTR Article 35 that describes in which situations deferred consent is allowed regarding medical research in emergency situations.

8.5 Study Duration for Subjects

8.6 Group Allocation & Blinding *(if applicable)*

9 Study Assessments and Procedures

9.1 Schedule of Activities

9.2 Study Assessments/Interventions per Visit

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 study and discontinuation visit.

The protocol must contain a detailed description of the procedures that subjects will undergo in the course of the research.

It should be clearly indicated which procedures are part of the medical treatment and which are extra for this study and whether diagnostic procedures or treatment will be postponed.

At least the following matters should be addressed (if applicable):

- Invasive procedures to be performed (injections, venapunction, liquor sampling, scopic examination, biopsy, catheterisation, radiation).

-Psychological/psychiatric investigations to be performed.

- Questionnaires (e.g. Quality of Life).

- Clinical laboratory tests to be performed (e.g. biochemistry, urinalysis, HIV).

- Pregnancy tests (frequency of testing). In case pregnancy tests will be performed during the study, consider the guidance 'CTFG recommendations related to contraception and pregnancy testing in clinical trials'

9.2.1 Screening

9.2.2 Treatment Period

9.2.3 Follow Up Period

9.2.4 End of Study Visit

9.3 Detailed Study Assessments

9.3.1 Physical Examination

9.3.2 Vitals Signs

9.3.3 Laboratory Testings

9.3.4 Efficacy Assessments

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

9.3.5 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 subjects after adverse reactions including the type and duration of follow-up. (CTR: Annex I D20d).

10 Interventions/Treatment

10.1 Investigational Medicinal Product(s) (IMP(s))

In case more than one IMP is used in the clinical trial, make separate sections per IMP (CTR: Annex I D17b). Also use of comparator IMP(s) and placebo should be described

10.1.1 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.
If a clinical trial is conducted with an active substance available in the EU under different trade names in a number of authorised medicinal products, the protocol may define the treatment in terms of the active substance or in terms of 'Anatomical Therapeutic Chemical (ATC) code' (level 3-5) only and not specify the trade name of each product (CTR: Annex I D18).

10.1.2 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.

10.1.3 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).

Include additional information required for specific medicinal products (e.g. radiopharmaceuticals or advanced therapy medicinal products).

In case of ATMPs also consider the EMA guidelines relevant for ATMP's on the EMA website.

10.2 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.

10.3 Placebo

If applicable.
Describe and justify the use of a placebo. For example, if no proven intervention exists or when the use of placebo is necessary to determine the efficacy of safety of an intervention, and the

patient who receives placebo is not subject to any risk of serious or irreversible harm.

For trials where the placebo group will receive placebo in addition to an active treatment, less justification will be required. Patients should receive at least the standard of care in the placebo arm.

10.4 Auxiliary Medicinal Product(s) (AxMP(s))

In case more than one AxMP is used in the clinical trial, make separate sections per AxMP (CTR: Annex I D17b).

An auxiliary medicinal product (AxMP) means a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product.

Examples are medicinal products used as rescue medication, challenge agents, to assess end-points in the clinical trial, or background treatment. Further, the medicinal product should be related to and relevant for the design of the clinical trial, which excludes 'concomitant medications'.

For more information on the definitions and requirements of AxMPs see the document 'Auxiliary Medicinal Products in Clinical Trials - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use'

10.4.1 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.)

10.4.2 Statement on authorization and justification unauthorized AxMP

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).

In principle, only authorised medicinal products should be used as AxMP in clinical trials (CTR: Article 59). However, in certain circumstances unauthorised auxiliary medicinal products may be used, for instance an authorised AxMP is not available in the EU or where the sponsor cannot reasonably be expected to use an authorised AxMP. This has to be justified in the protocol.

10.4.3 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).

10.5 Additional considerations for trials involving a medical device

If applicable.

Devices used in the clinical trial should have a CE marking and should be used in line with their intended use.

Provide information if the device is considered an investigational MD meaning that it is not CE-marked, or it is CE-marked but is not used in accordance with its intended use in the trial. The

most important data supporting use of such a device as well as technical specifications of the device should be included here. Also consider the Medical Device Regulation (EU) 201/745 (MDR)

10.6 Additional considerations for trials involving an in-vitro diagnostic or companion diagnostic

If applicable.

All IVDs used in the clinical trial should either have a CE marking and used in line with their intended use or should be an in-house developed IVD (see article 5.5 of the In Vitro Diagnostics Regulation (EU) 2017/746 (IVDR) (see List of background information)).

Investigational IVDs used in the clinical trial should be part of a performance study and comply with chapter VI of the IVDR. Provide the most important data supporting use of such an IVD as well as technical specifications of the IVD. Please consider the In Vitro Diagnostics Regulation (EU) 201/746 (IVDR).

10.7 Preparation and labelling of the study treatment(s)

Investigational and auxiliary medicinal products should be appropriately labelled in order to ensure subject safety and the reliability and robustness of data generated in clinical trials, and in order to allow for the distribution of those products to clinical trial sites throughout the EU.

Labelling requirements for IMPs and AxMP are set out in CTR Chapter X and Annex VI.

There is no need to submit a mock-up of the label. Only the text that is labelled on the IMP, as per CTR Chapter X and Annex VI, should be included in the application dossier.

Labelling requirements conform CTR are not applicable for radiopharmaceuticals used as diagnostic IMP or as diagnostic AxMP. Diagnostic IMP and diagnostic AxMP should be labelled according to GMP-Z.

10.8 Randomisation, Blinding & Unblinding Procedures

Describe the specific methods used to assign subjects to treatment groups and to minimise bias. If applicable, provide information about the procedures for randomisation and blinding (CTR: Annex I D17m).

- Describe the arrangements for the maintenance of clinical trial treatment randomisation codes and procedures for breaking code (CTR: Annex I D17q).

- Address issues regarding labelling and the unblinding of investigational medicinal products (CTR: Annex I D22).

10.9 Concomitant Treatment

10.9.1 Permitted medication(s)

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

Describe type, dose per unit and maximum dose allowed.

10.9.2 Prohibited medication(s)

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

Consider contraindications for IMP/comparator/AxMP. Consider medications with potential pharmacokinetic interactions.

Indicate (if relevant) what will happen if a prohibited medication is taken during the study (e.g. does this lead to discontinuation of study treatments?).

10.10 Lifestyle restrictions

10.10.1 Contraception measures

Discuss contraception measures proposed for women with childbearing potential (WOCBP) participated in the trial and if relevant for male participants with WOCBP partner.

Justify the proposed contraception methods based on non-clinical and clinical data and the risk of teratogenicity/fetotoxicity in pregnancy for IMP(s)/comparator IMP(s)/AxMP(s). Where the risk in early pregnancy is unknown the risk should be considered as possible.

Consider the following matters:
- The inclusion of WOCBP requires use of a highly effective contraceptive measure for IMPs with demonstrated or suspected human teratogenicity/fetotoxicity.

- Duration of contraceptive measures after the end of treatment.

- Definition of WOCBP or postmenopausal woman.

10.10.2 Other requirements

If applicable, describe other measures (e.g. diet restrictions or required periods of fasting during the study, or restriction on blood or tissue donation).

11 STUDY DISCONTINUATION AND COMPLETION

11.1 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 subject, give a specification of the estimated end date and a justification thereoff (CTR: Annex I D17o).

11.2 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 subject safety.

11.3 Discontinuation/withdrawal of individual subjects

Describe criteria for withdrawing individual subjects from treatment or from the clinical trial (CTR: Annex I D17v).

Consider also discontinuation criteria for IMPs (including comparator and placebo) and discontinuation criteria for background therapy. Consider also discontinuation criteria for vulnerable population.

Patients with disease progression or who are not responding to treatment should be withdrawn from the trial or this should otherwise be justified sufficiently.

Note that subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

Describe the procedure relating to the withdrawal of subjects from treatment or from the clinical trial (CTR: Annex I D17w).

Include information about the procedures for:

- Collection of data regarding withdrawn subjects
- Replacement of subjects after withdrawal
- Follow-up of subjects that have withdrawn from treatment or from the clinical trial (CTR: Annex I D17w).

11.4 Arrangements for subjects after their participation in the clinical trial ended

If applicable, describe the arrangements for taking care of the subjects after their participation in the clinical trial has ended, where such additional care is necessary because of the subjects' 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).

12 Traceability, storage, accountability and compliance

12.1 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).

Procedures must be appropriate and proportionate to ensure the safety of the subject and the reliability and robustness of the data generated in the clinical trial. In particular, take into account whether the IMP is an authorised IMP, and whether the clinical trial is a low-intervention clinical trial (CTR: Article 51).

For traceability in low-intervention clinical trials generally, routinely maintained pharmacy documentation on receipt, storage and handling may be sufficient, if:

- normal prescribing practice and documentation applies
and
- specific documentation of prescribed amounts and doses taken is available in the patient's medical records or other source documents, e.g. the patient's diary.

The protocol should include justifications for the level of IMP accountability undertaken.

12.2 Accountability of the study treatment(s) and compliance

Describe the accountability procedures for the supply and administration of medicinal products to

subjects including the maintenance of blinding, if applicable (CTR: Annex I D17ab).

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

13 Administrative aspects, monitoring and confidentiality

This study will be conducted in compliance with the protocol, with Clinical Trials regulation 536/2014 and with the principles of good clinical practice.

13.1 Approval initial application and substantial modifications

The trial protocol, informed consent form, subject information leaflet, 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 subjects or on the reliability and robustness of the data generated in the clinical trial.

This implies that a substantial modification can only be submitted and assessed after a decision is issued on a previously submitted application: initial application (CTR Article 8), additional member state (CTR Article 14), another SM on Part I only or Part II only or both Part I and II (CTR Articles 19, 20 and 23).

13.2 Monitoring

The investigator must make all trial documentation and related records available in case a monitoring visit or audit by the Sponsor is requested. Also in case of regulatory inspections all trial documentation should be made available to the inspector(s). All participant data must be handled and treated confidentially.
The Sponsor's monitoring frequency will be determined prior to the start of the trial. A monitoring plan will be generated detailing the frequency and scope of monitoring for the trial. Throughout the course of the trial the monitoring plan can be adjusted as necessary.

13.3 Recording, handling and storage of information

13.3.1 Handling of data and data protection

Include a statement by the sponsor or his or her representative that data will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679. (compliance with national requirements on data protection will be further assessed during Part II of the clinical trial application).

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 subjects. 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 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.

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.

An Electronic Data Capture system "***add name of the system in the text***" will be used for data collection. The system is validated and access to all levels will be granted/revoked by the Sponsor representative. Trial data should be entered within reasonable time after the subject attended the visit. Corrections/modifications will be automatically tracked by an audit trail detailing date and time of the correction and the name of person performing the correction.

13.3.2 Source documents and case report forms (CRF)

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 subject will be referred to by the study subject 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).

13.3.3 Clinical trial master file and data archiving

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 subjects 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

13.3.4 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).

Pay particular attention to how samples will be coded, by whom the key to the code is safeguarded, who has access to the samples and how long samples will be stored. In case of future use briefly include the overall goal (e.g. more insight into the disease, more insight into certain aspects of the IMP) and describe if samples will be stored for possible future use beyond the scope of this protocol and of related studies. (compliance with use of biological samples will be further assessed during Part II of the clinical trial application.

13.4 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).

This trial may be subject 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.

13.5 Reporting of serious breaches

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 seven days of becoming aware of that breach (CTR: Article 52).

13.6 Notification of the start and the end of the recruitment

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 subject 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 subjects for a clinical trial in that Member State through the EU (CTR: Article 36(3)).

13.7 Temporary halt/(early) termination

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)).

13.7.1 Temporary halt/early termination for reasons not affecting the benefit-risk balance

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 subjects will be provided as well (CTR: Article 37(7)).

13.7.2 Temporary halt/early termination for reasons of subject safety

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 subject 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 subject to the authorisation procedure laid down in Chapter III of the CTR (CTR: Article 38).

13.8 Summary of the results

Within one year from the end of a clinical trial in all Member States concerned, the sponsor will submit to the EU database 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 database 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)).

13.9 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)).

Public disclosure of sponsor and Member State (MS) documents and data (except data and documents related to Quality, like for instance the Q-section of the IMPD) in the public database of CTIS takes place at the time of the decision by the MSC, unless the sponsor requested for a deferral of

the public disclosure at the initial application when registering the clinical trial in CTIS.

This deferral is based on the clinical trial category. No deferral is possible for the main characteristics of the clinical trial, conclusion part I, conclusion part II, outcome and date of decision on clinical trial, start and end dates and temporary halt.

There are three categories of clinical trials (based on the use and status of their IMPs) for which the first category can have the longest deferral. Where a clinical trial protocol sets out a multiphase or adaptive study design that falls in both category 1 and 2, the trial will be treated according to the higher of the potential designations.

For more information on the rules and criteria for the application of these exceptions in relation to the
disclosure provisions of the CTR refer to 'EMA Appendix on disclosure rules EMA/228383/2015'.

14 Statistical Analysis

14.1 Description of statistical methods

Describe the statistical methods to be employed. If applicable, describe planned interim analysis in section 13.7 (CTR: Annex I D17u).

14.2 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

14.3 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

14.4 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.>

14.5 Sample size, trail power and level of significance used

Describe the number of subjects 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.

Describe for example total sample size, number of subjects per arm, assumptions made, the type I and type II error, superiority/non-inferiority, one- or two sided test(s).

The number of subjects should always be large enough to provide a reliable answer to questions addressed. Also the size of detectable differences should be of clinical relevance.

The number of subjects 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.

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 and power. The power of the study is the probability that the study will have a significant (positive) result – provided a positive effect exists. Ask advice from a statistician to help you with this matter.

In case of multiple primary objectives, e.g. evaluation of multiple endpoints, each objective should have its own power calculation and in each of these the multiplicity corrected alpha, if needed, should be taken into account.

14.6 Planned analysis

Describe for each of the endpoints:
- In general terms, how the data (categorical data and/or continuous variables) will be presented (quantitative and/or qualitative), and how derived parameters will be calculated (if applicable);
- How missing data will be handled;
- How the data will be statistically analysed, including information on subjects to be included in the analyses (e.g. intention-to-treat analysis or per-protocol analysis).

From the descriptions it has to be clear how the primary and secondary objectives of the study will be answered (CTR: Annex IV D).

14.6.1 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 subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects) (CTR: Annex I D17u).>

14.6.2 Analysis secondary endpoint(s)

Describe, if applicable

14.6.3 Analysis other study parameters/endpoints

Describe, if applicable

14.7 Interim analysis

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

Describe for example timing and number of IA, method to control overall type I error, possible outcomes (e.g. stopping early for overwhelming efficacy/futility/sample size re-assessment), details of who is responsible for performing the IA.

Also refer to the applicable charter in case a Data Safety Monitoring Board or Data Monitoring Board will be established to advice on stopping.

14.8 (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).

14.9 Procedure for accounting for missing, unused and spurious data

Describe the procedures (CTR: Annex I D17u).

14.10 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).

15 Safety Monitoring and Reporting

15.1 Definitions

15.1.1 Adverse Events

Adverse events are defined as any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.
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.

15.1.2 Serious Adverse Events

Serious adverse event is any untoward medical occurrence in a patient or trial subject 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.

15.1.3 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).

The RSI is either described in the Summary of Product Characteristics (SmPC, for an authorised medicinal product) or the Investigator's Brochure (IB, for an unauthorised medicinal product). The cover letter indicates the location in the application dossier of the RSI (CTR: Annex III 2.2(7)).

15.2 Recording of AEs/SAEs/SUSARS

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

15.3 Reporting of AEs and SAEs

In case of a low-intervention clinical trial safety recording and reporting can be simplified, applying a risk proportionate approach.

Risk adaptations to safety reporting refer to documenting of AEs in source documents, recording of AEs in the case report forms (and hence reporting to the sponsor) and to the requirements of immediate (not later than within 24 hours of obtaining knowledge of the event) reporting (of SAEs/SUSARs) by the investigator to the sponsor.

The protocol may select certain (and not all) adverse events not to be recorded in the CRF and reported to the sponsor. This applies to marketed products with a known safety profile:

(i) of the definition - IMPs are used according to the conditions of the marketing authorisation: A reduced or targeted safety data collection may be appropriate for IMPs with a well known safety

profile, depending on the CT objective and provided that no conflicting post-approval commitments regarding safety are in place.
(ii) of the definition - IMPs are marketed, but used differently to the conditions of the marketing authorisation: Any adaptation to safety reporting should be based on a trial-specific risk assessment and extent of use in clinical practice.

Please note that any such adaptation should be clearly stated and justified in the protocol.

15.3.1 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)).

15.3.2 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).

15.4 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. SAEs need to be reported till end of study within Belgium, as defined in the protocol.

15.5 Reporting of SUSARs by the sponsor to the EudraVigilance database

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 database all relevant information about any SUSAR (CTR: Article 42).

The period for the reporting of SUSARs by the sponsor to the EMA 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)).

15.6 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).

The annual safety report (ASR/DSUR) must be submitted in CTIS. The annual safety report will be presented in the DSUR format as per 'ICH guideline E2F on development safety update report' (see List of background information).

In the case of a clinical trial involving the use of more than one investigational medicinal product, the sponsor may submit a single safety report on all investigational medicinal products used in that clinical trial in accordance with CTR Article 43(2). However, the reasons and a relevant justification should be provided in the protocol (CTR: Annex I D21).

15.7 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).

Additional measures need to be in place to protect the blinding in the case where a particular laboratory finding or a specific adverse reaction might reveal the treatment allocation.

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

When reporting a SUSAR to the EMA, the sponsor will only unblind the treatment allocation of the affected subject 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)).

15.8 Temporary halt for reasons of subject safety

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject 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 subjects are kept informed.

15.9 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 subjects. 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).

15.10 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.

16 Ethical Considerations

16.1 Ethical Conduct of the Study

16.1.1 Declaration of Helsinki

The trial will be performed in accordance with the Declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

16.1.2 Ethics Committee

Before the start of the trial or implementation of any amendment, approval of the trial protocol and amendments, informed consent forms and other relevant documents will be obtained from the applicable ethical committee(s).

16.2 Recruitment and Informed Consent

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

Specify who will take informed consent, how and when it will be taken. Also how much time will subjects be given to consider their decision? (recruitment arrangements will be further assessed during Part II of the clinical trial application).

Informed consent will be obtained prior to any study related procedures being undertaken at screening. Informed consent will be written, dated and signed by the person performing the interview, and by the subject or, where the subject is not able to give informed consent, his or her legally designated representative. The investigator or his/her representative will explain the nature of the study to the subject or his or her legally designated representative, and answer all questions regarding this study. In the interview it will be verified that the subject has understood the information. The subject or, where the subject is not able to give informed consent, his or her legally designated representative will be provided with a copy of the document (or the record) by which informed consent has been given. The informed consent will be documented. Adequate time will be given for the subject or his or her legally designated representative to consider his or her decision to participate in the clinical trial (CTR: Article 29).

16.3 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.

Consider the special requirements for trials on vulnerable populations , e.g. in minors, incapacitated persons, pregnant or breastfeeding women and trials in emergency situations (CTR: Articles 31, 32, 33, 34, and 35), including any additional national measures.

For studies with capacitated adults and therapeutic research with minors/incapacitated subjects/pregnant or breastfeeding women, 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 which extent the research may be beneficial to the subject.

In case of non-therapeutic research with minors/incapacitated subjects/pregnant or breastfeeding women, it should be stated why the risks associated with participation can be considered negligible and the burden can be considered minimal.

If the study population includes minors/incapacitated subjects/pregnant or breastfeeding women or dependent subjects and the study is non-therapeutic, it should also be explained why the research may be regarded as group-related. A study may be deemed to be group-related if it is evident that it could not be conducted without the participation of subjects belonging to the group in question

16.4 Compensation for injury

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

In accordance with the Belgian law relating to experiments in humans dated May 7, 2004, and with the Belgian law relating to clinical trials dated May 7, 2017, UZ Brussel/VUB as Sponsor shall be liable, even without fault for any damages incurred by the Study Subject and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance program.

16.5 Compensation for subjects

Please shortly describe any special incentives, compensation or treatment that subjects will receive through participation in the clinical trial (compensation for subjects will be further assessed during Part II of the clinical trial application).

16.6 Compensation for investigators

Please shortly describe the compensation investigators will receive for performing the clinical trial (compensation for investigators will be further assessed during Part II of the clinical trial application).

16.7 Study Data Protection

The collection and processing of personal data from participants enrolled in the study will be limited to those data that are necessary to fulfill the objectives of this study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations.

16.8 Subject Identification

The participant identification will be treated as confidential and will be filed by the investigator in an identification log. This log is kept at the participating site and shall not be copied. In all reports and communication between the site and the Sponsor the participant shall be identified with a participant study number.

17 Reporting and Dissemination

The data and information collected during this trial will be reported in a clinical trial report and/or a publication in a scientific/medical journal. Reporting of trial results will be performed according

to local regulations.

Data collected within the UZ Brussel or VUB as an employee or (PhD) student of the VUB are owned by the UZ Brussel VUB. For the correct authorship rules we refer to the International Committee of Medical Journal Editors:
https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

18 Finance and Conflict of Interest Statement

Investigators and study team members will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities/ethics committee. Any update of information on financial interests should be disclosed during the course of the study.

19 Tables and Figures

20 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.

Note: Where a reference is made to data generated in a clinical trial, that clinical trial shall have been conducted in accordance with the Regulation (CTR: Article 25(4)).

Where the clinical trial has been conducted outside the EU, it shall have been conducted in accordance with principles equivalent to those of the Regulation as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial (CTR: Article 25(5)).

Data from a clinical trial started shall only be submitted in an application dossier if that clinical trial has been registered prior to its start in a public register which is a primary or partner registry of, or a data provider to, the WHO ICTR or if the results of that clinical trial have been published in an independent peer reviewed scientific (CTR: Article 25(6)).