

TEMPLATE RESEARCH PROTOCOL

(September 2018)

- May 2015: adaptation section 11.5: text in accordance to old and new Measure regarding Compulsory Insurance for Clinical Research in Humans
- Sept 2015: adaptation section 9.1, 9.2 and 12.5: text in accordance to WMO amendment on reporting SAE and temporary halt (section 10 of WMO)
- Oct 2015: adaptation section 4.4 – comment [CCMO15], 8.2 and 10.1 with respect to methodology/statistics
- Sept 2018: adaptation section 12.1 and comment [CCMO46] due to applicability GDPR as of May, 2018

PROTOCOL TITLE '*<Type full title of protocol>*'

Protocol ID	<i><include protocol ID given by sponsor or investigator></i>
Short title	
EudraCT number	<i><only applicable for studies with an investigational medicinal product></i>
Version	
Date	
Coordinating investigator/project leader	<i><if applicable, include name and contact data></i>
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder) <i><Multicenter research: per site></i>	<i><please include name and contact data></i>
Sponsor (in Dutch: verrichter/opdrachtgever)	<i><please include name and contact data></i>
Subsidising party	
Independent expert (s)	<i><please include name and contact data></i>
Laboratory sites <i><if applicable></i>	<i><please include name and contact data></i>
Pharmacy <i><if applicable></i>	<i><please include name and contact data></i>

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
<p>Sponsor or legal representative: <please include name and function></p> <p><For non-commercial research,> Head of Department: <include name and function></p>		
<p>[Coordinating Investigator/Project leader/Principal Investigator]: <please include name and function></p>		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: <Please specify background and hypothesis (if applicable) of the study>

Objective: <Please specify the main and secondary objectives of the study>

Study design: <Please describe the design of the study, e.g. observational study, double-blind placebo controlled intervention study, longitudinal study>

Study population: <Please describe the study population, e.g. healthy human volunteers, 18 - 55 yr old>

Intervention (if applicable): <Please describe which intervention is given, e.g. one group receives twice daily a 10 mg tablet of product X and the other group receives twice daily a placebo tablet>

Main study parameters/endpoints: <Please describe the main study parameters, e.g. the main study parameter is the percent change in the number of events from baseline to endpoint, or the difference in genetic profile between patients and controls, or the total number of adverse reactions or a blood parameter>

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: <Please describe the burden and risks associated with participation, e.g. the amount and number of blood samples, the number of site visits, physical examinations or other tests, questionnaires or diaries which have to be filled in, physical and physiological discomfort associated with participation, the risks associated with the investigational treatment. A risk-benefit analysis can be given, if applicable. If a non-therapeutic study is carried out with minors or incapacitated persons, it should be specified whether the risks are negligible and the burden minimal and why the study is group related (i.e., study can only be done using these patients groups).>

1. INTRODUCTION AND RATIONALE

2. OBJECTIVES

Primary Objective: <please include primary objective>

Secondary Objective(s): <please include secondary objectives, if applicable>

3. STUDY DESIGN

<Please include a description of the study design (examples of intervention studies are: double-blind randomized placebo-controlled trial, cross-over trial; examples of observational studies are: (nested) case-control study, cohort study), the duration and setting of the study.

If relevant, also include a justification of the design (for example for the type of control group, the duration of the treatment, the choice for cross-over or a parallel design)

A flow chart can be included to give an overview of the study design and the main procedures that subjects will undergo in the course of research.>

4. STUDY POPULATION

4.1 Population (base)

4.2 Inclusion criteria

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

4.3 Exclusion criteria

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

4.4 Sample size calculation

5. TREATMENT OF SUBJECTS

< This chapter is only applicable for intervention  studies >

5.1 Investigational product/treatment

<Please give a description of the intervention (medicinal product, medical device, food supplement, radiation, surgery, behavioural interventions, etcetera). Also use of comparator or placebo should be described.>

5.2 Use of co-intervention (if applicable)

< Please describe what subjects should do and not do (e.g. use co-medication, adequate contraception, diet). If it is allowed to use co-medication or other kind of intervention, it should be specified on forehand what is allowed.)>

5.3 Escape medication (if applicable)

<Please describe type, dose per unit and maximum dose allowed.>

6. INVESTIGATIONAL PRODUCT

<This chapter is applicable for research with any product; medicinal product, food product, medical device or other >

6.1 Name and description of investigational product(s)

6.2 Summary of findings from non-clinical studies

<One may refer to the Investigator's Brochure (IB), Investigational Medicinal Product Dossier (IMPD), Summary of Product Characteristics (SPC) or a similar document (if applicable), by mentioning the relevant pages in that document. Be sure that the information is up to date and references to peer reviewed papers in (biomedical/scientific) journals should be given where appropriate.>

6.3 Summary of findings from clinical studies

<See explanatory text of chapter 6.2, including remark>

6.4 Summary of known and potential risks and benefits

<See explanatory text of chapter 6.2, including remark>

6.5 Description and justification of route of administration and dosage

6.6 Dosages, dosage modifications and method of administration

6.7 Preparation and labelling of Investigational Medicinal Product

6.8 Drug accountability

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

7. NON-INVESTIGATIONAL PRODUCT

<This chapter is applicable for any other product that is used in the study, like challenge agents or products used to assess end-points in the trial. This can be a medicinal product or a food product or a chemical compound or stable isotope or other product.

This chapter does **not** include co-medication or escape medication, these are already mentioned in chapter 5

For products to be used as in usual clinical practice the information can be limited to the chapters 7.1, 7.6 and 7.7 >

7.1 Name and description of non-investigational product(s)

7.2 Summary of findings from non-clinical studies

<One may refer to the Investigator's Brochure (IB), Investigational Medicinal Product Dossier (IMPD), Summary of Product Characteristics (SPC) or a similar document (if applicable), by mentioning the relevant pages in that document. Be sure that the information is up to date and references to peer reviewed papers in (biomedical/scientific) journals should be given where appropriate.>

7.3 Summary of findings from clinical studies

<See explanatory text of chapter 7.2, including remark>

7.4 Summary of known and potential risks and benefits

<See explanatory text of chapter 7.2, including remark>

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

<Please describe the procedures for the shipment, receipt, disposition, return and destruction of the non-investigational medicinal products.>

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

< Please describe the main study parameter/endpoint, for example number of events/relapse, blood hormone levels, etcetera >

8.1.2 Secondary study parameters/endpoints (if applicable)

< Please describe the secondary study parameters/endpoints, for example number of adverse and serious adverse events, etcetera >

8.1.3 Other study parameters (if applicable)

<Please describe the other study parameters. For example, baseline values or parameters which might intervene with the main study parameter (confounders), like body weight, smoking, etcetera. >

8.2 Randomisation, blinding and treatment allocation

[<This chapter is only applicable for intervention trials and should also describe for blinded studies the indications for breaking the randomisation code. Describe by whom and how the randomization sequence is prepared and what measures are taken that “concealed allocation” in assigning patients to study arms is guaranteed >]

8.3 Study procedures

< Please give a description of the procedures, techniques, methods and/or tests to be used to assess the defined study parameters/endpoints. Include information on sample volumes. All procedures that subjects undergo must be listed. A schedule of assessments can be helpful >

8.4 Withdrawal of individual subjects

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.

8.4.1 Specific criteria for withdrawal (if applicable)

8.5 Replacement of individual subjects after withdrawal

8.6 Follow-up of subjects withdrawn from treatment

8.7 Premature termination of the study

< Please describe the criteria for terminating the study prematurely and the procedures in case the study will be terminated prematurely.>

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, 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 notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

< Please describe the procedures for handling the serious adverse events. If certain SAEs do not require immediate reporting by the investigator to the sponsor, please specify.>

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs: *<specify which*

SAEs do not require immediate reporting by the investigator to the sponsor, if applicable>

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

< If certain SAEs do not require(expedited) reporting to the accredited METC, please specify these SAEs as well as the frequency of reporting of these SAEs in line listings, or in a annual safety report or otherwise.>

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

<This chapter is only applicable for studies with an investigational medicinal product>

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

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

1. the event must be serious (see chapter 9.2.2);
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:
 - Summary of Product Characteristics (SPC) for an authorised medicinal product;
 - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC *<reporting via webportalToetsingOnline is only applicable for investigator initiated studies>*:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;

- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

< For multicentre studies the responsibilities of investigators in participating centres as well as of the coordinating investigator should be clearly defined >

<Please describe also the method of breaking the code for SUSAR reporting.>

9.3 Annual safety report

<This chapter is only applicable for studies with an investigational medicinal product>

< The annual safety report may be combined with the annual progress report (see chapter 12.4).>

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;

- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 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 the Netherlands, as defined in the protocol

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

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

The composition of the DSMB should be described and it should be clear that each member has no conflict of interest with the sponsor of the study.

The task and responsibility of the DSMB should be described (see chapter 10.4 for interim analyses either for safety or for futility or positive efficacy) >

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

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

< In case a DSMB 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>

10. STATISTICAL ANALYSIS

<Describe for each of the parameters (as mentioned in chapter 8.1), in the applicable chapter below:

- 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.

From the descriptions it has to be clear how the primary and secondary objectives of the study will be answered.

10.1 Primary study parameter(s)

<Describe in detail how the primary analysis will be done for the primary outcome parameter(s) in order to avoid subjective choices to be made during the analysis .

Discuss how the type I error will be controlled in case of multiplicities 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) should be labeled 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.>

10.2 Secondary study parameter(s)

10.3 Other study parameters

10.4 Interim analysis (if applicable)

< Please describe when the interim analysis will be done, which statistical methods will be used, who will perform the interim analysis and the stopping rules (if applicable). Also refer to the DSMB Charter in case a Data Safety Monitoring Board will be established to advice on stopping, see also chapter 9.5>

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

<In this chapter it can be stated that the study will be conducted according to the principles of the Declaration of Helsinki (version, date, see for the most recent version: www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts (if applicable, please specify)>

11.2 Recruitment and consent

<Please give a description of the recruitment and informed consent procedures. How and by whom (investigator, supervising doctor, other person) will subjects be informed about the study and asked for their consent? How much time will they be given to consider their decision? The patient information letter and informed consent form should be attached as a separate document.>

11.3 Objection by minors or incapacitated subjects (if applicable)

<Please specify which code of conduct is applicable for minors and/or incapacitated adults participating in non-therapeutic research. This should also be specified in the informed consent letter.>

11.4 Benefits and risks assessment, group relatedness

<Please give a justification of the proposed study.>

11.5 Compensation for injury

<Please give information about the liability insurance and the insurance for the subjects participating in the study.>

<The sponsor or investigator should also have a liability insurance.>

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

<Please describe any special incentives, compensation or treatment that subjects will receive through participation in the study.>

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

< Please describe the procedures for handling data, how data are coded, who has access to the source data, by whom the key to the code is safeguarded, how long data and/or human material will be kept, which steps are taken to ensure data security and how the subjects privacy is protected.>

12.2 Monitoring and Quality Assurance

< If monitoring of the conduct of the study takes place, please describe who will monitor, what will be monitored, frequencies etc. One can refer to a monitoring plan for details >

12.3 Amendments

<The following text is applicable for studies without an investigational medicinal product.>

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

<The following text is applicable for studies with an investigational medicinal product.>

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

< Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation.>

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

<The following text is applicable for studies without an investigational medicinal product.>

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

<The following text is applicable for studies with an investigational medicinal product.>

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study,

to the accredited METC and the Competent Authority.

<In case the final study report will not be available within one year, another term should be defined including the reasons.>

12.6 Public disclosure and publication policy

<Please mention the arrangements made between the sponsor and the investigator concerning the public disclosure and publication of the research data. >

13. STRUCTURED RISK ANALYSIS

<This chapter is applicable for research with any product: medicinal product, food product, medical device or other (as described in chapter 6 and 7)>

13.1 Potential issues of concern

< In this final paragraph of the research protocol a structured risk analysis which consists of a number of steps is required. The analysis should result in a comprehensive overall synthesis of the direct risks for the research subjects in this study in chapter 13.2. 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 METC. For details one may refer to the previous chapters, 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 METC 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 13.1 can be skipped; explain in chapter 13.2 why 13.1 is skipped >

- a. Level of knowledge about mechanism of action

- b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

- c. Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material?

- d. Selectivity of the mechanism to target tissue in animals and/or human beings

- e. Analysis of potential effect

- f. Pharmacokinetic considerations

- g. Study population

h. Interaction with other products

i. Predictability of effect

j. Can effects be managed?

13.2 Synthesis

<should include uncertainties and the unknown and the overall risk:

Make clear what measures have been taken to reduce what risks

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

14. REFERENCES

<Include all key references published in peer reviews journals that are relevant for the study and are discussed in the protocol. Do make sure that the references are up to date.>