|  |  |  |  |
| --- | --- | --- | --- |
|  | | Clinical interventional study protocol (Template) | Clinical trial Center |
| AAHRPP-DSQ-037\_EN | Version 6.0 | Application date :  02/04/2024 |

*DELETE THIS PAGE IN THE FINAL VERSION OF YOUR DOCUMENT*

**DEFINITION**

A clinical research protocol is a document describing the objective(s), design, methodology, statistical aspects and organization of an experiment. The term protocol covers the original protocol as well as its successive versions and modifications (Art 2,22° Law May 7, 2004[[1]](#footnote-1))

**INSTRUCTIONS D’UTILISATION**

* This document is a protocol template based on the Good Clinical Practice Guidelines for Research (ICH GCP E6 R2[[2]](#footnote-2)).
* It should be used to write a protocol for prospective interventional, non-drug, non-medical device trials.
* The sections proposed in this template can be adapted to suit your needs.
* Some information may also be provided in other documents, which must be referenced in the protocol as appendices (e.g. informed consent).
* The red text corresponding to the instructions for use should be removed, as should this first page.
* Text in black should be retained.
* Text in green should be adapted to your study.
* You can modify the title and layout styles. Don't forget to update the table of contents.
* Each protocol version should be numbered and dated in the footer.
* The protocol should preferably be written in English if you wish to publish the results of your study. This document is also available in French, to be used according to your choice.
* Final format: PDF

Protocol Title

|  |  |
| --- | --- |
| Short title | Fill in |
| Acronym / Protocol code | Fill in |
| Protocol version and date | Fill in |
| Sponsor | Cliniques universitaires Saint-Luc  Belgium |
| Financial/Material support | Institutions (corporations, governments, etc.) that provide any type of support should not be listed as sponsor, but should be mentioned here |
| Investigator-Sponsor | Name and contact details |

The information contained in this document is the property of the Sponsor/ Investigator-Sponsor and may not be reproduced, published or disclosed to others without written authorization of the Sponsor/ Investigator-Sponsor.

Version History

| **Version** | **Approval Date** |  | **Changes** |
| --- | --- | --- | --- |
| 1.0 |  | Original |  |
| 2.0 |  | Amendment |  |
| 3.0 |  | Amendment |  |
| 4.0 |  | Amendment |  |

1. Signature page

**INVESTIGATOR-SPONSOR**

Name Signature Date

**SITE PRINCIPAL INVESTIGATOR**

I agree to conduct this study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects.

I agree to personally conduct or supervise this study and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I will conduct the study in accordance with the protocol, Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. The study will be conducted in accordance with all relevant laws and regulations relating to clinical experimentation and the protection of patients.

I will ensure that the requirements relating to Ethics Committee review and approval are met.

I agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements including the provision of direct access to data and source documents.

I agree to promptly report to the Ethics Committee any changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without Ethics Committee approval, except where necessary to ensure the safety of study participants.

Name Signature Date

1. Protocol synopsis

1-2 pages max

You can use this table for separate synopsis

|  |  |
| --- | --- |
| Title of Study |  |
| Acronym / Protocol code |  |
| Sponsor | Cliniques universitaires Saint-Luc |
| Investigator-sponsor |  |
| Department / Study centre(s) and site(s) principal investigator(s) |  |
| Pathology |  |
| Rationale / Publication (reference) |  |
| Objectives | * Primary: * Secondary: |
| Study Design |  |
| Number of patients |  |
| Main criteria for inclusion (inclusion/exclusion criteria) |  |
| Total study duration:   * date of planned first enrolment * date of planned last completed |  |
| Study procedures |  |

1. Schedule of activities

Insert the study flowchart

Table of contents to be updated

To ensure that your headings are included in the table of contents, you need to use the heading styles configured in the document. Use the headings available in the Word document toolbar, or create your own.

Table of content

[1. Signature page 4](#_Toc162943868)

[2. Protocol synopsis 5](#_Toc162943869)

[3. Schedule of activities 6](#_Toc162943870)

[4. List of abbreviations and definitions 9](#_Toc162943871)

[5. Ethics 10](#_Toc162943872)

[6. Objectives 11](#_Toc162943873)

[6.1. Primary 11](#_Toc162943874)

[6.2. Secondary 11](#_Toc162943875)

[7. Endpoints 11](#_Toc162943876)

[7.1. Primary 11](#_Toc162943877)

[8. Background Information and Scientific Rationale 12](#_Toc162943878)

[9. Investigational plan 12](#_Toc162943879)

[9.1. Design 12](#_Toc162943880)

[9.2. Description of population 12](#_Toc162943881)

[9.3. Strategies for participant recruitment 14](#_Toc162943882)

[10. Study interventions and procedures 16](#_Toc162943883)

[10.1. Method of assigning participant to interventions groups 17](#_Toc162943884)

[10.2. Sample lab collection 17](#_Toc162943885)

[10.3. Protocol Amendements 17](#_Toc162943886)

[10.4. Protocol Deviations 17](#_Toc162943887)

[11. Safety reporting 18](#_Toc162943888)

[11.1. Definitions and reporting process 18](#_Toc162943889)

[11.2. Assessing, Recording, and Analyzing Safety Parameters 19](#_Toc162943890)

[12. Data Management Responsibilities 20](#_Toc162943891)

[12.1. Data Quality Assurance 20](#_Toc162943892)

[12.2. Statistical Analysis 21](#_Toc162943893)

[12.3. Data handling and record keeping 21](#_Toc162943894)

[12.4. Case Report Form 22](#_Toc162943895)

[12.5. Data storage 22](#_Toc162943896)

[12.6. Access to data 23](#_Toc162943897)

[13. Insurance 23](#_Toc162943898)

[14. End of study 23](#_Toc162943899)

[14.1. For an individual subject 23](#_Toc162943900)

[14.2. For the whole study 23](#_Toc162943901)

[15. Dissemination of Results and Publication Policy 24](#_Toc162943902)

[16. Archiving 24](#_Toc162943903)

[17. Study Report 24](#_Toc162943904)

[18. Literature References 24](#_Toc162943905)

[19. Appendix 24](#_Toc162943906)

1. List of abbreviations and definitions
2. Ethics

* *This protocol, any protocol amendments, informed consent form and other relevant documents (eg. recruitment advertisements) will be submitted to the Ethics Committee (EC) for formal approval to conduct the study. The decision of the EC concerning the conduct of the study will be made in writing to the sponsor. All correspondence with the Ethics Committee will be retained in the Investigator File.*
* *The study will be conducted in accordance with legal and regulatory requirements (Belgian law of 7 May 2004, Belgian law for Patient rights 22 August 2002, Private life GDPR 2018), as well as the Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the last version of Declaration of Helsinki (World Medical Association).*
* *All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC. The formal consent of a subject, using the EC-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. The written informed consent document should be prepared in the language of the potential patient population.*
* *The identity of the participant will remain kept confidential according to the General Data Protection Regulation of 27 April 2016 (in application on 25 May 2018), to the Belgian law of 30 July 2018 on the protection of natural persons with regard to the processing of personal data and the Belgian patient’s right law (22 August 2002). Personal data will be coded. Subjects will not be identified by name or in any other recognizable way in any of the records, results or publications related to the experiment.*

1. Objectives

An objective is the purpose for performing the study in terms of the scientific question to be answered. Express each objective as a statement of purpose (e.g. to assess, to determine, to compare, to evaluate) and include the general purpose (e.g. efficacy, effectiveness, safety) and/or specific purpose (e.g. effect of an intervention on disease incidence, disease severity, health behavior).

Objectives should be simple (not complex), specific (not vague), and stated in advance (not after the research is done). After statement of the primary objective, secondary objectives may be mentioned.

* 1. Primary
  2. Secondary

1. Endpoints

A study endpoint is a specific measurement or observation to assess the effect of the study variable (study intervention). Study endpoints should be prioritized and should correspond to the study objectives and hypotheses being tested.

Always specify the timepoint (of measurement) along with the endpoint concerned, especially when it is possible to be measured more than once during the study.

The primary endpoint(s) should be clearly specified and its importance and role in the analysis and interpretation of study results should be defined. The primary endpoint is the basis for concluding that the study met its objective. Generally, there should be just one primary endpoint that will provide a clinically relevant, valid, and reliable measure of the primary objective.

The primary endpoint should be a clear, unarguable, quantitative measure of effect that will be the focus of the primary analysis and will drive the choice of sample size.

* 1. Primary

1. Background Information and Scientific Rationale

* Scientific explanation to define the issue : Discussion of important literature and data that are relevant to the study and that provide background for the study (literature revue with references listed)
* Justification of the study considering the current knowledge: A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance, and a summary from relevant clinical studies
* Benefits expected for the research
* A summary of the known and potential risks and benefits, including an assessment of the expected benefits and risks
* Perspectives for the scientific community, the hospital, the public health.

1. Investigational plan
   1. Design

Definition of the characteristics of the biomedical research by standard terms

* Experimentation type
* Monocenter or multicenter (national or international) ; number of centers
* With or without direct individual benefit
* Method of assignment to procedures (randomization, stratification)
* Number of study groups
* Study configuration : parallel groups or cross-over
* Approximate time to complete study enrollment
* Expected duration of subject participation
* Methods for collecting data for assessment of study objectives
* Other protocol-specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans)
* Interim analysis plans
  1. Description of population
     1. Patient population studied
* Characteristics of the subjects to be included: age, sex, weight, size, race, medical history, biological parameters, definition of the pathology and the enumeration of its characteristics.
* Rationale for gender and age distribution of participants
* Description of the groups and subgroups of participants, including, if applicable, groups of participants with specific needs, participation of healthy volunteers, participants with rare and ultra-rare diseases
* Justification for inclusion of participants unable to give informed consent or other special populations such as minors
* Number of patients planned
  + 1. Inclusion criteria

Provide a statement that subjects must meet all of the inclusion criteria in order to be eligible to participate in the study and then list each criterion.

* + 1. Exclusion criteria

Provide a statement that all subjects meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion.

* + 1. Subject eligibility screening

Screen failures are subjects who consent to participate in the study but do not meet one or more criteria required for participation in the study during the screening procedures. Screen failures will not be enrolled in the study. A minimal set of screen failure information will be kept to ensure transparent reporting of screen failure subjects.

Screen failures may not be rescreened / may be rescreened if [fill in].

* + 1. Withdrawal

Subjects are free to withdraw from participation in the study at any time. A subject must be discontinued from the study if he or his legal representative withdraws consent.

An investigator may withdraw a subject from the study for the following reasons: Adjust the reasons below if they do not fit the design of your study. You can also add other reasons

* Pregnancy;
* Significant study intervention non-compliance;
* If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject;
* If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation;
* Other :

In all cases, the reason why subjects are withdrawn must be recorded in detail in the electronic Case Report Form (eCRF) and in the subject’s medical records. The gathered subject data should be taken into account in the analysis of the study data.

A subject will be considered lost to follow-up if he or she fails to return for [Fill in] scheduled visits and/or is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return for a required study visit:

* The site will attempt to contact the subject and reschedule the missed visit within [Fill in] and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study;
* Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (i.e. three telephone calls and a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record or study file;
* Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
  + 1. Patient follow-up after study participation

Please describe the arrangements for taking care of the subjects after their participation in the study has ended, where such additional care is necessary because of the subjects’ participation in the study and where it differs from that normally expected for the medical condition in question.

* 1. Strategies for participant recruitment
     1. Recruitment process

Detailed description of the recruitment process :

* How will potential participants be identified?
* What resources will be used for recruitment? (Describe the format of the resources, e.g. paper or electronic and how these will be presented to potential participants e.g. via the post, in the clinic, through social media or on the radio)
* Provide a clear indication of what the first act of recruitment is
* Will identification of potential participants involve access to identifiable information? If yes, describe what measures will be in place to confirm that access to this information will be lawful
* Who will be approaching potential participants and who will be obtaining informed consent? (Describe the professional role and whether there is a prior clinical relationship with potential participants)
  + 1. Informed consent process

Information related to the study is provided to patients or their legal representative by the investigator during the consultation, according to the requirements pertaining to consent covered by ICH-GCP (E6).

There are also informed they could withdraw their consent at any time during the study without any consequence. This point is written in the informed consent form.

Patients or their legal representative receive the patient information and consent form and have time to think about their participation to the study (how many time ?). They have the opportunity to ask questions to the investigator (by email, phone or in consultation).

Patients or their legal representative come back after the reflection period. The investigator makes sure they have understood the information. They sign and date the informed consent form simultaneously with the investigator.

Patients or their legal representative receive a copy of the signed informed consent form.

If patients or their legal representative refuse the study, they will receive the standard treatment.

Special requirements : keep the applicable text below

* participants with temporary or definitive disabilities to give consent (intensive care/emergency unit, cognitive disorders, participants deprived of their rights) : not applicable (delete the following text) or (delete “not applicable”) provide justification for recruiting incapacitated adults. The legal representative expresses in place of the participant who will be invited to sign an informed consent form as soon as he/she retrieves his/her ability to give his/her consent, at any moment during the clinical study. In case of disability, the legal representative exercises the rights of the patient. The adult participant who is unable to give his consent in full knowledge is associated to the decision as much as possible and taking into account his ability of understanding (importance to provide an adapted oral information).
* emergency situations where an informed consent cannot be obtained prior the inclusion of the participant : not applicable (delete the following text) or (delete “not applicable”) describe why it would not be possible to obtain consent from potential participants or a legal representative prior to recruiting into the clinical study. The investigator will document the approaches to have a contact with the legal representative of the participant. The investigator will verify if the patient has not expressed any previous objection to participate in the study. This information is written in the patient’s chart. The participant will be invited to sign an informed consent form as soon as he/she retrieves his/her ability to give his/her consent, at any moment during the study.
* participants unable to sign or read the inform consent form (because of a health issue) : not applicable (delete the following text) or (delete “not applicable”) an impartial witness should be present during the entire process of consent. The impartial witness will be identified (complete with description of how the witness is identified). After the written consent document and any other written information to be provided to participants have been read and explained to the participant or his legal representative, and after the participant or his legal representative has orally consented to his participation in the study and, if capable of doing so, has personally signed and dated the consent document, the witness must personally sign and date the consent document. By signing the consent document, the witness attests that the information contained in the consent document and any other written information has been accurately explained and apparently understood by the participant or his/her legal representative, and that consent has been freely given by the participant or his/her legal representative.
* potential participants (or their legal representative) who do not speak the national language : not applicable (delete the following text) or (delete “not applicable”) the inform consent will be also given in different languages (Dutch, English and French). If necessary, an impartial translator should be present during the entire process of consent. Translator could be asked to our social department or could be a participant’s family member. After the written consent document and any other written information to be provided to participants have been read and explained to the participant or his legal representative, and after the participant or his legal representative has personally signed and dated the consent document, the translator must personally sign and date the consent document. By signing the consent document, the translator attests that the information contained in the consent document and any other written information has been accurately explained and apparently understood by the participant or his/her legal representative, and that consent has been freely given by the participant or his/her legal representative.
* Minors : not applicable (delete the following text) or (delete “not applicable”) provide justification for recruiting minors. Information would be given to the two parents, guardian or other mandated representative of the minor participant. The inform consent form would be signed by them. The minor should be involved in the process of informed consent, taking into account his age, his maturity degree (capacity of understanding) and his medical care if he is selected to participate. The deliberate objection of a minor to take part to the experiment should always be respected even if the parents gave their consent except if the child needs a treatment not yet available out of the experiment, if experimental intervention could be therapeutically beneficial or if no other therapies are possible. In this particular context, if the child is very young or immature, a parent or a guardian can skip this objection. If the child is older and closer to be able to give his consent, the investigator must try to get the express assent or the favorable opinion of the Ethics Committee to begin or continue the experimental treatment. After the age of 6 years, the minor should sign an information form adapted to his age and capacity of understanding.

The minor participant would sign an inform consent form when he reaches the age of legal competence. At this time, the participation will be rediscuss between the participant and the investigator.

Remarks : The participant’s legal representative is the person designated by a written mandate dated and signed by both parties to represent the rights and defend the interests of the participant. If there is no legally designated person, the legal representative would be, in order, the cohabitant (spouse, legal or effective), the adult child, the father or mother, the adult brother or sister.

1. Study interventions and procedures

Refer to the Schedule of activities (Study Flowchart)

The schedule must include clinic visits (screening, study period, follow-up visits), all contacts (e.g., telephone contacts) and all study interventions and procedures to be done during the protocol.

The protocol should specify the time that each phase of the project is likely to take, along with a detailed month by month timeline for each activity to be undertaken.

* 1. Method of assigning participant to interventions groups

The specific methods used to assign patients to interventions groups, to screen and randomize eligible patient, perform subsequent assignment should be described.

* 1. Sample lab collection
     1. Types and number of samples

List all separate types of biological samples and the amount and volume of samples that you will collect during the study.

* + 1. Timepoints of sample collection

When should the samples be taken during the study, and is there a time window that is allowed without creating a protocol deviation?

* + 1. Sample handling and analysis

How will the samples be taken and which methods will be used for analyzing them. Also explain where the analyses will be performed.

Please make sure all participating centers are covered.

* + 1. Sample storage and shipment

Describe the specific storage conditions and locations. Describe the way the biological samples will be shipped and in what conditions (if applicable). Also mention in which biobank(s) they will be stored and who is the medical guardian of the biobank(s).

Please make sure all participating centers are covered.

* + 1. Future use of stored samples

Please describe what you will do with the biological samples after the study has ended. Will all samples be destroyed or will you store them after the end of the study?

If you will store them: for which purpose, where, for how long and under which conditions will the biological samples be stored?

* 1. Protocol Amendements

If amendments to the protocol (modifying sense or objectives or modifying the undergone constraints or the risks incurred by the subjects) turn out to be necessary, they will be submitted to the opinion of the Ethic Committee having examined the initial protocol.

* 1. Protocol Deviations

Sponsor and all investigators agree to take any reasonable actions to correct protocol deviations/violations. All deviations must be documented on a protocol deviation log by the study team that is kept available at any time for audit/inspection purposes. Under emergency circumstances, deviations from the protocol to protect the rights, safety or well-being of human subjects may proceed without prior approval of the sponsor and the EC.

Any significant deviation from study inclusion or exclusion criteria, study conduct, patient management or evaluation will be described, justified and communicated to the ethics committee, as appropriate.

1. Safety reporting

Keep this section if study procedures could cause adverse events or safety events or justify if there is no safety assessment to perform

* 1. Definitions and reporting process

|  |  |
| --- | --- |
| **EVENTS** | |
| **Term** | **Definition** |
| **ADVERSE EVENT (AE)** | Any untoward medical occurrence in a subject which does not necessarily have a causal relationship with the study procedures. |
| **SERIOUS ADVERSE EVENT (SAE)** | Any untoward medical occurrence in a subject that meets at least one of the following seriousness criteria:   * Results in death; * Is life-threatening (immediate risk of death); * Requires inpatient hospitalisation or prolongation of existing hospitalisation; * Results in persistent or significant disability/incapacity; * Results in congenital anomaly/birth defect |
| **RELATED UNEXPECTED SERIOUS ADVERSE EVENT** | Any SAE where in the opinion of the Investigator the event was considered to be:   1. **Related** –results from administration of any research procedures 2. **Unexpected**–the type of event that not listed in the protocol as an expected occurrence |

|  |  |
| --- | --- |
| **CAUSALITY** | |
| **Term** | **Definition** |
| **NOT RELATED** | An adverse event which is not related to the study intervention. |
| **UNLIKELY RELATED** | An adverse event for which an alternative explanation is more likely and/or the relationship in time suggests that a causal relationship is unlikely. |
| **POSSIBLY RELATED** | An adverse event which might be due to the study intervention. An alternative explanation is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded. |
| **PROBABLY RELATED** | An adverse event which might be due to the study intervention. The relationship in time is suggestive. An alternative explanation is less likely. |
| **DEFINITELY RELATED** | An adverse event which is listed as related to the study intervention and cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive. |

* 1. Assessing, Recording, and Analyzing Safety Parameters
     1. Time Period and Frequency for Collecting AE and SAE Information

#### Adverse events

Collect and record on the CRF from the time the patient has signed the consent through last patient visit, all AEs/SAEs, including laboratory abnormalities, that are not known for the study intervention, that are potentially related to the study intervention and unrelated to the patient's disease or known history. Collect related events during the intervention and for a minimum of xxx hours/days after.

#### Serious adverse events

All SAEs must be collected and require immediate (within 24 hours) notification from the time of signing the consent through last patient visit, during the intervention and for a minimum of xxx hours/days after. The investigator must report any SAE that occurs after these time periods and that is believed to be related to study intervention or protocol-specified procedure.

In the event that the investigator does not become aware of the occurrence of a serious adverse event immediately, the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

* + 1. Method of Detecting AEs and SAEs

AEs will be reported by the participant (or, when appropriate, by a caregiver, a surrogate, or the participant’s legally acceptable representative).

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

AEs including SAEs occurring during at home period should be collected during in-clinic visits or during call with participants, and reported as early as possible (In the case of SAE, within 24 hours of learning of the event).

* + 1. Follow-up of AEs and SAEs

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious.

For adverse events with a causal relationship to study intervention, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention as appropriate.

All identified non-serious AEs and/or laboratory abnormalities must be recorded and described on CRF.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

* + 1. Regulatory Reporting Requirements for SAEs

#### Investigator’s reporting

The investigator will report all SAEs to the sponsor within 24 hours after learning of it and document the time of his/her first awareness of the adverse event. Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants are met.

The investigator uses the standard CIOMS SAE FORM (see Appendix) to submit the SAE to the sponsor. The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

The investigator will inform the sponsor in case of patient death, whatever the cause of the death could be, during the patient participation period within 24 hours after learning of it. The investigator will also inform the Ethics committee of patient death related to study intervention.

An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator’s Brochure.

* + 1. Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the CRF :

* Any laboratory test result that is clinically significant or meets the definition of an SAE
* Any laboratory test result abnormality that required the participant to have study intervention discontinued or interrupted
* Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that, wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia vs low hemoglobin value)

1. Data Management Responsibilities
   1. Data Quality Assurance

All study data will be handled in accordance with the law on General Data Protection Regulation (GDPR) and institutional rules [Belgian law dated on 20 July 2018 and 22 Aug. 2002].

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

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor and site personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, Ethics Committee review and regulatory inspection. This consent also addresses the transfer of the data to other entities, if applicable.

Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data. The investigator will ensure that the confidentiality of subjects' data will be preserved. On CRFs or any other documents, the subjects will not be identified by their names, but by their study number. Documents that identify the names of participants against their study number will be maintained by the investigator in strict confidence.

Monitors, auditors and other authorized agents will be granted direct access to study subject’s original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentations of the results of this study at meetings or in publications, the subjects’ identity will remain confidential.

* 1. Statistical Analysis
* Reasons for the sample size selected, statistical power of the study, level of significance to be used
* Describe planned analyses, comparisons and statistical tests
* Reasons for excluding subject from an analysis
* Planned monitoring of the results
* Frequency and nature of interim analyses
  1. Data handling and record keeping

Subjects who are included in the study will be assigned a unique study number. On all documents submitted to the sponsor, patients will only be identified by their study number. The subject identification list will be safeguarded by the site. The name and any other directly identifying details will not be included in the study database.

An electronic case report form (eCRF) will be used in REDCap software. The eCRF will be completed for subjects who have signed the informed consent. This eCRF will include specific pages for inclusion and exclusion criteria, and for reporting each visit. Other specific pages will be dedicated to concomitant treatments and AEs (non-serious and serious). The investigator will review, approve and validate each completed eCRF; the investigator’s signature (validation) serving as attestation of the investigator’s responsibility for ensuring that all data entered on the eCRF are complete, accurate and authentic.

All data will be processed according to the principles that the new European General Data Protection Regulation (GDPR) imposes, which is in force since 25 May 2018.

1. Who will responsible for the processing of personal data?

Complete. In general, it is the investigator-sponsor

2. Who is Data Protection Officer for the processing?

The institutional DPO could be reached by this email address : rgpd@saintluc.uclouvain.be

3. The purpose of the processing:

Scientific research

4. The legal basis of the processing:

Consent, but this can be withdrawn

4. Who are potential recipients of the personal data?

All researchers involved in this clinical study or in research projects that use materials original from this clinical study. Staff involved in monitoring and ethical evaluation and people from competent authorities. Subcontracted parties that perform analysis on study-related data or materials.

5. It is possible that the personal data will be viewed by people who are in countries that do not use the same standards as the EU in terms of legal protection of data. In that case, we guarantee that the conditions of European and Belgian legislation on the protection of personal data will be respected.

6. The storage period:

Study-related documents will be stored for at least 20 years, data included in the medical file for 30 years.

* 1. Case Report Form

An electronic data capture (EDC) system, i.e. REDCap, will be used for data collection. Data reported on each eCRF should be consistent with the source data. If information is not known, this must be clearly indicated on the eCRF. All missing and ambiguous data will be clarified.

The eCRFs will be developed, based on the protocol. The final eCRF design will be approved by the Coordinating Investigator.

All data entries and corrections will only be performed by study site staff, authorized by the investigator. Data will be checked by trained personnel (monitor) and any errors or inconsistencies will be clarified. The investigator must verify that all data entries in the eCRF are accurate and correct.

REDCap is provided and maintained by Vanderbilt University; a license for use was granted to the CUSL. REDCap is a web-based system.

* 1. Data storage

The data is accessed through a web browser directly on the secure REDCap server. The server is hosted within the Cliniques universitaires Saint-Luc campus and meets hospital level security and back-up requirements.

* 1. Access to data

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

Login in REDCap is password controlled. Each user will receive a personal login name and password and will have a specific role which has predefined restrictions on what is allowed in REDCap. Any activity in the software is traced and transparent via the audit trail and log files.

1. Insurance

The experimentation is covered under the Belgian Law of May 7, 2004 by a no-fault insurance (type of coverage: liability insurance).

Policy holder:

Cliniques universitaires Saint-Luc

Avenue Hippocrate, 10

1200 Brussels

Issuer of the certificate of insurance:

MS Amlin Insurance SE

Boulevard du Roi Albert II, 37

1030 Brussels

N° de police : LXX00259

1. End of study
   1. For an individual subject

The subject has completed the study if he or she has completed all of study procedures, including the last visit or the last scheduled procedure, as described in this protocol (see section “Study Specific Procedures”.

* 1. For the whole study

Overall, the end of the study is reached when the last study procedure for the last subject has occurred: last subject, last visit (LSLV).

As soon as the whole study has ended (cfr the definition above), the Investigator-sponsor shall notify the Ethics Committee in a timely manner according to the regulatory requirements (within 90 days after the end of the study, or if the study had to be terminated early, this period must be reduced to 15 days and the reasons should clearly explained).

1. Dissemination of Results and Publication Policy

The protocol should specify not only dissemination of results in the scientific media, but also to the community and/ or the participants, and consider dissemination to the policy makers where relevant. Publication policy should be clearly discussed- for example who will take the lead in publication and who will be acknowledged in publications, etc.

This study is registered on Clinicalstudys.gov ([https://clinicalstudys.gov/](https://clinicaltrials.gov/) ) and is available to the public.

1. Archiving

Essential clinical study documents are kept at least 20 years after the study termination according to the Belgian legislation: RD 18 May 2006 art.24.

Source documentation are kept for 30 years, according to the Belgian legislation (Art 35 Belgian Law of 22 April 2019).

Specify who archives, where and access conditions.

1. Study Report

Deadline of writing final report, who will draft it and to whom it will be transmitted.

1. Literature References

List of bibliographic references related to the clinical investigation

1. Appendix

* CRF / questionnaires
* CIOMS SAE form (delete if not applicable)
* Other

**CIOMS SAE FORM**

|  |  |
| --- | --- |
| **SERIOUS ADVERSE EVENT REPORT** | **SUSAR** (Suspect Unexpected Serious Adverse Reaction):  **⁯ YES ⁯NO** |
| PROTOCOL NAME: | |
| ETHICS COMMITTEE REFERENCE NUMBER: | EUDRACT / SITE N° / PATIENT N°  …. - …… - .. / … / …. |

**I. REACTION INFORMATION**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1. PATIENT INITIALS | 1a. COUNTRY | 2. DATE OF BIRTH | | | 2a. AGE | 3. SEX | 4-6 REACTION ONSET | | | 9-12 CHECK ALL APPROPRIATE |
| (first, last) |  | Day | Month | Year | Years |  | Day | Month | Year | TO ADVERSE REACTION |
| 7 DESCRIBE REACTION(S) (including relevant tests/lab data) | | | | | | | | | | PATIENT DIED  INVOLVED OR PROLONGED INPATIENT HOSPITALISATION  INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY  LIFE THREATENING  CONGENITAL ANOMALY  OTHER MEDICALLY IMPORTANT CONDITION |
| 8 MedDRA : SYSTEM ORGAN CLASS  LOWEST LEVEL TERM | | | | | | | | | |
| 14: OUTCOME: DAY/MONTH/YEAR: …. / …. / ….  RESOLVED: RESOLVED WITH SEQUELAEONGOING:  UNKNOWN: FATAL (+date of death): | | | | | | | | | |

**II. SUSPECT DRUG(S) / DEVICE(S) INFORMATION**

|  |  |  |
| --- | --- | --- |
| 15. SUSPECT DRUG(S) (include generic name)/ DEVICE(S) | | 22. DID REACTION ABATE AFTER STOPPING DRUG / REMOVING DEVICE?  YES NO NA |
| 16. CAUSALITY: CERTAIN: PROBABLE: POSSIBLE:  UNLIKELY: CONDITIONAL: UNASSESSABLE: | |
| 17. DAILY DOSE(S) | 18. ROUTE(S) OF ADMINISTRATION | 23. DID REACTION REAPPEAR AFTER REINTRODUCTION?  YES NO NA |
| 19. INDICATION(S) FOR USE | |
| 20. THERAPY DATES (from/to) | 21. THERAPY DURATION | |

**III. CONCOMITANT DRUG(S) AND HISTORY**

|  |
| --- |
| 24. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) |
| 25. OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with last menstrual period, etc.) |

**IV. INVESTIGATOR INFORMATION**

|  |  |  |
| --- | --- | --- |
| 26a. NAME OF REPORTER | | 28-28a. NAME AND ADDRESS OF INVESTIGATOR |
| 26b. MFR CONTROL NO. | 26c. DATE RECEIVED BY MANUFACTURER |
| 26d. REPORT SOURCE STUDY LITERATURE HEALTH PROFESSIONAL REGULATORY AUTHORITY OTHER | SPONSOR USE: REPORT NO. |
| DATE OF THIS REPORT | 27a. REPORT TYPE INITIAL FOLLOW-UP | INVESTIGATOR / REPORTER SIGNATURE |

1. [Loi du 7 Mai 2004](http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=fr&la=F&cn=2004050732&table_name=loi) relative aux expérimentations sur la personne humaine [↑](#footnote-ref-1)
2. [ICH GCP E6 (R2) Good](https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf) clinical practice guideline [↑](#footnote-ref-2)