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|  | **POLICY – CLINICAL TRIAL PROTOCOL TEMPLATE** |
| N° : AAHRPP-DSQ-034 / REV003 | N° ENGLISH VERSION : 243 |

***"Please do take into account that this is a translation of the original French version validated in the Quality Management System (QMS) of Cliniques universitaires Saint-Luc through the SharePoint PaCo GED. Therefore in case of doubt, differences, inconsistency or discrepancy in this English version, the French version shall prevail"***

**DEFINITION**

A clinical research protocol is a document describing the objective(s), design, methodology, statistical aspects and organization of the clinical trial (Art 2,§22° European Regulation 536/2014).

**INSTRUCTIONS FOR USE**

* This document is a protocol template based on the guidelines of European Regulation 536/2014 (Annex 1, D) and Good Clinical Research Practice (ICH GCP ).
* The parts suggested in this template must **ALL** be included in your final document in order to meet regulatory requirements. If a section is not applicable, indicate "NA" in the section (no section should be deleted).
* Some information may also be provided in other documents that must be referenced in the protocol as appendices (investigator's brochure, informed consent, research contract, statistical plan, risk management plan, monitoring plan, etc.).
* The text in red that corresponds to the instructions for use must be removed, as well as this first page.
* The black text should be kept.
* You can change the headings and layout styles. Don't forget to update the table of contents.
* Each version of the protocol must be numbered and dated in the footer.
* The protocol must be written in English.
* Final format: PDF

Protocol Title

|  |  |
| --- | --- |
| Short title | Fill in |
| Acronym / Protocol code | Fill in |
| Protocol version and date | Fill in |
| EU reference number  Investigational product | CTIS study number – ask to CTC  Name of test drug |
| Phase of the trial | 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* |
| Coordinating Investigator | Name and contact details |

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

Version History

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

1. Signature page

**SPONSOR REPRESENTATIVE – COORDINATING INVESTIGATOR**

Name Signature Date

**SITE PRINCIPAL INVESTIGATOR**

I agree to conduct this clinical 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 trial 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 studies and the protection of patients.

I will ensure that the requirements relating to Regulatory Authorities and 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 Sponsor, the Regulatory Authorities and 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 the Sponsor and Regulatory Authorities approval, except where necessary to ensure the safety of study participants.

Name Signature Date

1. Protocol synopsis

You can use this table for separate synopsis – Adapt the language according to participant population language (FR, NL, GE)

|  |  |
| --- | --- |
| Title of Study |  |
| Acronym / Protocol code |  |
| EU reference number |  |
| Phase |  |
| Sponsor | Cliniques universitaires Saint-Luc |
| Coordinating investigator |  |
| Study centre(s) |  |
| Investigational Medicinal Product (IMP) |  |
| Active Ingredient |  |
| Dosage and mode of administration |  |
| Indication / Pathology |  |
| Rationale |  |
| Objectives |  |
| Endpoints |  |
| Study Design |  |
| Number of patients |  |
| Main criteria for inclusion (inclusion/exclusion criteria) |  |
| Total trial duration:   * date of planned first enrolment * date of planned last completed |  |
| Study procedures and treatment duration |  |
| Statistical Considerations |  |
| Publication (reference) |  |

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 must use the heading styles configured in the document. Use the headings available in the Word document toolbar, or create your own.

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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 Regulatory Authorities (RA) for formal approval to conduct the study. The decision of the RA concerning the conduct of the study will be made in writing to the sponsor via CTIS portal. All correspondence with the RA should be find in the portal.*
* *The study will be conducted in accordance with legal and regulatory requirements (European Regulatory 536/2014, Belgian law for clinical trials of 7 May 2017, 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 designed by the RA. 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 trial 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. dose-response, superiority to placebo, 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 trial 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 trial.

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 trial met its objective. Often phase II and III studies include primary objectives, and therefore primary endpoints, to demonstrate effectiveness. 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. Less is more, e.g. “the primary end point is the two-year survival rate”.

* 1. Primary
  2. Secondary

1. Background Information and Scientific Rationale
   1. Medical Background

* The name and description of the study intervention/investigational products(s)
* Scientific explanation to define the issue : Discussion of important literature and data that are relevant to the trial and that provide background for the trial (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 trials and any history of human use or exposure to the study intervention, including use in other countries, and clinical pharmacology studies
* Benefits expected for the research : Importance of the study and any relevant treatment issues or controversies
* Perspectives for the scientific community, the hospital, the public health.
  1. Drug Profile

Substance, toxicology, pharmacokinetics, clinical studies.

Description of the route of administration and dosage, dosing regimen, intervention periods.

* 1. Rationale
* Statement of the hypothesis
* Description of the study population, disease, current standard of care
* Discussion of known risks and benefits, if any, to human subjects
* A summary of the known and potential risks and benefits, including an assessment of the expected benefits and risks; for participants in a clinical trial in an emergency situation, the scientific grounds for considering that their participation is likely to produce a direct clinically relevant benefit are documented;
* Where patients have been involved in the design of the clinical trial, a description of how they were involved;
* An analysis of the relevance of the clinical trial

1. Investigational plan
   1. Design

Definition of the characteristics of the biomedical research by standard terms

* Physio-(patho)logical experimentation, genetic, epidemiological, genetics, therapy,…
* Monocenter or multicenter (national or international) ; number of centers
* Clinical Phase
* With or without direct individual benefit
* Nature of control(s) (e.g., placebo, no treatment, active drug, dose-response)
* Method of assignment to treatment (randomization, stratification)
* Number of study groups/arms
* Level and method of blinding/masking (e.g., open, double-blind, single-blind, blinded evaluators, and unblinded patients and/or investigators)
* Prospective, retrospective
* Study configuration : parallel groups or cross-over
* Approximate time to complete study enrollment
* Expected duration of subject participation
* Description of the sequence and duration of all trial periods, including follow-up
* 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
* Patient population studied

a description of the groups and subgroups of participants in the clinical trial, including, if applicable, groups of participants with specific needs, e.g., age, gender, participation of healthy volunteers, participants with rare and ultra-rare diseases

* Number of patients planned
  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 clinical trial and therapeutic alternatives 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 trial (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 trial, 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 trial. 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 trial. 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 clinical trial. 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 clinical trial.
* 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 trial 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. Participants eligibility

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

Justification for inclusion of participants unable to give informed consent or other special populations such as minors

* + 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.

If individuals of a specific gender or age group are not included in clinical trials or are underrepresented in clinical trials, an explanation of the reasons and justification for these non-inclusion criteria

* + 1. Subject eligibility screening

Screen failures are subjects who consent to participate in the trial but do not meet one or more criteria required for participation in the trial during the screening procedures. Screen failures will not be enrolled in the trial. 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 trial at any time. A subject must be discontinued from the trial if he or his legal representative withdraws consent.

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

• Pregnancy;

• Significant trial intervention or treatment non-compliance;

• If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the trial would not be in the best interest of the subject;

• Disease progression which requires discontinuation of the trial intervention;

• If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further trial 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 trial 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 trial site staff.

The following actions must be taken if a subject fails to return for a required trial 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 trial;

• 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 trial with a primary reason of lost to follow-up.

* + 1. Patient follow-up after trial participation

Please 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 and where it differs from that normally expected for the medical condition in question.

* 1. Start of the trial

The trial is considered started upon the first act of recruitment of a potential subject. For this trial this is considered as [Describe here what the first action of recruitment involves (e.g. date of first screening in electronic patient file, putting up posters or providing flyers in the waiting room, first meeting with the first potential subject…).].

The start of the trial shall be notified to the CA/IEC within 15 calendar days.

The first visit of the first subject (i.e. when the first subject or his/her legally designated representative signs his/her first informed consent to participate in the trial) (FVFS) will also be notified to the CA/IEC within 15 calendar days.

* 1. Investigational Medicinal Product (IMP)

|  |  |
| --- | --- |
| Also refer to | Summary of Product Characteristics (SmPC)  Investigator's Brochure (IB) and Investigational Medicinal Product Dossier (IMPD) |
| Name of the IMP |  |
| Qualitative and quantitative composition |  |
| Pharmaceutical form |  |
| Authorised in the EU | Yes / No  (If the IMP is not authorised in the EU, but it is authorised elsewhere: please elaborate) |
| Used within scope | Yes / No / NA  (If not: please explain. If the IMP is not authorised (worldwide): choose ‘N.A.’) |
| Marketing authorisation holder |  |
| Marketing authorisation number(s) |  |
| Manufacturer |  |
| Distributor |  |
| Responsible for batch release |  |

* + 1. Treatments Administered

The precise treatments or diagnostic agents to be administered in each arm of the study, and for each period of the study, should be described.

Route and mode of administration, dose, and dosage schedule.

* + 1. Selection of Doses in the Study

The doses or dose ranges used in the study should be given for all treatments and the basis for choosing them described (e.g., prior experience in humans, animal data).

* + 1. Method of Assigning Participant to Treatment Groups

The specific methods used to assign patients to treatment groups, to screen and randomize eligible patient, perform subsequent assignment, manage initial/resupply ordering of drug supplies and handle emergency unblinding (e.g. IVRS, IWRS …) should be described.

* + 1. Selection and Timing of Dose for Each Patient

Assignment of medication numbers to eligible patients should be described (e.g. IVRS, IWRS …).

Time of day, interval of dosing and the relation of dosing to meals should be described and, if timing was not specified, this should be noted.

* + 1. Permitted dose adjustments and interruption of treatment

Please include the allowed time window in which the IMP may be administered to the subject without creating a protocol deviation in doing so. Also describe whether the dosage will be modified in accordance with the subject’s results (e.g. lab results – and what the results should be), or in case of certain adverse events. Specify the exact dose modifications and/or accepted ranges.

* + 1. Duration of treatment

Describe the foreseen duration of the treatment of the IMP; also include the maximal duration of the treatment for a single subject.

Also provide a justification for the treatment period for the IMP.

* + 1. Blinding

If applicable, please describe the blinding process. Who is responsible for the blinding, how will the blinding be performed, which software/system will be used, where are the blinding codes to be found, arrangements for the maintenance of clinical trial treatment blinding codes…

This section should include a description how study subjects will be assigned to study groups, without being so specific that blinding might be compromised (e.g. the ratio between intervention and placebo groups may be stated).

Unblinded information should be accessible only to persons who need to be involved in the safety reporting to the Agency, to Data Safety Monitoring Boards (‘DSMB’), or to persons performing ongoing safety evaluations during the clinical trial.

* + - 1. Deblinding procedures

Delete this text if there is no blinding

The study code should only be broken for valid medical or safety reasons, e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the subject is receiving before he or she can be treated. If possible, other study team members should remain blinded.

The code breaks for the trial are kept at [Fill in]; in the event a code is required to be unblinded a formal request for unblinding will be made by the local PI to the Coordinating Investigator (CI).

The CI/PI documents the breaking of the code and the reasons for doing so on the eCRF/study documents, in the site file and medical notes. It will also be documented at the end of the trial in any final study report and/or statistical report.

The study team will notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break.

As the investigator is responsible for the medical care of the individual study subject (Declaration of Helsinki §3 and ICH 4.3) the coding system should include a mechanism that permits rapid unblinding (ICH GCP 5.13.4). The investigator cannot be required to discuss unblinding if he or she feels that emergent unblinding is necessary.

* + 1. Treatment Compliance

Description of measures taken to ensure and document treatment compliance (e.g., drug accountability, diary cards, blood, urine or other body fluid drug level measurements, or medication event monitoring).

* + 1. Investigational product management

- A description of the procedures adopted for the traceability, retention, destruction and reshipment of investigational medicinal products and unauthorized ancillary medicinal products

- Procedures for accountability for the provision and administration of drugs to participants, including the maintenance of the blinding procedure, if applicable

- Packaging/labeling of the IMP should be in accordance with the relevant GMP guidelines (if applicable). Please explain how and by whom the packaging and labeling of the IMP will be performed. Please make sure the description covers all participating centers. Please add an example of the label that will be used (in appendix). NOTE: in Belgium, the label has to be drawn up at least in the three national languages (Dutch, French, German).

NOTE: labeling of the IMP is not necessary in case of low-intervention trials. This means:

• the treatment is given according to the leaflet and the standard of care; and

• delivery takes place in accordance with the marketing authorisation (and thus without any changes to the medicinal product)

* + 1. Prior and concomitant therapy

Medication allowed and not allowed before and during the trial

Drug-drug interactions and effect on trial endpoints

* 1. Study 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 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. Sample lab collection

This section should contains a description of the arrangements for complying with applicable rules for the collection, storage and future use of biological samples from clinical trial participants, if applicable, unless provided in a separate document

* + - 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 trial.

* + - 1. Timepoints of sample collection

When should the samples be taken during the trial, 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 trial has ended. Will all samples be destroyed or will you store them after the end of the trial?

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

* 1. Efficacy and Safety Variables
     1. Efficacy and Safety Measurements Assessed and Flow Chart

Schedule (days of study, time of day, relation to meals, and the timing of critical measures in relation to test drug administration), methods for measurements and persons responsible, specific instructions, definitions used to characterize outcome, laboratory techniques.

Means of obtaining AE data.

AE rating (seriousness, severity).

* + 1. Appropriateness of Measurements

If any of the efficacy or safety assessments was not standard, its reliability, accuracy, and relevance should be documented.

* + 1. Primary Efficacy Variable(s)

The primary measurements and endpoints used to determine efficacy should be clearly specified.

* + 1. Drug Concentration Measurements
* Drug concentrations to be measured
* Sample collection times
* Periods in relation to the timing of drug administration
* Relation of drug administration and sampling to ingestion of food, posture, and the possible effects of concomitant medication/alcohol/ caffeine/nicotine
* Biological sample measured, handling of samples (storage, labeling …) and method of measurement used (referring to published and/or internal assay validation documentation for methodological details).
* Other (e.g. pharmacodynamics, pharmacogenomics, …)
* Samples shipment: frequency, address and contact information for laboratory personnel (Include days and times shipments are allowed, any labeling requirements for specimen shipping and any special instructions such as dry ice or wet ice or the completion of a specimen-tracking)
  1. Safety Reporting
     1. Definitions and reporting process

|  |  |
| --- | --- |
| **ADVERSE EVENTS and ADVERSE REACTIONS** | |
| **Term** | **Definition** |
| **Adverse Event (AE)** | Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. |
| **Unexpected Adverse Event** | An adverse event of which the nature or severity is not consistent with the Reference Safety Information (RSI) of the product (i.e. the applicable information in the Investigator’s Brochure (IB) for an investigational medicinal product which is not authorised or in the Summary of Product Characteristics (SmPC) for an authorised investigational medicinal product). |
| **Adverse Reaction (AR)** | An untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject. The phrase “response to an investigational medicinal product” means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions. |
| **Serious Adverse Event (SAE)** | Any untoward medical occurrence at any dose that:   * Results in death; * Is life-threatening (immediate risk of death); * Requires inpatient hospitalization or prolongation of existing hospitalization; * Results in persistent or significant disability/incapacity; * Results in congenital anomaly/birth defect. |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | A serious adverse reaction, the nature, severity or outcome of which is not consistent with the Reference Safety Information (RSI) |
| **Annual Safety Report (ASR)** | The sponsor writes a safety report annually. The sponsor sends the report about the safety of the trial medication to the regulatory authority.  The key date is the date of the first authorization of the clinical trial by the regulatory authority. All data obtained up to this date (each year) will be included in the ASR. Beginning with the key date, there is a time-limit of 60 days for the preparation and submission of the ASR. |

|  |  |
| --- | --- |
| **ATTRIBUTIONS** | |
| **Term** | **Definition** |
| **Not related** | An adverse event which is not related to the use of the drug. |
| **Unlikely related** | An adverse event for which an alternative explanation is more likely - e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely. |
| **Possibly related** | An adverse event which might be due to the use of the drug. An alternative explanation - e.g. concomitant drug(s) or concomitant disease(s) - 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 use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely - e.g. concomitant drug(s) or concomitant disease(s). |
| **Definitely related** | An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant drug(s) or concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge). |

An adverse event is considered associated with the use of the drug if the attribution is ‘possibly’, ‘probably’ or ‘definitely related’.

* + 1. Assessing, Recording, and Analyzing Safety Parameters

The evaluated risk for this trial is a xxx risk.

A separate trial-specific risk assessment plan (RAP) will be available to address, in detail, the most relevant potential risks and to specify the mitigation of those risks.

**Adapt the text below to the protocol-specific reporting procedures**

* + - 1. Time Period and Frequency for Collecting AE and SAE Information

Adverse events (serious and non-serious) should be recorded on the CRF from the time the patient has signed the consent through last patient visit**.** Collect all non-serious adverse events (not only those deemed to be treatment-related) continuously during the treatment period and for a minimum of xxx days following discontinuation of dosing.

For all adverse events, sufficient information should be obtained by the investigator to determine the causality, the severity and the seriousness of the adverse event.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue before completing the study.

All SAEs must be collected and require immediate (within 24 hours) notification from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within xxx days following discontinuation of dosing. 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 (eg, if an outpatient trial patient initially seeks treatment elsewhere), 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.

For reported death of a subject, whatever the cause could be, the investigator shall supply the sponsor with any additional information requested.

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.

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. 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 the investigational product, 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.

* + - 1. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.

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.

The Sponsor or designee must report to regulatory authorities :

* Via CTIS portal :
  + Unexpected events : Events that affect the benefit-risk balance of a [clinical trial](https://www.ema.europa.eu/en/glossary/clinical-trial) that were unforeseen, e.g. an unexpected increase in the incidence of expected [serious adverse reactions](https://www.ema.europa.eu/en/glossary/serious-adverse-reaction) that may be clinically important. Unexpected events do not include SUSARs.
  + Urgent safety measures : Measures taken to protect [clinical trial](https://www.ema.europa.eu/en/glossary/clinical-trial) subjects due to an unexpected event that is likely to seriously affect the benefit-risk balance of the [clinical trial](https://www.ema.europa.eu/en/glossary/clinical-trial)
  + Annual safety reports : Yearly updates on the safety of each [investigational medicinal product](https://www.ema.europa.eu/en/glossary/investigational-medicinal-product) used in a [clinical trial](https://www.ema.europa.eu/en/glossary/clinical-trial)
* Via EudraVigilance portal :
  + Suspected unexpected [serious adverse reactions](https://www.ema.europa.eu/en/glossary/serious-adverse-reaction) (SUSARs) : as soon as possible and at the latest within 7 days for any event resulting in death or endangering the life of the participant; at the latest within 15 days for any other event.
    - 1. Pregnancy

If, following initiation of the study intervention, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for xx months after study product administration, the investigator must immediately notify the sponsor.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported au sponsor. Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

* + - 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. Site Monitoring Plan

The document *AAHRPP-DSQ-023 Monitoring Plan* will be completed by the CRA responsible to conduct the study monitoring.

Site monitoring is conducted to ensure the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH and regulatory guidelines.

Monitoring of the study will be performed in compliance with GCP E6(R2) and the applicable regulatory requirements. The study team will be trained in an initiation visit. A detailed description of the monitoring tasks can be found in the latest version of the (study-specific) ‘Monitoring plan’ (see Appendix). The investigator will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

* + 1. Monitoring team

Monitoring services will be provided in collaboration with the clinical trial centre of the Cliniques universitaires Saint-Luc. All relevant contact details (e.g. primary contact person) can be found in the ‘Monitoring plan’ (see Appendix).

* + 1. Scope

Quality control measures will be followed throughout the study. The clinical study monitor will observe the progress of the study. Contacts with the investigator and on-site visits for the purpose of data review will occur in collaboration with the clinical trial centre of the Hospital Saint-Luc. The monitor will ensure compliance of the study site with the protocol, applicable SOPs and guidelines as described in this protocol. The review of the subjects’ medical records will be performed in a manner to ensure that subject confidentiality is maintained. The investigator agrees to allow the monitor access to any or all of the study materials needed for the monitor to properly review the study progress. The investigator (or deputy) agrees to assist the monitor in resolving any problem that may be detected during the monitoring visit.

* 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

Use the document *AAHRPP-DSQ-020 Statistical Analysis Plan (guideline)* to complete this section

* 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. Changes in the Conduct of the Study or Planned Analyses

In the event that the Ethics Committee requires, as a condition of approval, substantial changes to the clinical protocol, or in the event of a decision to modify the previously accepted clinical protocol, the investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment describing any change to the clinical protocol that significantly affects the safety of the subjects. For changes that do not affect critical safety assessments, the revisions to the clinical protocol will be notified to the Ethics Committee(s).

* 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 subjected at first opinion of the promoter of the study. After agreement by the promoter, these amendments will then be submitted to the opinion of the Regulatory Authorities and 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 noted during monitoring/inspection, in consultation with the monitoring team. All deviations must be documented on a protocol deviation log by the study team that is kept available at any time for monitoring/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.

1. Data Management Responsibilities

1) Data management plan : Complete the document *AAHRPP-DSQ-021 Data Management Plan* if the study has an high risk level. Place this document in appendix and refer to it. Remove all information below in this case.

2) no data management plan :

* 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

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 trial or in research projects that use materials original from this clinical trial. 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 25 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 Co-ordinating/Principal 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. Data breach

A description of the measures taken to comply with the rules in force relating to the protection of personal data, and in particular the technical and organizational arrangements that will be applied to prevent unauthorized access, disclosure, dissemination, modification or loss of the information and personal data processed

A description of the measures that will be applied to guarantee the confidentiality of the information and personal data of the participants

A description of the measures that will be applied in the event of a data security breach, in order to mitigate the possible adverse effects

The Sponsor or designee must report to regulatory authorities, via CTIS portal, serious data breaches : transgressions against the [clinical trial](https://www.ema.europa.eu/en/glossary/clinical-trial) protocol or the [Clinical Trials](https://www.ema.europa.eu/en/glossary/clinical-trial) Regulation that are likely to significantly affect the safety and rights of a subject or the reliability and robustness of the data generated in the [clinical tria](https://www.ema.europa.eu/en/glossary/clinical-trial)l.

Critical issues that significantly affect patient safety, data integrity and/or study conduct should be clearly documented and will be communicated with the Coordinating Investigator, the sponsor and possibly both the applicable Ethics Committee(s) and Competent authority.

1. Finance and Insurance

The sponsor has taken a no fault insurance for this study, in accordance with the relevant legislation (article 29, Belgian Law of May 7, 2017).

The subjects taking part in this study will be covered by the insurance taken by the sponsor, if they were to suffer any prejudice as a result of taking part in the study and according to ICH-GCP requirements, the institution has taken out personal liability insurance with an Insurance company following the Belgian regulations. This insurance was taken out with MS Amlin Insurance SE.

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

See details of the research funding and any cost which will be incurred in Appendix (déclaration financière).

No compensation is offered to trial participants. Participants will not pay for study drugs and procedures outside the scope of standard care (detailed in the financial statement).

1. End of trial
   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 co-ordinating/Principal Investigator shall notify the sponsor, so that the Competent Authority and the Ethics Committee can be informed 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

This trial is registered on EU Clinical Trials portal (<https://euclinicaltrials.eu/home>) and is available to the public.

Study results will be published on EU Clinical Trials portal one year after the end of the study.

Duly justified reasons for submitting the summary of clinical trial results after more than one year

1. Archiving

Essential clinical trial documents are kept for 25 years after the end of the study, in accordance with the Art. 58 of the EU regulation 536/2014.

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

* Monitoring plan
* CIOMS SAE form

**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 |