**DEFINITION[[1]](#footnote-1)**

Documentqui rassemble les informations relatives à l'étude : informations de base, justification, objectifs, résultats, conception, analyse pré-spécifiée, méthodologie, monitoring, sécurité et suivi, enregistrement des données de l'investigation clinique. Ce document est nommé plan d’investigation clinique ou protocole d’investigation clinique.

**INSTRUCTIONS D’UTILISATION**

* Ce document est un modèle de protocole basé sur les directives du règlement européen 2017/745[[2]](#footnote-2), les guidelines de l’AFMPS1, la Norme Internationale ISO[[3]](#footnote-3) et les bonnes pratiques cliniques de recherche (ICH GCP[[4]](#footnote-4)).
* Les parties proposées dans ce modèle doivent TOUTES figurer dans votre document final afin de répondre aux requis réglementaires. Si une section n’est pas applicable, indiquez « NA » dans la section (aucune section ne doit être effacée).
* Certains renseignements peuvent également être fournis dans d'autres documents qui doivent être référencés dans le protocole en annexes (consentement éclairé, plan de monitoring, etc).
* Le texte en rouge qui correspond aux instructions d’utilisation doit être retiré, ainsi que cette première page.
* Le texte en noir doit être conservé.
* Le texte en vert doit être adapté aux spécificités du protocole.
* Vous pouvez modifier les styles de titres et de mise en page. N’oubliez pas de mettre à jour la table des matières.
* Chaque version de protocole doit être numérotée et datée en pied-de-page.
* Le protocole doit être écrit en anglais.
* Format final : PDF

Protocol Title

|  |  |
| --- | --- |
| Short title | Fill in |
| Acronym / Protocol code | Fill in |
| Protocol version and date | Fill in |
| EU reference number  Tested device | CESP study number – ask to CTC – to be removed if not submitted to authorities  Name of test device |
| 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 and date of protocol

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 investigation 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 investigations and the protection of patients.

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

Name Signature Date

Name Signature Date

1. Protocol synopsis

|  |  |
| --- | --- |
| Title of Study |  |
| Acronym / Protocol code |  |
| EU reference number |  |
| Sponsor | Cliniques universitaires Saint-Luc |
| Coordinating investigator |  |
| Study centre(s) |  |
| Study device |  |
| Mode of use |  |
| Indication / Pathology |  |
| Rationale |  |
| Objectives | * Primary * Secondary |
| Endpoints | * Primary * Secondary |
| 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 |  |
| Statistical Considerations |  |
| Publication (reference) |  |

1. Schedule of activities

Insert the study flowchart

Table des matières à mettre à jour

Pour que vos titres soient repris dans la table des matières, vous devez utiliser des styles de titres configurés dans le document. Utilisez les titres proposés dans la barre d’outils du document Word ou créez vos propres styles de titres.

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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) and/or Ethics Committee (EC) for formal approval to conduct the study. The decision of the RA and/or of the EC concerning the conduct of the study will be made in writing to the sponsor.*
* *The study will be conducted in accordance with legal and regulatory requirements (European Regulatory 2017/745, Belgian law of 22 December 2020, 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 lead 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. Identification and description of the investigational device

* Brief description of the device.
* Details of the device manufacturer.
* Model or type name or number, including software version and accessories, if any, allowing full identification.
* Description of how to ensure traceability during and after the clinical investigation, e.g., by assigning lot numbers or serial numbers.
* Intended use of the device in the proposed clinical investigation.
* Population and indications for use of the device.
* Detailed description of the device, including all materials that will be in contact with tissue or body fluids. The description should detail all drug substances, human or animal tissues or their derivatives, or other biologically active substances and mention compliance with applicable national regulations.
* Summary of training and experience required for use of the device, taking into account risk assessment.
* Description of the medical or surgical procedures specific to the use of the device.
* References to the investigator's brochure and instructions for use.

The above information should also be provided, where possible, for the comparator where applicable.

1. justification for the design of the clinical investigation

* Assessment of the results of relevant preclinical trials/analyses and prior clinical investigations, if any, conducted to justify the use of the device in human subjects.
* References to literature and data relevant to the clinical investigation and serving as background information for the proposed clinical investigation.

1. Benefits and risks

* Expected adverse effects of the device.
* Risks associated with participation in the clinical investigation.
* Steps taken to control or mitigate the risks.
* Expected clinical benefits.
* Justification of the benefit/risk ratio

1. Objectives and hypotheses

* Purpose of the clinical investigation, statements regarding the clinical performance, efficacy or safety of the device under investigation to be verified.
* Objectives, primary and secondary, described in terms of "superiority", "non-inferiority" or "equivalence", if applicable.
* Scientific rationale and clinical relevance regarding magnitude of effects, margins of non-inferiority or limits of equivalence, if applicable.
* Primary and secondary assumptions, if any.
* Expected risks and adverse effects of the device, which should be evaluated.

The objective(s) should address the purpose of the clinical investigation and should relate to the hypotheses (if any) and corresponding endpoints relevant to the target population. The objectives of the clinical investigation should translate directly into the pre-specification andimplementation of the primary endpoint(s). Statements should be linked to eligibility criteria for the subject and users.

1. Design of the clinical investigation
   1. General description

* Type of clinical investigation to be conducted (e.g., randomized, blinded or open-label, parallel or crossover, multicenter, international), the control group (e.g., comparative statement and reversible treatment of a chronic condition), and the comparator, with rationale and justification for choice.
* Description of the development phases of the device.
* Number of medical devices and comparators (if any) used per subject.
* Follow-up provided and expected duration (total and per subject) of the study. Justification for the duration of follow-up is recommended.
* Details of measures taken to minimize bias
* Definition of the end of the clinical investigation.
  1. Study subjects
     1. Description of population
* Number of expected subjects
* 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
* Representativeness of the study population in relation to the target population
  + 1. Recruitment procedure

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)
* Estimated time required to recruit the expected number of subjects
  + 1. Informed consent procedure

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 investigations or are underrepresented in clinical investigations, an explanation of the reasons and justification for these non-inclusion criteria

* + - 1. Withdrawal

Provide a list of reasons for which subjects may be discontinued from the study. Also note that subjects may withdraw voluntarily from participation in the study at any time. Describe the efforts to follow subjects who withdraw from the study.

* + - 1. Patient follow-up

A description of how participants will be cared for after their participation in the clinical investigation, if additional care is required as a result of their participation in the clinical investigation and if it differs from the care normally expected for their medical condition.

* 1. Procedures
* Clinical procedures and diagnostic tests used during the clinical investigation and any deviations from standard clinical practice.
* Activities performed by the sponsor's representatives.
* Any known or foreseeable factors that may compromise the results of the clinical investigation or the interpretation of the results. For example, any comparator or other device or drug used, and therefore any concomitant authorized or prohibited treatments, but also subject factors such as age, sex, lifestyle.
* The methods for considering these factors in the clinical investigation, for example by the choice of subjects, by the design of the clinical investigation (such as stratified randomization) or by the statistical analysis, should be described.
* The follow-up period of the clinical investigation must be adequate to demonstrate clinical performance, efficacy or safety over a period of time sufficient to represent a realistic trial of the device and to allow identification and assessment of the risks associated with any adverse effects of the device.
* The specific and appropriate medical care to be provided to subjects after completion of the clinical investigation, if any.
* Recommended follow-up of subjects after completion of the clinical investigation.

The extent and nature of follow-up activities for the successful completion of the investigation in accordance with the clinical investigation plan should be described and, in accordance with Section 72 of the MDR, should be based on the objective(s), methodology, and degree of deviation of the intervention from normal clinical practice. Overall, the study should be designed to minimize pain, discomfort, fear, and any other possible foreseeable risks to subjects. For this, a rationale in relation to the available preclinical data and the results of the clinical evaluation may be recommended.

* 1. 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 ‘Monitoring plan’. 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’.

* + 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. Amendments

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. Deviations from the clinical investigation plan (deviation, violation)

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. Device accountability

* Description of device accountability procedures.
* Procedures, specific materials and instructions for the safe return of devices under investigation, including potentially hazardous devices.

1. Safety reporting
   1. Definitions

|  |  |
| --- | --- |
| **EVENTS** | |
| **Term** | **Definition** |
| **ADVERSE EVENT (AE)** | Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device. |
| **SERIOUS ADVERSE EVENT (SAE)** | Any adverse event that led to any of the following:   * death, * serious deterioration in the health of the subject, that resulted in any of the following:   + life-threatening illness or injury,   + permanent impairment of a body structure or a body function,   + hospitalisation or prolongation of patient hospitalisation,   + medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,   + chronic disease, * foetal distress, foetal death or a congenital physical or mental impairment or birth defect |
| **adverse device effect (ADE)** | An adverse event (ADE) related to the use of an investigational device. |
| **serious adverse device effect (SADE)** | An adverse device effect that has resulted in any of the consequence characteristics of a serious adverse event |
| **device deficiency** | Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer |
| **incident** | Malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect. |
| **serious incident** | A serious incident means any incident that directly or indirectly led, might have led or might lead to any of the following:   * the death of a patient, user or other person, * the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, * a serious public health threat. |
| **serious public health threat** | An event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time |

|  |  |
| --- | --- |
| **CAUSALITY** | |
| **Term** | **Definition** |
| **Not related** | An adverse event which is not related to the use of the device. |
| **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 device. 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 device. 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 device effect 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). |

All causality assessments must be performed in accordance with Section 9 of the MDCG 2020-10 (Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745).

* 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 any necessary risk mitigation measures.

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

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

#### Adverse events

Adverse events, adverse device effects, device deficiency, incident (serious and non-serious, including laboratory abnormalities) should be recorded **on the CRF** from the time the patient signed consent through last patient visit / xx hours after the use of the device *(choose and add the justification)*.Collect all non-serious adverse events (not only those deemed to be device-related) / collect non-serious adverse event only device-related *(choose)*.

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, ADE or SAE, SADE 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.

#### Serious adverse events

All SAEs, SADEs must be collected and recorded on the CRF from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within xxx days/hours following discontinuation of patient/use of device *(define safety following period)*. The investigator must report any SAE, SADEs that occurs after these time periods and that is believed to be related to study intervention or protocol-specified procedure. (i.e. for implantable device, if specific safety follow-up, …).

In the event that the investigator does not become aware of the occurrence of a serious adverse event immediately, the investigator is to record 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, ADEs will be reported by the participant (or, when appropriate, by a caregiver, a surrogate, or the participant’s legally acceptable representative) or by the research team using the device.

AEs, ADEs 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, ADEs and/or SAEs, SADEs. Inquiry about specific AEs, ADEs should be guided by clinical judgement in the context of known AEs, ADEs, when appropriate for the program or protocol.

AEs, ADEs including SAEs, SADEs 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 or SADE, within 24 hours of learning of the event).

* + 1. Follow-up of events

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

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

Investigators are not obligated to actively seek AEs, ADEs or SAEs, SADEs in former study participants. However, if the investigator learns of any SAE or SADE, 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 or SADEs

#### Investigator’s reporting

The investigator will report all SAEs, SADEs 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 or SADEs 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.

If CE marked device, used within scope (CE only submission): The investigator uses the Serious adverse event report form (CIOMS form - see Appendix) to submit the SAE or SADE to the sponsor. The investigator will submit any updated data to the sponsor or designee within 24 hours of updated information being available.

If CE marked device, used out of scope or non-CE marked device (AFMPS submission): The investigator uses the standard [Clinical Investigation Summary Safety Report Form](https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-2_guidance_safety_report_form_en.xlsx?web=1) to submit the SAE or SADE to the sponsor. The investigator will submit any updated 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. For reported death of a subject, the investigator shall supply the sponsor with any additional information requested.

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

#### Sponsor’s reporting

If CE marked device, used within scope (CE only submission): In the case of devices with a CE label and therefore already marketed, the reporting of SAEs/SADEs must be carried out in accordance with the material safety reporting rules to [vigilance.meddev@fagg-afmps.be](mailto:vigilance.meddev@fagg-afmps.be) (first contact the material safety reporting manager of the institution).

Any serious adverse event that has resulted in the death of the patient should be reported to the ethics committee within 24 hours after learning of it.

If CE marked device, used out of scope or non-CE marked device (AFMPS submission):

The following events should be reported by the **sponsor** to the FAMHP (and to all Member States in which the clinical investigation is conducted):

1. any serious adverse event (SAE) with a causal relationship to the investigational device, comparator or investigative procedure or where such a causal relationship is reasonably possible ;
2. any device deficiency that could have resulted in a serious adverse event if appropriate action had not been taken, if an intervention had not occurred, or if the circumstances had been less favorable;

any new finding related to an event described in (a) and (b).

SAEs related, probably related or possibly related to the use of the medical device should be reported to the FAMHP via the standard  [Clinical Investigation Summary Safety Report Form](https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-2_guidance_safety_report_form_en.xlsx?web=1) and sent by e-mail to [ct.rd@fagg-afmps.be](mailto:ct.rd@fagg-afmps.be) with the following mention in the subject line: "Notification of SAE - EudraCT number".

#### Deadlines for reporting events from the sponsor to authorities

**Immediately and no later than 2 calendar days** after the sponsor becomes aware of a new reportable event or new information in relation to a previously reported event, for all reportable events that indicate **an imminent risk of death, serious injury, or serious illness** and that require prompt corrective action for other patients/subjects, users, or others, or a new finding in this regard

**Immediately and no later than 7 calendar days** after the sponsor becomes aware of a new reportable event or new information related to a previously reported event, **for any other reportable event** or new discovery/update

There is no annual safety report for clinical investigations involving a medical device.

* + 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. Statistical design and analysis

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

The description and justification of the statistical model and analysis of the clinical investigation should cover the following

* Analysis population (e.g., intention-to-treat [ITT], per-protocol [PP], and actual treatment [AT] analysis) and procedures considering the data set.
* Descriptive statistics of baseline, treatment, safety data, and, where appropriate, primary and secondary endpoints.
* Analytical procedures including measures of precision, such as confidence intervals, where appropriate.
* Significance and power of primary endpoint(s) and, if applicable, overall statistical verification strategy.
* Sample size calculation and justification considering:
* all relevant clinical data on the outcome variable and effect size, if applicable;
* expected outcome assumptions in treatment groups, if any;
* adjustments due to pre-planned interim analyses, if any
* the magnitude of detectable effects and the non-inferiority margin, which should be less than the magnitude of detectable effects and justified relative to the comparator effect, if applicable
* the allocation ratio used for randomization (e.g., 1:1, 1:2), if applicable
* the expected dropout rate, such as withdrawal, loss of sight, death (unless death is an endpoint).
* All statistical parameters and methods used to calculate the sample size or non-inferiority margin should be clearly stated.
* Exploratory and sensitivity analysis (e.g., to test the robustness of the results of the primary and secondary analyses to the different methods used to deal with missing data), if applicable.
* Procedures for reporting deviations from the original statistical analysis plan.
* In the case of multicenter clinical investigations, a strategy for managing potential imbalances in enrollment at different investigative sites.
* Strategy for pooling data, if appropriate.

1. Data management

1) Data management plan : Complete the document *AAHRPP-DSQ-021 Data Management Plan* if the study has an high risk level. 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.

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.

Choose the appropriate wording: The subject identification list will be retained by the site. The name and any other direct identification details will not be included in the study database.

Or Subjects will be recorded in REDCap with their identification data and study number. Only participant numbers will appear in the extracted data at the end of the study.

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 10 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 or ethics committee serious data breaches : transgressions against the [clinical investigation](https://www.ema.europa.eu/en/glossary/clinical-trial) protocol or the [European](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 the applicable Ethics Committee(s) or Competent authority.

* 1. Archiving

Essential clinical trial documents are kept for 10 years after the end of the study, in accordance with the EU regulation 2017/745.

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. Finance and Insurance

The sponsor has taken a no fault insurance for this study, in accordance with the relevant legislation (article 32, Belgian Law of December 22, 2020).

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

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 the clinical investigation
   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 sponsor shall notify the Competent Authority or the Ethics Committee according to the regulatory requirements (within 15 days after the end of the study).

The sponsor must notify the Competent Authority or the Ethics Committee in case of a temporary halt or early termination of the clinical investigation. This notification must be made within 15 days of the temporary halt or early termination, providing a justification of the event. In the event that the sponsor has temporarily halted or terminated early the investigation on safety grounds, the Competent Authority or the Ethics committee must be informed within 24 hours of the event.

1. Publication policy

This clinical investigation is registered on clinicaltrials.gov and is available to the public.

The final report will be published on CUSL website (<https://www.saintluc.be/index.php/fr/recherche-clinique-etudes-academiques> ) one year after the end of the study. In case of a temporary halt or early termination this report must be provided within 3 months.

Authorship will be discussed prior to publication.

The following text would be added to publication for REDCap use :

*“Study data were collected and managed using REDCap electronic data capture tools hosted at Cliniques universitaires Saint-Luc. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures ; 3) automated export procedures for seamless data downloads to common statistical packages ; and 4) procedures for data integration and interoperability with external sources.”*

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

1. Bibliography

List of bibliographic references related to the clinical investigation

1. Appendix

* CIOMS SAE form 🡪 only if CE only submission = delete if AFMPS submission

**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. [AFMPS/FAMHP](https://www.afmps.be/fr/humain/produits_de_sante/dispositifs_medicaux/evaluation_clinique/etudes_a_notifier) Clinical investigations – Guidance on Dossier Content [↑](#footnote-ref-1)
2. [RÈGLEMENT (UE) 2017/745 DU PARLEMENT EUROPÉEN ET DU CONSEIL du 5 avril 2017 relatif aux dispositifs médicaux](https://eur-lex.europa.eu/legal-content/FR/TXT/HTML/?uri=CELEX:32017R0745&from=EN) [↑](#footnote-ref-2)
3. Norme internationale ISO 14155 : 2020 (F) [↑](#footnote-ref-3)
4. [ICH GCP E6 (R2) Guide de bonnes pratiques cliniques](https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf) [↑](#footnote-ref-4)