**Clinical Investigation Plan (CIP)**

*Vul hier de volledige titel van de studie in*

*Vul hier de protocol code / acroniem van de studie in*

*Vul hier het versienummer en de versiedatum van het protocol in. Zorg dat dit overeenkomt met versienummering in de voetnoot op elke pagina*

*< verwijder alle oranje tekst in de finale versie >*

**Protocol Amendment History:**

*Please list all amendments (substantial and non-substantial) to the protocol and describe the changes. Protocol version number of an amendment should be 2.0, 3.0 etc… -* ***All draft versions should be numbered 0.1, 0.2, etc...****The final version for initial submission should be numbered 1.0. The draft versions should not be mentioned here.>*

*Example:*

|  |  |  |
| --- | --- | --- |
| ***Version*** | ***Date*** | ***Description of amendment*** |
| ***1.0*** | ***01-Jan-2019*** | ***Initial submission*** |
| ***2.0*** | ***18-OCT-2019*** | ***- Page 8 and 11: 1 inclusion criterion added:***  ***Systolic blood pressure must be < 140***  ***mmHg during screening***  ***- throughout the protocol: correction of***  ***spelling errors*** |

|  |  |  |
| --- | --- | --- |
| **Version** | **Date** | **Description of amendment** |
| **1.0** |  | **Initial Submission to EC and FAMHP** |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

Table of contents

[1 List of Abbreviations 5](#_Toc77606450)

[2 Synopsis of the clinical investigation 6](#_Toc77606451)

[3 Title of the clinical investigation 7](#_Toc77606452)

[4 Single identification number of the clinical investigation 7](#_Toc77606453)

[5 General information 7](#_Toc77606454)

[5.1 Sponsor – Coordinating Investigator 7](#_Toc77606455)

[5.2 Device Name and Manufacturer 7](#_Toc77606456)

[5.3 Investigational sites and Principal Investigator(s) 7](#_Toc77606457)

[5.4 Departments/laboratories involved in the clinical investigation 8](#_Toc77606458)

[5.5 Financing of the clinical investigation 8](#_Toc77606459)

[A brief description of how the clinical investigation is financed. 8](#_Toc77606460)

[6 Introduction 8](#_Toc77606461)

[6.1 Background information 8](#_Toc77606462)

[6.2 Rationale of the clinical investigation 8](#_Toc77606463)

[6.3 Hypothesis of the clinical investigation 8](#_Toc77606464)

[7 Objective of the clinical investigation 8](#_Toc77606465)

[7.1 Primary objectives 9](#_Toc77606466)

[7.2 Secondary objectives 9](#_Toc77606467)

[8 Endpoints 9](#_Toc77606468)

[8.1 Primary Endpoint 9](#_Toc77606469)

[8.2 Secondary Endpoints 9](#_Toc77606470)

[9 Design of the clinical investigation 9](#_Toc77606471)

[10 Population 9](#_Toc77606472)

[10.1 Number of subjects 9](#_Toc77606473)

[10.2 Vulnerable population (pregnant, children, elderly, immune-compromised or breastfeeding population) 10](#_Toc77606474)

[10.3 Inclusion criteria 10](#_Toc77606475)

[10.4 Exclusion criteria 10](#_Toc77606476)

[10.5 Withdrawal and replacement of subjects 10](#_Toc77606477)

[10.6 Restrictions and prohibitions for the subjects 11](#_Toc77606478)

[10.7 Possible advantages and risks for the subjects 11](#_Toc77606479)

[11 Identification and description of the investigational device 12](#_Toc77606480)

[11.1 Medical device description 12](#_Toc77606481)

[11.2 Manufacturer 12](#_Toc77606482)

[11.3 Intended use 12](#_Toc77606483)

[11.4 Instructions for use 12](#_Toc77606484)

[11.5 Summary of necessary training and experience needed to use the investigation device 12](#_Toc77606485)

[11.6 Description of the specific medical or surgical procedures involved 13](#_Toc77606486)

[11.7 Delivery and return of the medical device 13](#_Toc77606487)

[11.8 Storage of the medical device 13](#_Toc77606488)

[11.9 Packaging and labeling of the medical device 13](#_Toc77606489)

[11.10 Traceability and accountability of the medical device 13](#_Toc77606490)

[11.11 Known reactions/side effects of the medical device 13](#_Toc77606491)

[12 Identification and description of the comparative device 14](#_Toc77606492)

[13 Methodology 14](#_Toc77606493)

[13.1 Study Specific Procedures 14](#_Toc77606494)

[13.2 Analysis of biological samples 14](#_Toc77606495)

[13.3 Flowchart 14](#_Toc77606496)

[13.4 Start of the clinical investigation 15](#_Toc77606497)

[13.5 End of clinical investigation 15](#_Toc77606498)

[13.6 Randomisation 16](#_Toc77606499)

[13.7 Blinding 16](#_Toc77606500)

[13.8 Prior and concomitant medication/treatments 16](#_Toc77606501)

[14 Safety reporting 16](#_Toc77606502)

[14.1 Definitions 16](#_Toc77606503)

[14.2 Causality assessment 17](#_Toc77606504)

[14.3 Reporting of adverse events 20](#_Toc77606505)

[14.3.1 Reporting of (S)AEs and device deficiencies by the investigator to the sponsor 20](#_Toc77606506)

[14.3.2 Reporting of reportable events by the sponsor to the CA 20](#_Toc77606507)

[14.4 Annual Safety and progress Reporting 21](#_Toc77606508)

[15 Notification of end of clinical investigation, early termination and temporary halt 21](#_Toc77606509)

[16 Study analysis 22](#_Toc77606510)

[16.1 Sample size calculation 22](#_Toc77606511)

[16.2 Statistical analysis 22](#_Toc77606512)

[17 Final clinical investigation report 24](#_Toc77606513)

[18 Publication policy 24](#_Toc77606514)

[19 Indemnity insurance 24](#_Toc77606515)

[20 Authorization of the clinical investigation 24](#_Toc77606516)

[21 Protocol compliance 24](#_Toc77606517)

[22 Good Clinical Practice (ISO 14155) 25](#_Toc77606518)

[23 Subject information and informed consent 25](#_Toc77606519)

[23.1 Recruitment and informed consent procedure 25](#_Toc77606520)

[23.2 Compensation for study participants 26](#_Toc77606521)

[24 Data Handling 26](#_Toc77606522)

[24.1 Data collection and processing 26](#_Toc77606523)

[24.2 Case Report Form (CRF) 27](#_Toc77606524)

[24.3 Data directly collected in the CRF (no source available) 27](#_Toc77606525)

[24.4 Access to source data / documents 27](#_Toc77606526)

[24.5 Archiving 28](#_Toc77606527)

[25 Quality assurance and periodic monitoring 28](#_Toc77606528)

[26 References 28](#_Toc77606529)

[27 Appendices 29](#_Toc77606530)

[28 Signature page 30](#_Toc77606531)

# List of Abbreviations

ADE = Adverse Device Effect

AE = Adverse Event

CA = Competent Authority

CIP = Clinical Investigation Plan

CTU = Clinical Trial Unit

EC = Ethics Committee

eCRF = electronic Case Report Form

GCP = Good Clinical Practice

GDPR = General Data Protection Regulation

HIRUZ = Health, Innovation and Research Institute UZ Ghent

ICF = Informed Consent Form

IEC = Independent Ethics Committee

ISO = International Organization for Standardization

LSLV = Last subject, last visit

PI = Principal Investigator

SADE = Serious Adverse Device Effect

SAE = Serious Adverse Event

SOP = Standard Operating Procedure

USADE = Unanticipated Serious Adverse Device Effect

# Synopsis of the clinical investigation

|  |  |
| --- | --- |
| TITLE |  |
| ACRONYM |  |
| SPONSOR |  |
| COORDINATING INVESTIGATOR |  |
| NAME OF DEVICE |  |
| MANUFACTURER |  |
| STUDY DESIGN |  |
| CENTER(S) / COUNTRY(IES) |  |
| OBJECTIVES | Primary Objective  Secondary Objectives |
| ENDPOINTS | Primary Endpoint  Secondary Endpoints |
| STUDY DURATION |  |
| NUMBER OF PATIENTS |  |
| INCLUSION CRITERIA |  |
| EXCLUSION CRITERIA |  |
| PROCEDURES |  |
| COMPARATIVE DEVICE | *Indien van toepassing* |

# Title of the clinical investigation

Vul hier de volledige titel van het onderzoek in en eventuele naam van de studie/acronym

# Single identification number of the clinical investigation

Eudamed number: TBC

# General information

## Sponsor – Coordinating Investigator

Sponsor of the clinical investigation: University Hospital Ghent (of UGent)

Department of XX

C. Heymanslaan 10

9000 Ghent

Coordinating Investigator: XX

Contact person: XX

## Device Name and Manufacturer

Vul hier de naam van het toestel in en van de fabrikant

## Investigational sites and Principal Investigator(s)

Vul hier de naam, functie en de coördinaten in van de hoofdonderzoeker(s) van de deelnemende centra.

## Departments/laboratories involved in the clinical investigation

Vul hier de naam en de coördinaten in van de dienst(en), laboratoria, CROs die betrokken zijn bij de studie indien van toepassing

## Financing of the clinical investigation

## A brief description of how the clinical investigation is financed.

# Introduction

## Background information

Geef een korte samenvatting van de **aandoening** waarop de focus ligt in uw klinisch onderzoek. Verwijs naar de meest belangrijke literatuur gepubliceerd rond dit onderwerp.

Geef aan wat de ‘state of the art’ diagnose/behandeling is voor deze aandoening/doelgroep en waarom deze studie relevant is.

Geef eveneens background literatuur over het device dat getest zal worden.

Wat is momenteel de gouden standaard (anders dan het device dat getest wordt)? Welk voordeel zal het device hebben in vergelijking met de momenteel geldende gouden standaard?

## Rationale of the clinical investigation

Beschrijf de rationale van het uitvoeren van deze studie. Vanwaar de nood voor deze studie, hoe kan dit bijdragen tot het verwerven van kennis, … Verwijs naar (pre)klinisch onderzoek reeds uitgevoerd met het toestel.

## Hypothesis of the clinical investigation

Beschrijf de hypotheses dat je zal onderzoeken in deze studie.

# Objective of the clinical investigation

## Primary objectives

Beschrijf hier de primaire doelstellingen van de studie, wat je met de studie wenst te bereiken. De data die verzameld wordt in de studie dient om de doelstelling te bereiken.

## Secondary objectives

Beschrijf hier de secundaire doelstellingen van de studie

# Endpoints

## Primary Endpoint

Beschrijf hier het primair eindpunt van de studie, terug gekoppeld naar de primaire doelstelling met rationale voor selectie.

## Secondary Endpoints

Beschrijf hier de secundaire eindpunten die bewijs van de primaire doelstelling ondersteunen of gericht zijn op de secundaire doelstellingen.

# Design of the clinical investigation

Beschrijf hier het design van de studie:

* Exploratory/ conformatory/ observational
* First in human / not first in human
* Pilot / pivotal
* Case control / controlled / cross-sectional / double blind / parallel / randomised / open / other
* Beschrijving van de controle groep en comparator device

Beschrijf hier de rationale voor de design keuze:

# Population

## Number of subjects

Beschrijf hier het aantal proefpersonen die in de studie zullen geïncludeerd worden. In geval van multicenter studie, beschrijf het aantal proefpersonen per site indien gekend of geef aan dat geen aantal per site gedefinieerd wordt.

## Vulnerable population (pregnant, children, elderly, immune-compromised or breastfeeding population)

Beschrijf kwetsbare doelgroepen volgens de richtlijnen hieronder of geef aan dat deze groepen niet deelnemen aan de studie.

*Describe the vulnerable population that is included in the clinical investigation. The specific screening process to identify and protect the vulnerable population and the informed consent process must be defined. Finally, the medical care, if any, that will be provided for the subjects after the clinical investigation has been completed must also be given. (MDR Art. 64-68)*

## Inclusion criteria

Beschrijf hier de karakteristieken die de populatie van uw studie bepalen. Elke deelnemer moet voldoen aan de inclusie (en exclusie) criteria om aan de studie te mogen deelnemen. Voorbeelden kunnen zijn leeftijdsgrens, bepaalde lab waarden, bloeddruk binnen bepaalde grens, medische voorgeschiedenis,…

## Exclusion criteria

Zorg ervoor dat de exclusie criteria niet het omgekeerde zijn van de inclusie criteria. Indien bepaald criterium reeds vermeld is bij inclusie (bv. > 18 jaar), moet je het hier niet herhalen bij exclusie (bv. ≤ 18 jaar).

## Withdrawal and replacement of subjects

**Criteria for withdrawal**

Subjects may prematurely discontinue from the clinical investigation at any time. Premature discontinuation from the study is to be understood when the subject did not undergo end of study examination.

Subjects can be withdrawn under the following circumstances:

* at their own request
* if the investigator feels it would not be in the best interest of the subject to continue
* if the subject violates conditions laid out in the informed consent form or disregards instructions by the clinical investigation personal
* in case of significant study intervention non-compliance
* nog aan te vullen met studiespecifieke/device afhankelijke redenen waarom subject als drop-out wordt beschouwd, bv. Pregnancy, disease progression which requires discontinuation of the study intervention

Beschrijf of en hoe deze patiënten verder opgevolgd/verzorgd zullen worden.

In all cases, the reason why subjects are withdrawn must be recorded in detail in the (e)CRF and in the subject’s medical records.

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

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

• The site will attempt to contact the subject and reschedule the missed visit.

• Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, 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 as a drop-out with a primary reason of lost to follow-up.

**Replacement policy**

Beschrijf hier de maatregelen die genomen zullen worden bij drop-outs (al dan niet vervangen). Let op, het totaal aantal verzekerde proefpersonen is inclusief de drop-outs.

## Restrictions and prohibitions for the subjects

Beschrijf hier de beperkingen voor de proefpersonen indien deze er zijn (vb geen alcohol tijdens studie, nuchter naar site komen, ..)

## Possible advantages and risks for the subjects

Beschrijf hier de mogelijke direct en indirecte voordelen en risico’s voor de deelnemers en zijn omgeving (zorgpersoneel, familie, volksgezondheid..) aan de studie.

Beschrijf alle mogelijke risico’s en aantal verwachte A(D)E, SA(D)E, device deficiencies gerelateerd aan het medical device en de procedures (en eventuele interacties met concomitant medical treatments/medications) waaraan zowel de deelnemers als zijn omgeving (zorgpersoneel, familie,..) blootgesteld zullen worden (risk characterization: type risico, waarschijnlijkheid van voorkomen, duur van het risico en ernst van het risico ) en beschrijf hoe je deze risico’s gaat beperken (risk mitigation).

And the risks related to the interpretation of the study data. In specific, the risk of drawing a false conclusion based on clinical data obtained, and the risk of data which are inconclusive or difficult to interpret.

Other information providing useful context is appreciated and may include: consideration of patient preference information (when available) characterizing the subjects’ perspective on benefit, i.e.; the value that the patients place on the use of the medical device, as well as information characterizing subjects’ tolerance for risk.

Give rationale for benefit-risk ratio.

# Identification and description of the investigational device

## Medical device description

Beschrijf hier uw medical device dat getest wordt in de studie met aandacht op het materiaal dat in contact komt met de patiënt. Beschrijf ook eventuele medische substanties, weefsels of derivaten of biologische substanties die opgenomen worden in het medical device. Informatie uit of verwijzing naar de investigator’s brochure en/of gebruikshandleiding kan gebruikt worden. Beschrijf of het toestel CE gecertifieerd is en voor welke indicatie. Vermeld naam of nummer van het model/type, inclusief eventuele software versie en toebehoren.

## Manufacturer

Geef hier de details van de fabrikant

## Intended use

Beschrijf de intended use van het toestel in de studie Beschrijf tevens de populaties en indicaties waarvoor het toestel bedoeld is.

*‘Intended use’ means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation*

*= what do you claim about your device? What does it do? What is it made for?*

*Examples:*

*The XX stent system is indicated for improving coronary artery luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease due to de novo native coronary artery lesions (length ≤ 32 mm) with reference vessel diameters of ≥ 2.25 mm to ≤ 4.25 mm. In addition, the XX stent system is indicated for treating de novo chronic total coronary occlusions.*

*The XX is intended to assist a surgeon during vitreoretinal surgical tasks to treat vitreoretinal diseases*

## Instructions for use

Beschrijf hier hoe het toestel gehanteerd moet worden. Eventueel kan verwezen worden naar de gebruikshandleiding (instructions for use) indien beschikbaar.

## Summary of necessary training and experience needed to use the investigation device

## Description of the specific medical or surgical procedures involved

## Delivery and return of the medical device

Beschrijf hoe het toestel geleverd zal worden op de site (shipment records zullen bijgehouden moeten worden). Is de apotheek betrokken bij de levering?

Wat moet er gebeuren met gebruikte devices. Wat met ongebruikte devices, verlopen devices (na houdbaarheidsdatum), wat met defecte devices? Wat moet er gebeuren met de devices op het einde van de studie?

## Storage of the medical device

Beschrijf hoe en waar het toestel bewaard moet worden op site/in de apotheek

The investigational medical devices will only be accessible for study team members as listed on the delegation log. ….

## Packaging and labeling of the medical device

Beschrijf hoe het device verpakt en gelabeld zal zijn. Voeg een voorbeeld van het label toe dat op het device zal verschijnen of beschrijf welke informatie op het label zal staan. Voor software kan het label als eerste verschijnen wanneer men de software opent of op een andere manier geïntegreerd worden.

## Traceability and accountability of the medical device

Beschrijf hoe de registratie on site van de medical devices zal gebeuren alsook registratie van de medical devices die in gebruik zijn. Er zal een device accountability log bijgehouden moeten worden voor de devices die door de site ontvangen worden alsook voor de devices die aan de patiënt gegeven/teruggegeven worden (Bv bijhouden van LOT nummer, batch nummers, serial nummer). Beschrijf eveneens wat er zal gebeuren met devices die niet gebruikt zijn, expired zijn of malfunctioning.

Beschrijf hoe de devices teruggeroepen zullen worden in geval van nood.

## Known reactions/side effects of the medical device

The risks and clinical benefits of the device to be examined are described in the latest approved version of the Investigator’s Brochure.

# Identification and description of the comparative device

# Methodology

## Study Specific Procedures

Beschrijf hier alle studie specifieke procedures/interventies die zullen uitgevoerd worden tijdens de studie (vb vragenlijsten, ECG, bloedafname, biopsie, …) en op welk tijdspunt. Geef waar mogelijk een motivatie waarom en verwijs eventueel naar (pre)klinische data. Geef eveneens aan op welke vlakken je afwijkt van de standaard of care diagnose/behandeling van de patiënt in kader van de studie.

De procedures worden best chronologisch opgelijst. Bv. Screening assessments, randomisatie, gebruiken van device (hoeveel en hoelang), gebruik van comparator device, follow-up visite 1, follow-up visite 2,… Zorg dat er steeds een realistische time window voorzien wordt bij de tijdspunten (tijd waarin de interventie kan plaatsvinden). Geef een verantwoording voor de follow-up periode.

De standaard of care interventies waarvan data verzameld wordt voor de studie dienen hier eveneens beschreven te worden. In geval van multicentrische studies dient men goed op voorhand te achterhalen of de SOC interventies in alle sites dezelfde zijn. Maak duidelijk een onderscheid tussen studiespecifieke procedure en standard of care procedure.

## Analysis of biological samples

Indien van toepassing, beschrijf hier door wie (naam en coördinaten) biologische stalen zullen geanalyseerd worden, alsook welke analyses en op welke manier deze zullen uitgevoerd worden. Waar zullen de biologische stalen bewaard worden? Wie is de medische beheerder van de biobank? Zullen de stalen gebruikt worden voor toekomstig onderzoek na de studie?

## Flowchart

Geef hier het schematisch verloop van de studie weer (geplande activiteiten per visite). Onderstaand vindt u een voorbeeld:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Screening** | **Baseline** | **Treatment Phase** | | **Follow Up** |
| Informed consent |  |  |  |  |  |
| Inclusion/exclusion criteria check |  |  |  |  |  |
| Randomisation |  |  |  |  |  |
| Add all study specific interventions\* |  |  |  |  |  |
| Device Compliance |  |  |  |  |  |
| Adverse event check |  |  |  |  |  |
|  |  |  |  |  |  |

*Put an asterisk with all the interventions that are standard of care, so that it remains clear which interventions are study specific and which are not.*

## Start of the clinical investigation

Beschrijf hier wat de eerste actie van rekrutering is (bv. datum van eerste screening in EPD, datum van ophangen posters in wachtzaal, datum van flyers uitleggen in wachtzaal, eerste gesprek met eerste patiënt,…). Beschrijf wat als inclusie beschouwd wordt (te baseren op waarop de sample size werd berekend bv first subject randomized OR first subject that signed ICF).

The clinical investigation is considered started upon the first act of recruitment. For this clinical investigation this is considered as ….. A subject is included in the clinical investigation when….

## End of clinical investigation

Beschrijf hier wat als end of study wordt beschouwd in uw studie, welke assessment? Dit moet opgedeeld worden in einde van de studie voor 1 deelnemer en einde van de totale studie.

The subject has completed the clinical investigation if he or she has completed all phases of the study, including the last visit or the last scheduled procedures, as described in this protocol

Overall, the end of the clinical investigation is reached when last subject has completed last study visit (LSLV).

The expected total duration of the clinical investigation is xxx (vul hier het vermoedelijke aantal dagen/weken/maanden/jaren in dat de studie zal lopen tot overall LSLV)

## Randomisation

Beschrijf hier de procedures voor randomisering indien van toepassing. Wie doet dit? Hoe? Via software of gesloten enveloppe trekken? Waar worden de randomisatie codes bewaard? Hoeveel deelnemers in de ene groep en hoeveel in de andere?

## Blinding

Beschrijf wie geblindeerd is in de studie, hoe dit georganiseerd wordt en welke procedures er zijn om de blindering op te heffen indien noodzakelijk.

## Prior and concomitant medication/treatments

Beschrijf hier de toegelaten en verboden medicatie of behandelingen vóór en tijdens studie indien u restricties oplegt. Of geef aan dat er geen restricties zijn.

# Safety reporting

## Definitions

**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 context of a clinical investigation, whether or not related to the investigational medical device. (MDR Art 2(57))

Note:

a. This definition includes events that are anticipated as well as unanticipated events

b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

**Serious Adverse Event (SAE)**

Any adverse event that led to any of the following:

a) death,

b) serious deterioration in the health of the subject, that resulted in any of the following:

i. life-threatening illness or injury,

ii. permanent impairment of a body structure or a body function,

iii. hospitalisation or prolongation of patient hospitalisation,

iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body

function,

v. chronic disease,

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

(MDR Article 2(58))

**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.

**Adverse Device Effect (ADE)**

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

**Serious Adverse Device Effect (SADE)**

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

**Unanticipated Serious Adverse Device Effect (USADE)**

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Procedures associated with the use of a device should be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are Unanticipated Serious Adverse Device Effect or not. SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device should not be considered Serious Adverse Device Effects.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk assessment.

## Causality assessment

The relationship between the use of the medical device (including the medical – surgical procedure) and the occurrence of each adverse event shall be assessed and categorized. During causality assessment activity, clinical judgment shall be used and the relevant documents, such as the Investigator’s Brochure and the Clinical Protocol shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality. The investigators and the sponsor will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device, the comparator or the investigation procedures.

**1) Not related**: relationship to the device or procedures can be excluded when:

* the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
* the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
* the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
* the event involves a body-site or an organ that cannot be affected by the device or procedure;
* the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
* the event does not depend on a false result given by the investigational device used for diagnosis9, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

**2) Possible** the relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

**3) Probable** the relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot reasonably explained by another cause.

**4) Causal relationship:** the serious event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:

* the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
* the event has a temporal relationship with investigational device use/application or procedures;
* the event involves a body-site or organ that
* the investigational device or procedures are applied to;
* the investigational device or procedures have an effect on;
* the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
* the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
* harm to the subject is due to error in use;
* the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related..

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the serious event, the sponsor should not exclude the relatedness and classify the event as “possible” and the reporting should not be delayed.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

## Reporting of adverse events

### Reporting of (S)AEs and device deficiencies by the investigator to the sponsor

Adverse events will be reported between the first use of the medical device and the last study related activity. Medical events that occur between signing of the Informed Consent and the first use of the medical device will be documented as medical history data.

All (S)AEs will be recorded in the patient’s file and in the eCRF. For this study, the following (S)AEs should not be reported in the eCRF:

Beschrijf hier welke (S)AE’s voor uw studie niet gerapporteerd moeten worden in het eCRF (bv. hospitalisatie wegens sociale redenen, behandeling van een pre-existing ziekte die niet verergerd is, monitoring van een pre-existing ziekte die niet verergerd is,…). Gelieve hiervoor ook een rationale te geven.

**All SAEs and device deficiencies will be reported immediately but no later than 3 calendar days** after investigational site study personnel’s awareness of the event to:

* Sponsor/National coordinator: Voeg hier de contactgegevens toe en schrap wat van toepassing is (sponsor of national coordinator)
* Health Innovation and Research Institute:

E-mail: hiruz.ctu@uzgent.be

Tel: 09/332.09.05.00

Fax +32 9 332 05 20

Address: Corneel Heymanslaan 10, 1K5, 9000 Gent

This reporting is done by using the **appropriate SAE form and device deficiency form**. Follow-up information should be provided as necessary.

### Reporting of reportable events by the sponsor to the CA

The following events are considered reportable events**:**

a) any serious adverse event that has a causal relationship\* with the investigational device, the comparator or the investigation procedure or

where such causal relationship is reasonably possible;

b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

c) any new findings in relation to any event referred to in points a) and b).

*\* If either the sponsor or the investigator has assigned a higher causality level than "not related", the event is considered as having a causal relationship and therefore a reportable event.*

The sponsor will report all reportable events or a new finding to it to the CA immediately, but not later than 7 calendar days after awareness of the sponsor. All reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it will be reported immediately but not later than 2 calendar days after awareness by the sponsor to the CA. This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals. These concerns may be identified by either the National CA or the manufacturer.

## Annual Safety and progress Reporting

Sponsor will inform all principal investigators at least annually in writing of all the serious adverse events at all investigation sites that have been reported to the sponsor, and ensure that they are reported to their local EC, if defined by their institution’s procedure.

The Sponsor may submit an annual report containing information on the status of the clinical investigation and an overview of all SAEs and a summary regarding the safety of the clinical investigation to the CA if requested with the authorization.

# Notification of end of clinical investigation, early termination and temporary halt

The end of clinical investigation will be notified by sponsor within 15 days of the end of the clinical investigation to the CA.

Early termination or temporary halt of the clinical investigation or an investigational site may be necessary in case of major non-compliance, critical safety issues or premature study discontinuation. This can occur at any time by the sponsor, principal investigator of the local site, IEC or regulatory authority. ISO 14155:2011 shall be followed. Beschrijf hoe de deelnemers in dat geval verder opgevolgd/verzorgd zullen worden.

In the event that the clinical investigation would be discontinued prematurely or suspended, the sponsor will notify the CA within 15 days of the early termination or temporary halt, providing a justification of the event. In the event that the sponsor has temporarily halted or terminated early the investigation on safety grounds, the sponsor will inform the CA within 24 hours of the event.

In case of an early termination, all study materials will be retained and the terminating party shall justify its decision in writing.

# Study analysis

## Sample size calculation

Beschrijf hier op basis van welke criteria het aantal proefpersonen bepaald werd.

1) all relevant clinical data on outcome variable and effect size, if applicable;

2) assumptions of expected outcomes across treatment groups, if applicable;

3) adjustments due to any pre-planned interim analyses, if applicable;

4) detectable effect size and non-inferiority margin, which shall be smaller than the detectable effect size and justified with reference to the effect of the comparator, if applicable;

5) randomization allocation ratio (e.g. 1:1, 1:2), if applicable;

6) expected drop-out rate, such as withdrawal, lost to follow-up, death (unless death is an endpoint).

All the statistical parameters and methods used to calculate sample size or the non-inferiority margin shall be clearly provided.

## Statistical analysis

Beschrijf hier de statistische analyses die zullen gebeuren, alsook wie de statistisch analyse zal uitvoeren (naam en coördinaten). Beschrijf de statistische analyses tot in detail (vb aanvaard niveau van significantie, intention to treat,…). Zal er een interim analyse plaatsvinden? Zo ja, wanneer en met welk doel? Beschrijf eveneens welke maatregelen je neemt om bias te voorkomen (bv. randomisering, managen van mogelijke confounding factoren,…) Onderstaand kan opgenomen worden, afhankelijk van welke soort studie:

a) Analysis population (e.g. intention-to-treat, per-protocol, as-treated) and procedures that take into account all the data.

b) Descriptive statistics of baseline data, treatments, safety data and where applicable, primary and secondary endpoints.

c) Analytical procedures including measures of precision such as confidence intervals, if applicable.

d) The significance level and the power of primary endpoint(s) and the overall statistical testing strategy, if applicable.

If a hypothesis is tested, a significance level alpha 0,05 (two-sided) and 0,025 (one-sided) and powers between 0,8 and 1 minus alpha need no justification. Depending on the characteristics of the investigational medical device or the clinical investigation, higher or lower levels of significance can be used. Examples of justifications include but are not limited to: product standards, scientific reasons or discussion with regulatory authorities.

f) The rationale for the number of procedures to be performed by a single user as part of the learning curve and how these data are to be analysed, if applicable.

Methods and timing for assessing, recording, and analysing variables.

g) Pass/fail criteria to be applied to the results of the clinical investigation.

h) The provision for an interim analysis, criteria for the termination of the clinical investigation on statistical grounds, where applicable.

i) Management of bias and, when randomization, matching, or blinding are applied, plan for assessment of success thereof.

j) Management of potential confounding factors (e.g. adjustment, stratification, or stratified randomization).

k) Description of procedures for multiplicity control and adjustment of error probabilities, if applicable.

l) The specification of subgroups for analysis, if applicable, or if response to treatment is expected to be different in these groups.

m) Management, justification, and documentation of missing, unused or spurious data, including drop-outs.

n) Exploratory analysis and sensitivity analysis (e.g. to explore robustness of results of primary and secondary analysis with respect to different methods used for handling missing data), if applicable.

o) Procedures for reporting any deviation(s) from the original statistical analysis plan.

p) For multicentre clinical investigations, a strategy for handling the potential imbalance of the numbers of subjects across investigation sites.

q) A strategy for pooling data, if applicable.

# Final clinical investigation report

Within one year after the final completion of the clinical investigation, a full final report will be written by the sponsor and submitted to the CA. In case of early termination of the clinical investigation this report will be submitted within 3 months after LPLV. This report shall contain a critical evaluation of all the data collected during the clinical investigation and shall include any negative findings.

# Publication policy

Beschrijf hier het publicatiebeleid dat voor deze studie van toepassing is.

This study will be registered in a public trial register prior to inclusion of the first subject. Results information from this study will be submitted to the public trial register.

# Indemnity insurance

During their participation in the study the patients will be insured as defined by legal requirements. An insurance with no fault responsibility has been foreseen for the Belgian participants by the sponsor in accordance with the Belgian law of 22 december 2020 concerning medical devices.

# Authorization of the clinical investigation

This study must obtain approval from the CA and IEC prior to the start of the study. Any additional requirements imposed by the CA or IEC shall be followed. Substantial protocol amendments will be notified to the CA/IEC during the course of the study according to the requirements and within the timelines as defined by the national law.

# Protocol compliance

Prospective, planned deviations or waivers to the CIP are not allowed. Under emergency circumstances, deviations from the CIP to protect the rights, safety or well-being of human subjects may proceed without prior approval of the sponsor and the CA/IEC. Such deviations shall be documented and reported to the sponsor by email (*enter contact details sponsor* and [hiruz.ctu@uzgent.be](https://infoland.ai.internal.uzgent.be/iProva/management/hyperlinkloader.aspx?hyperlinkid=529d90f0-482a-4567-a318-b85e259e4983)) and the CA/IEC as soon as possible. Accidental protocol deviations must be adequately documented and reported in the eCRF on the protocol deviation log. In case accidental protocol deviations are considered as critical issues that significantly affect patient safety, data integrity and/or study conduct these should be reported to the sponsor immediately by email (*enter contact details sponsor* and [hiruz.ctu@uzgent.be](https://infoland.ai.internal.uzgent.be/iProva/management/hyperlinkloader.aspx?hyperlinkid=fc4473c0-ff6e-4f8d-a581-8b55406bc62e)). The sponsor will subsequently communicate and discuss this with the CA/IEC.

The following items will be documented on the protocol deviation log: date of deviation, description of deviation, actions taken and classification of deviation. Deviations will be classified as minor or major. A minor protocol deviation is a deviation that does not affect the safety, rights or well-being of subjects or the quality of their data. A major protocol deviation is a deviation that affects safety, rights or well-being of subjects or quality of their data.

Any deviation that potentially interferes with and/or affects the efficiency and/or quality conduct of the study will be discussed by the monitor with the PI and will be documented on the monitoring report including a proposed plan of action for resolution if applicable.

# Good Clinical Practice (ISO 14155)

This study will be conducted in accordance with the protocol, ISO 14155 which addresses good clinical practices and applicable national and European legislations including but not limited to the General Data Protection Regulation EU2016/679 (“GDPR”), the EU Medical Device Regulation MDR 2017/745, the Belgian royal decree of 18 May 2021 concerning clinical investigations of medical devices and the Belgian law of 22 Dec 2020 concerning medical devices.

ISO 14155 is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical investigations that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the study data are credible.

# Subject information and informed consent

## Recruitment and informed consent procedure

Beschrijf hier hoe je de deelnemers zal rekruteren: Waar? Door wie? Hoe? Suggestie wordt onderstaand geschreven, aanpassen naar hoe zal verlopen (moet voor alle centra van toepassing zijn).

Prior to entry in the study, the investigator will explain to potential subjects or their legal representatives the study and the implication of participation. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Participating subjects will be told that their records may be accessed by competent authorities and by authorized persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF), the subjects or legally acceptable representatives are authorizing such access.

After this explanation and before entry to the study, written, dated and signed informed consent should be obtained from the subject or legally acceptable representative. The ICF should be provided in a language sufficiently understood by the subject. Subjects must be given the opportunity to ask questions.

The subject or legally acceptable representative will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry to the study, consent should be appropriately recorded by means of either the subject's or his/her legal representative's dated signature or the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the ICF must be given to the subject.

In case the subject or legally acceptable representative is unable to read, an impartial witness must attest the informed consent.

Subjects who are unable to comprehend the information provided or pediatric subjects can only be enrolled after consent of a legally acceptable representative.

The participant or the participant’s legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant’s willingness to continue participation in the study.

## Compensation for study participants

Beschrijf hier of de deelnemers een vergoeding/compensatie (financieel of andere) zullen ontvangen. Zorg ervoor dat dit op dezelfde manier vermeldt wordt in het ICF.

# Data Handling

## Data collection and processing

Data collection and processing will be done in full compliance with the European Regulation 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (GDPR).

## Case Report Form (CRF)

Beschrijf hier welk CRF gebruikt zal worden (papier of elektronisch), hoe datamanagment zal uitgevoerd worden, wanneer de CRF’s naar de sponsor gaan, … Een excel bestand wordt niet toegestaan als elektronisch CRF (geen audit-trail, geen beveiligde toegang, geen aangepaste rechten per studie member,…) Onderstaand een voorbeeld waarop u zich kan baseren:

The source documents are to be completed at the time of the subject’s visit. The eCRFs are to be completed within reasonable time after the subject’s visit. Only the data required by the protocol are captured in the eCRF. For this study an electronic data capture system (eCRF) … will be used / paper CRF will be used. REDCap is provided and maintained by Vanderbilt University; a license for use was granted to the Health, Innovation and Research Institute (HIRUZ). REDCap is a web-based system.

The study site staff is responsible for data entry in REDCap. For each subject enrolled the eCRF will be signed by the principal investigator or co-investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF. CRF entries and corrections will only be performed by study site staff, authorized by the investigator and in accordance with ISO 14155.

The entries will be checked by trained personnel (Monitor) and any errors or inconsistencies will be changed immediately.

The Principal investigator must verify that all data entries in the eCRFs are accurate and correct. If certain information is Not Done, Not Available or Not Applicable, "N.D." or "N.AV." or "N.AP", should be entered in the appropriate space.

Data cleaning of the study database will be performed by ….

## Data directly collected in the CRF (no source available)

The following data will be considered source data and entered directly on the CRF: …

## Access to source data / documents

Appropriate technical and organizational measures should be installed to protect information and personal data processed against unauthorized or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves transmission over a network.

The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

## Archiving

The investigator and sponsor specific essential documents will be retained for at least 10 years. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirement(s).

# Quality assurance and periodic monitoring

Beschrijf hier eventuele maatregelen die genomen worden om de datakwaliteit te bewaken.

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: investigator's file, and subject clinical source documents.

The investigator's file will contain the documents as per EUROPENAN Standard of EN ISO 14155 (incl. GCP) and local regulations.

Regular monitoring will be performed by Hiruz CTU according to ICH GCP and ISO 14155. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical investigation is conducted and data are generated, documented and reported in compliance with the protocol, ISO 14155 and the applicable regulatory requirements. An initiation visit, routine monitoring visits and a final visit after the last patient had finished the study. The frequency, extent and nature of the monitoring will depend on the risk assessment of the study. The monitor will be working according to SOPs and will provide a monitoring report after each visit for the sponsor and a follow-up letter to the investigator. Depending on the quality of the data, additional monitoring visits will be necessary according to the sponsor’s discretion.

More detailed information regarding the monitoring can be found in the monitoring plan.

# References

# Appendices

Voeg hier bijlagen toe indien gewenst

# Signature page

I certify that I will conduct the study in compliance with the protocol, any amendments, GCP/ISO 14155, the declaration of Helsinki, and all applicable regulatory requirements.

*Coordinating Investigator:*

Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Title/Function:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*Principal Investigator:*

Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Title/Function:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

I certify that I will conduct the study in compliance with the protocol, any amendments, GCP/ISO 14155, the declaration of Helsinki, and all applicable regulatory requirements.

*Principal Investigator:*

Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Title/Function: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Institution: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_