Deze template dient enkel te worden gebruikt voor prospectieve interventionele studies met medical device die vallen onder art 62 van de Medical Device Regulation.

Universitair Ziekenhuis Brussel

Clinical Trial Center

Clinical Investigation Plan

Study Title:
Study Acronym:
Clinical Investigation Plan Version and Date:
Eudamed Registry Number:
ClinicalTrials.gov Registry Number:
Sponsor:
Coordinating/Principal Investigator:
Condition:
Investigational Medical Device:
Manufacturer Medical Device:

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More information on the submission process under MDR can be found via:
https://www.fagg.be/nl/MENSELIJK_gebruik/gezondheidsproducten/medische_hulpmiddelen_hulpstukken/klinische_evaluatie/aan_te_melden_onderzoeken

CLINICAL INVESTIGATIONAL PLAN SIGNATURE PAGE

Clinical Investigation Plan Version and date:

Clinical Investigation Plan Title:

Sponsor:

Principal Investigator:

I agree:

- to assume responsibility for the proper conduct of this study
- to conduct the study in compliance with this clinical investigation plan and any future amendments
- not to implement any deviations from or changes to the clinical investigation plan without prior review and written approval from the Ethics Committee, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements)
- that I am thoroughly familiar with the appropriate use of the investigational medical device, as described in this protocol
- to ensure that all persons assisting me with the study are adequately informed about the investigational medical device and their study-related duties and functions as described in the clinical investigation plan
- that I am aware of and will comply with the current good clinical practice (GCP) guidelines and ethical principles outlined in the Declaration of Helsinki
- to conduct the study in accordance with all applicable laws and regulations

Printed name _____ Signature _____ Date

Table of Contents

1 General Information

1.1 Information Clinical Investigation

Title Clinical Investigation	
CIP reference number	
CIP Version	
CIP Date	

1.2 Summary of Revision History

Version No.	Release Date	Summary of Changes

1.3 Abbreviations and acronyms

CIP Clinical Investigation Plan

1.4 Synopsis

Sponsor	
Local Representative (if applicable)	
Principle Investigator	
Local Investigator (if applicable)	
Investigational sites	
External Organizations:	
Laboratories	
CRO	
Consultants	

A brief description of how the clinical investigation is financed and a brief description of the agreement between the sponsor and the site(s) must also be included in the submission package.

Eudamed number:	
Date of registration:	
ClinicalTrials.gov:	
Official Title:	
Study Phase/Type:	
Condition:	
Objectives:	
Investigational Medical Device:	
Interventions:	

Endpoints:	
Study population:	
Number of patients:	
Overview of study design:	
Statistical Considerations:	
Inclusion Criteria:	
Exclusion Criteria:	
Target Date of first enrolment:	
Target sample size:	

2 Identification and Description of the investigational device

Summary Description	
Manufacturer	
Name or number of the model/type	
Software version (if applicable)	
Intended purpose	
Populations (for which the device is intended)	
Indications (for which the device is intended)	

2.1 Traceability during and after clinical investigation

(For example assignment of lot numbers, batch numbers or serial numbers)

2.2 Detailed description of investigational device

(Including a list of all materials which will be in contact with tissues or body fluids. Also any medicinal substances, human or animal tissues or their derivates, or other biological active substances incorporated in the device must be defined.)

2.3 Summary of the necessary training and experience

(Training and experience needed to use the investigational device based on risk assessment)

2.4 Description of the specific medical or surgical procedures

(Procedures involved in the use of the investigational device)

3 Justification for the design of the clinical investigation

(This section includes a justification for the design of the clinical investigation. It should comprise an evaluation of the results of the relevant pre-clinical and clinical data, if applicable, to justify

the use of the investigational device in human subjects. If appropriate a description of the clinical developmental stage can be included.)

4 Benefits and Risks

4.1 Risk characterization

(All incremental risks to which subjects will be exposed by participating in the clinical investigation, related to the investigated medical device and procedures

The following factors should be considered, individually and in aggregate:

a) Types of risk (taking account of the study design as well)
b) Their likelihood and duration along with the severity.
c) The risk factors for health care personnel, family members or caregivers, if any.
d) 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.

A list of anticipated A(D)E, SA(D)E, DD, including those considered critical, must be prepared.)

4.2 Risk mitigation

(The manner(s) used to minimize these risks. It is not necessary to include specific mitigations for hypothetical risks that are not supported by scientific evidence or risks that are determined to be negligible due to a low probability of occurrence and low severity of harm.

a) Protective measures, e.g.; physical protective measures; staged enrolment and interim pre-specified subject safety assessment; pre-specified stopping rules; narrow study population with more favourable benefit-risk profile; performance of study at trained/specialized sites or investigators meeting certain criteria; study oversight (monitoring committees); frequent reporting of SAEs; accurate recording of AEs, including the timing and clinical context and a description of any medical interventions provided and the associated outcomes.
b) Communication of safety information and residual risks, e.g.; through labelling or informed consent, training of investigational staff, optimizing communication among sites, communicating safety data and residual risks with ethics committee(s) and competent authority to determine if any additional subject protection measures are needed.)

4.3 Anticipated benefits of the proposed clinical investigation

(This concerns the direct benefit(s) to the study subjects, but may also cover the benefit(s) to others. In particular, regarding the direct benefit(s) to the study subject, the following factors should be considered, individually and in aggregate:

a) type of benefit(s) and magnitude of the benefit(s);
b) if possible, probability evaluation of the participant experiencing one or more benefits, or identification of subgroups more likely to experience a benefit;
c) duration of the benefit(s), i.e.; how long the benefit can be expected to last for the participant;
d) medical necessity, if a medical device provides benefits or addresses needs unmet by other medical devices or therapies. Benefit considerations should also include an assessment of whether another medical device or therapy could be used in substitution, and the availability of that other medical device or therapy. Benefit(s) to others include(s) benefits to caregivers or family members and health care personnel, and public health. 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.)

5 Study Objectives and Hypothesis

5.1 Purpose of the clinical investigation

(Claims for clinical performance, effectiveness or safety of the investigational device that are to be verified)

5.2 Primary Objectives

(Described as 'superiority', 'non-inferiority', or 'equivalence', if applicable.
Scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits, where applicable.)

5.3 Secondary Objectives

5.4 Risks and anticipated adverse device effects

6 Design of the clinical investigation

6.1 Study Type

6.2 Phase of device development

6.3 Endpoints

6.4 Subject number

6.5 Selection of Subjects

6.5.1 Selection of Study Population

6.5.2 Representativeness in relation to target population

6.5.3 Vulnerable subjects involved

6.5.4 Inclusion Criteria

6.5.5 Exclusion Criteria

6.5.6 Contraception/Pregnancy Avoidance

6.6 Clinical Procedures

6.6.1 Procedures in the investigation

6.6.2 Study Schematic of study assessments and visits

6.6.3 Diagnostic tests

6.6.4 Deviation from normal clinical practice

6.6.5 Comparator or medication

(Any concomitant treatments permitted or prohibited, number of medical devices and comparators, if applicable, used per subject)

6.7 Study Duration for Subjects

6.7.1 Screening

6.7.2 Treatment Period

6.7.3 Unscheduled Visit(s)

6.7.4 Early Study Termination

6.7.5 End of Study

6.8 Study Design

6.8.1 Randomization Procedures

6.8.2 Blinding Procedures

(Use of either single arm or (choice of) comparator or other (historically) controlled design and the concept of blinding and unblinding, or running open label need to be covered, with rationale and justification.)

7 Safety Monitoring

(Definitions of adverse events (AE), adverse device effects (ADE), device deficiencies (DD), serious adverse events (SAE) including serious health treat and serious adverse device effects (SADE). A list of non-reportable adverse events should be given, including a rationale. Also, a list of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation, or treatment must be specified. Details of the process for reporting adverse events and device deficiencies should be described, including the time period in which the principal investigator must report to the sponsor and, where appropriate, the sponsor must report to the competent authority. Emergency contact details for reporting serious adverse events and serious adverse device effects must be specified. For Belgium it must be specified that the reporting of SAE must be done to the FAMHP at ct.rd@fagg.be, by using the European form. Please consult the guidance on safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 (May 2020) and the FAMHP Submission Guidance for more information on the reporting of SAE.)

7.1 Adverse Events

7.1.1 Definitions and Reporting

7.1.2 Reporting Period

7.2 Adverse Device Effect

8 Statistical design and anaylsis

(This section describes and justifies the statistical design and analysis of the clinical investigation and should cover following points, if applicable:
- Analysis population and procedures that take into account all the data.
- Descriptive statistics of baseline data, treatments, safety data and where applicable, primary and secondary endpoints.
- Analytical procedures including measures of precision such as confidence intervals.
- Sample size calculation and justification.
- 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.
- Pass/fail criteria to be applied to the results of the clinical investigation.
- The provision for an interim analysis, criteria for the termination of the clinical investigation on statistical grounds.
- Management of bias and, when randomization, matching, or blinding are applied, plan of assessment of success thereof.
- Management of potential confounding factors (e.g. adjustment, stratification, or stratified randomization).
- Description of procedures for multiplicity control and adjustment of error probabilities.
- The specification of subgroups for analysis or if response to treatment is expected to be different in these groups.

- Management, justification, and documentation of missing, unused or spurious data, including drop-outs.
- 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).
- Procedures for reporting any deviations(s) from the original statistical plan.
- For multicentre clinical investigations, a strategy for handling the potential imbalance of the numbers of subjects across investigation sites.
- A strategy for pooling data.

9 Data Management

9.1 Data Collection

9.2 Database Management and Quality Control

9.3 Data protection

(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.)

9.4 Data Monitoring

(Procedures accounting for data accuracy, data completeness, resolving of queries, and the presence or absence of a data safety monitoring board)

9.4.1 Composition of data monitoring committee

9.4.2 Interim analysis

9.5 Monitoring Activities

(The extent and nature of monitoring activities for the proper conduct of the investigation in accordance with the clinical investigation plan should be described and, conform MDR article 72, be based on objective(s) and methodology and degree of deviation of the intervention from normal clinical practice.)

10 Amendments to the CIP

Once approved, the competent authority shall be notified of all proposed changes to the approved clinical investigation that are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation.

The sponsor shall notify, within one week, by means of the electronic system CESP, the Member State(s) in which the clinical investigation is being or is to be conducted of the reasons for and the nature of those modifications. The sponsor shall include an updated version of the relevant documentation as part of the notification. Changes to the relevant documentation shall be clearly identifiable.

The response of no objection will be awaited, the sponsor may implement the modifications at the earliest 38 days after the notification, unless:

- the Member State in which the clinical investigation is being or is to be conducted has notified the sponsor of its refusal, or
- an ethics committee in that Member State has issued a negative opinion in relation to the substantial modification to the clinical investigation, which, in accordance with national law, is valid for that entire Member State.

11 Deviations from the CIP

(Statement specifying that the investigator is not allowed to deviate from the CIP. Except if to protect the rights, safety and well-being of human subjects under emergency circumstances may the investigator deviate without prior approval of the sponsor. Procedures for recording, reporting and analysing CIP deviations should be described, including notification requirements and time frames. Also, corrective and preventive actions and principal investigator disqualification criteria can be included.)

12 Device Accountability

(Adequate procedures for the accountability and traceability of the investigational device should be incorporated in the CIP, in particular control of access to and adequate storage of the device, follow-up in relation to the device used in the clinical investigation and the return of unused, expired or malfunctioning devices. Further, conform MDR article 72 the sponsor should establish a procedure for emergency situations which enables the immediate identification and, where necessary, an immediate recall of the devices used in the investigation.)

13 Statements of compliance

(Following statements should be included:

- Statement specifying that the clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.
- Statement specifying compliance with the national and European legislation.
- Statement specifying that the clinical investigation shall not begin until the required approval/favourable opinion from the EC and regulatory authority have been obtained, if appropriate.
- Statement specifying that any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.
- Statement specifying the type of insurance that shall be provided for subjects, if appropr ate.
- Statement addressing the financing of the clinical investigation including a description of the agreement between the sponsor and investigation site(s), and where applicable with the investigator(s) if not addressed in a separate agreement.)

14 Informed consent process

(Description of the general process for obtaining informed consent, including the process for providing subjects with new information and process for incentives for subjects, as needed. If applicable, the description of the process in circumstances where the subject is unable to give informed consent, e.g. for emergency treatment, must also be included.)

15 Insurance

UZ Brussel/VUB is, as Sponsor of the trial, responsible for ensuring appropriate general/product liability insurance and as required in accordance with applicable laws and regulations, country-specific liability insurance coverage for claims made by a trial subjects for injury arising from the subject's participation in the trial.

16 Vulnerable population

(If applicable, this section describes 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))

17 End, suspension or premature termination of the clinical investigation

(The clinical investigation plan should consider appropriate subject and study stopping criteria as well as procedures for the follow-up (care) of subjects following the end or temporary halt of the investigation, for follow-up of subjects who have withdrawn their consent and for subjects lost to follow-up. Further, it must be clear from the clinical investigation plan that the competent authority shall be notified of the end of the clinical investigation, and that a justification shall be provided in case of a temporary study halt or early termination. In accordance with MDR article 77 study end reporting is mandatory within 15 days (but 24 hours if based on safety grounds). In addition, a clinical investigation report needs to be submitted within one year of the end of the clinical investigation or within three months of the early termination or temporary halt. The end of a clinical investigation shall be deemed to coincide with the last visit of the last subject unless another point in time for such end was set out in the clinical investigation plan.)

18 Publication Policy

(Following statements must be included:

- Statement that the clinical investigation will be registered in a publicly available database.

- Statement indicating that the results of the clinical investigation will be made publicly available.

- Statement indicating the conditions and timeframes under which the results of the clinical investigation will be offered for publication including the role of the sponsor and criteria for authorship.)

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https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

19 References