

# Template - Clinical Investigation Plan (CIP)

Clinical Investigations with Medical Devices

**Detta dokument är framtaget och kvalitetssäkrat av Kliniska Studier Sverige.**

Vi utvecklar och erbjuder stöd för kliniska studier i hälso- och sjukvården.

Stödet vi erbjuder ger goda förutsättningar för kliniska studier av hög kvalitet.

## Introduction to the Clinical Investigation Plan (CIP) template

This page is not included as part of the CIP template, but gives a short introduction to you, who will write a CIP. This page should be removed when using this template. The CIP template is designed for clinical investigations performed in Sweden, modifications are required for multinational clinical investigations. For multinational clinical investigations, additional information is given after this introduction.

This CIP template aims to serve as a help document to facilitate your work. It is not required to use all sections of the template. Sections can be removed and/or new sections can be added. This applies also to subsections. The template should be adjusted so that it fits your clinical investigation.

* Throughout the CIP (including headings), <<Text>> should be replaced with study-specific information.
* Text written in *red Italics* include information about what can or should be described under that respective section. This text should be deleted from the final document.
* Examples of partial wordings that can be used for part of the text, are written in plain font/style.
* Note that both the instructive text and the text suggestions must be considered for the sections to be complete.
* When the CIP is final, update the table of contents.

The planning and execution of a clinical investigation with a medical device shall comply with the EU Regulation 2017/745 on Medical Devices (MDR). In Sweden, national legislations complementing MDR shall also be followed. Clinical investigations with medical devices are recommended to be planned and executed according to the Good Clinical Practice (GCP) standard SS-EN ISO 14155:2020. This CIP template is developed to comply with MDR, Swedish complementary legislation and SS-EN ISO 14155:2020. Note also that other regulations and guidelines apply to clinical investigations with medical devices (as applicable), such as the Biobanks in Medical Care Act, The General Data Protection Regulation (GDPR), etc.

For safety reporting during clinical investigations, reference is made to the guidance document “MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745”.

For risk management of medical devices, reference is made to SS-EN ISO 14971:2020. In SS-EN ISO 14155:2020 it is described how SS-EN ISO 14971:2020 shall be applied to clinical investigations.

For more information and useful links, please visit the websites of the Swedish Medical Products Agency (Läkemedelsverket) and the Swedish Ethical Review Authority (Etikprövningsmyndigheten).

**Version 1.0, 17 Jan 2022.**

The national working group for clinical investigations on medical devices within the node organization connected to Clinical Studies Sweden (Kliniska Studier Sverige) is responsible for the template.

The template will be reviewed regularly by the national working group. Any suggestions for improvement of this template can be sent to any of the email addresses provided below.

Contact information for the regional nodes:

* Gothia Forum: gothiaforum@vgregion.se
* Forum Norr: forumnorr@regionvasterbotten.se
* Forum Uppsala-Örebro: Info-fou@ucr.uu.se
* Forum Sydost: forumo@regionostergotland.se
* Forum Stockholm-Gotland: feasibility.karolinska@regionstockholm.se
* Forum Söder: forumsoder@skane.se

### **Additional information**

This page is not included as part of the CIP template but gives information regarding the safety reporting of Post-Market Clinical Follow Up (PMCF) studies and multinational studies. This page should be removed from the final CIP. In the template, references are made to this additional information, in applicable sections.

### **Safety reporting in Post-Market Clinical Follow Up (PMCF) studies**

*For PMCF investigations of CE marked devices used within the intended purpose covered by the CE-marking, reporting requirements of MDR Article 80(5) and (6) apply, i.e. vigilance reporting. However, reporting of serious adverse events where a causal relationship to the preceding investigational procedure has been established shall follow the reporting procedures of clinical investigations as outlined in Article 80.*

*Those PMCF investigations that involve procedures additional to those performed under the normal conditions of use of the device, and where those additional procedures imposed by the clinical investigation plan are invasive or burdensome, are covered by MDR Article 74(1). For these clinical investigations the safety reporting for events pertaining to MDR Article 80(6) follow the Serious Adverse Event reporting process only, i.e., only SAEs related to the investigational procedures are reported (the sponsor has to specify which level(s) of causality(ies) that will be reported to the MPA during the clinical investigation). Events pertaining to MDR Article 80(5) are reported following the vigilance process only.*

### **Multinational clinical investigations**

For clinical investigations conducted in more countries than Sweden, additional information to some of the sections in the CIP template are given below. Note that country specific regulations may apply.

### **End of the clinical investigation**

*If the clinical investigation is conducted in more than one member state, the national competent authority in all involved member states will be notified within 15 days after the clinical investigation has ended in all member states.*

### **Reporting of adverse events**

*Text suggestion:* “The sponsor will report, **to all national competent authorities** in which this clinical investigation is conducted, all of the following:…..” (see list under section “Reporting”, applicable both for national and international clinical investigations).

“Reporting by the sponsor will be done by filling out the “Summary Reporting Form” (MDCG 2020-10/2). The form will be filled in/updated for each reportable event or for new findings/updates to already reported events. The form will be transmitted **to all national competent authorities** where the clinical investigation is being performed. For events that….”

“….*Note that a different periodic reporting than above can be agreed between the* ***participating national competent authorities*** *and the sponsor according to the design of the clinical investigation and the pathology studied, for example where SAE frequency is expected to be high*.”

*If the clinical investigation is performed in a third country with the same CIP, describe that the sponsor shall report all events specified above occurring in that clinical investigation to all national competent authorities of the European countries in which the clinical investigation is being conducted. Events occurring in Third Countries after the participating European sites have closed shall continue to be reported.*

## CLINICAL INVESTIGATION PLAN

**<<Title>>**

<<Short title/Acronym>>

<< Single identification number>>/ <<CIV-ID>>

*Single identification number is used after the clinical investigation module of EUDAMED is in use, until then, CIV-ID is used. CIV-ID is created before the application to the Medical Products Agency.*

Version number: << Version number >>

Date: << YYYY-MM-DD >>

Sponsor: << Name, Title, Address, Phone number>>

Principal Investigator << Name, Title, Address, Phone number>>

*(If a multicenter clinical investigation, replace with Coordinating Investigator)*

Revision history

|  |  |  |
| --- | --- | --- |
| **Document version** | **Date of Issue** | **Summary of Change** |
| << Version number >> | << YYYY-MM-DD >> |  |
|  |  |  |

## Table of Contents

[Signatures 10](#_Toc105587021)

[Contact information 12](#_Toc105587022)

[Funding and research agreement 13](#_Toc105587023)

[List of used acronyms and abbreviations 13](#_Toc105587024)

[1. Synopsis 14](#_Toc105587025)

[2. Identification and description of the investigational device 14](#_Toc105587026)

[2.1. Description of the investigational device 15](#_Toc105587027)

[2.2. Intended purpose 15](#_Toc105587028)

[2.3. Manufacturer of the investigational device 15](#_Toc105587029)

[2.4. Model/type 15](#_Toc105587030)

[2.5. Target population 15](#_Toc105587031)

[2.6. Medical or surgical procedures 15](#_Toc105587032)

[2.7. Summary of required training/experience needed 15](#_Toc105587033)

[3. Background and justification for the design of the clinical investigation 16](#_Toc105587034)

[3.1. Background 16](#_Toc105587035)

[3.2. Evaluation of results of prior testing, assessments and clinical investigations 16](#_Toc105587036)

[3.3. Evaluation of clinical data 16](#_Toc105587037)

[3.4. Description of the clinical development stage 16](#_Toc105587038)

[4. Risks and clinical benefits of the investigational device and clinical investigation 16](#_Toc105587039)

[4.1. Expected clinical benefits 16](#_Toc105587040)

[4.2. Anticipated adverse device effects 16](#_Toc105587041)

[4.3. Risks associated with participation in the clinical investigation 16](#_Toc105587042)

[4.4. Possible interactions with concomitant medical treatments 16](#_Toc105587043)

[4.5. Steps to be taken to control or mitigate risks 17](#_Toc105587044)

[4.6. Rationale for benefit-risk ratio 17](#_Toc105587045)

[5. Objectives and hypotheses of the clinical investigation 17](#_Toc105587046)

[5.1. The purpose of the clinical investigation 17](#_Toc105587047)

[5.2. Objectives 17](#_Toc105587048)

[5.2.1. Primary objective 17](#_Toc105587049)

[5.2.2. Secondary objective(s) 17](#_Toc105587050)

[5.2.3. Safety objectives 17](#_Toc105587051)

[5.3. Hypotheses 17](#_Toc105587052)

[5.3.1. Primary hypothesis 17](#_Toc105587053)

[5.3.2. Secondary hypothesis(es) 17](#_Toc105587054)

[6. Design of the clinical investigation 17](#_Toc105587055)

[6.1. General information 17](#_Toc105587056)

[6.2. Endpoints 18](#_Toc105587057)

[6.2.1. Primary endpoint 18](#_Toc105587058)

[6.2.2. Secondary endpoint (s) 19](#_Toc105587059)

[6.2.3. Safety endpoint(s) 19](#_Toc105587060)

[6.2.4. Description of the comparator (applicable if the comparator is a medical device) 19](#_Toc105587061)

[6.3. Subjects 19](#_Toc105587062)

[6.3.1. Inclusion criteria 19](#_Toc105587063)

[6.3.2. Exclusion criteria 19](#_Toc105587064)

[6.3.3. Investigation population 19](#_Toc105587065)

[6.3.4. Criteria and procedures for subject withdrawal or discontinuation. 19](#_Toc105587066)

[6.4. Methods to minimize bias 19](#_Toc105587067)

[6.5. Unblinding 20](#_Toc105587068)

[6.6. Description of the clinical procedures and diagnostic methods relating to the clinical investigation 20](#_Toc105587069)

[6.7. End of the clinical investigation 21](#_Toc105587070)

[6.8. Biological sampling procedure (if applicable) 22](#_Toc105587071)

[6.8.1. Handling, storage, and destruction of biological samples 22](#_Toc105587072)

[6.8.2. Total volume of blood per subject 22](#_Toc105587073)

[6.8.3. Biobank 22](#_Toc105587074)

[6.9. Monitoring plan 22](#_Toc105587075)

[7. Statistical considerations 23](#_Toc105587076)

[7.1. Analysis population 23](#_Toc105587077)

[7.2. Descriptive statistics 23](#_Toc105587078)

[7.3. Analytical procedures 23](#_Toc105587079)

[7.4. Sample size calculation 23](#_Toc105587080)

[7.5. Number of procedures to be performed by a single user 24](#_Toc105587081)

[7.6. Pass/fail criteria 24](#_Toc105587082)

[7.7. Interim analysis 24](#_Toc105587083)

[7.8. Multiplicity control 24](#_Toc105587084)

[7.9. Subgroup analysis 24](#_Toc105587085)

[7.10. Missing data 24](#_Toc105587086)

[7.11. Exploratory analysis and sensitivity analysis 24](#_Toc105587087)

[7.12. Reporting deviations 24](#_Toc105587088)

[7.13. Handling of imbalance of subjects per site 25](#_Toc105587089)

[8. Data management and protection 25](#_Toc105587090)

[8.1. Case Report Form 25](#_Toc105587091)

[8.2. Data cleaning and database lock 25](#_Toc105587092)

[8.3. Archiving 25](#_Toc105587093)

[8.4. Data protection 26](#_Toc105587094)

[9. Amendments to the CIP 26](#_Toc105587095)

[10. Deviations from the CIP 26](#_Toc105587096)

[11. Device traceability and accountability 27](#_Toc105587097)

[12. Statements of compliance 27](#_Toc105587098)

[12.1. Compliance to the investigational plan, good clinical practice, and regulations 27](#_Toc105587099)

[12.2. Ethical review of the clinical investigation 27](#_Toc105587100)

[12.3. Insurance 28](#_Toc105587101)

[13. Informed consent process 28](#_Toc105587102)

[13.1. General process for informed consent 28](#_Toc105587103)

[13.2. Informed consent process for vulnerable populations 29](#_Toc105587104)

[14. Adverse events, adverse device effects and device deficiencies 29](#_Toc105587105)

[14.1. Definitions 30](#_Toc105587106)

[14.1.1. Adverse Event 30](#_Toc105587107)

[14.1.2. Adverse Device Effect 30](#_Toc105587108)

[14.1.3. Serious Adverse Event 30](#_Toc105587109)

[14.1.4. Serious Adverse Device Effect 30](#_Toc105587110)

[14.1.5. Unanticipated Serious Adverse Device Effect 31](#_Toc105587111)

[14.1.6. Device Deficiency 31](#_Toc105587112)

[14.2. Recording and Reporting 31](#_Toc105587113)

[14.2.1. Recording 31](#_Toc105587114)

[14.2.2. Reporting 31](#_Toc105587115)

[14.2.3. Assessment of Causality 32](#_Toc105587116)

[14.3. List of foreseeable Adverse events 33](#_Toc105587117)

[14.4. Data Monitoring Committee 33](#_Toc105587118)

[15. Premature termination of the clinical investigation 33](#_Toc105587119)

[16. Publication policy 34](#_Toc105587120)

[17. Bibliography 35](#_Toc105587121)

[18. Appendix 35](#_Toc105587122)

## Signatures

### **Sponsor**

I am responsible for ensuring that this CIP includes all essential information to be able to conduct this clinical investigation. I will submit the CIP and all other important clinical investigation-related information to the responsible investigator(s) so that they can conduct the clinical investigation correctly. I am aware that it is my responsibility to hold the staff members who work with this clinical investigation informed and trained.

Sponsor’s signature Date

Printed name

**Coordinating Investigator***(remove this section if the clinical investigation is a single center clinical investigation). If the sponsor and the coordinating investigator is the same person, this person shall sign both as sponsor and coordinating investigator.*

I have read this CIP and agree that it includes all essential information to be able to conduct the clinical investigation. By signing my name below, I agree to conduct the clinical investigation in compliance with this Clinical investigation plan, the Declaration of Helsinki, SS-EN ISO14155:2020 (Good Clinical Practice), and the current national and international regulations governing the conduct of this clinical investigation.

I will submit this CIP and all other important clinical investigation-related information to the staff members and investigators who participate in this clinical investigation, so that they can conduct the clinical investigation correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this clinical investigation informed and trained.

I am aware that quality control of this clinical investigation will be performed in the form of monitoring, audit, and possibly inspection.

Coordinating Investigator’s signature Date

Printed name

### **Principal Investigator**

I have read this CIP and agree that it includes all essential information to be able to conduct the clinical investigation. By signing my name below, I agree to conduct the clinical investigation in compliance with this Clinical investigation plan, the Declaration of Helsinki, SS-EN ISO14155:2020 (Good Clinical Practice), and the current national and international regulations governing the conduct of this clinical investigation.

I will submit this CIP and all other important clinical investigation-related information to the staff members who participate in this clinical investigation, so that they can conduct the clinical investigation correctly. I am aware of my responsibility to continuously keep the staff members who work with this clinical investigation informed and trained.

I am aware that quality control of this clinical investigation will be performed in the form of monitoring, audit, and possibly inspection.

Principal Investigator’s signature Date

Printed name

## Contact information

|  |  |
| --- | --- |
| **Role** |  |
| Sponsor *(Add also legal representative, MDR Article 62(2), if applicable)* | <<Name, title>><<Contact address>><<Phone number>> |
| Coordinating Investigator *(remove if the clinical investigation is a single center clinical investigation)* | <<Name, title>><<Site/Institution>><<Contact address>><<Phone number>> |
| Principal Investigator *(Duplicate if the clinical investigation is a multicenter clinical investigation)* | <<Name, title/profession>><<Site/Institution>><<Contact address>><<Phone number>> |
| Emergency contact details*(For emergency code breaking, SAE reporting, etc.)* | <<Name, title>><<Site/Institution>><<Contact address>><<Phone number>> |
| Contract research organization *(remove if non-applicable)* | <<Contact address>><<Phone number>> |
| Laboratory *(remove if non-applicable)* | <<Contact address>><<Phone number>> |
| *Include other contractors/institutions as applicable* |  |

## Funding and research agreement

*Provide a brief description of how the clinical investigation is financed and a brief description of the agreement between the sponsor and the site. Include information about the economical arrangement between sponsor and site (e.g., does site receive payments after specified accomplished parts of the* *clinical investigation, does the sponsor pay for more than the investigational device, does the sponsor pay for personnel costs at site, is the clinical investigation initiated by a company or is the* *clinical investigation initiated by an academic researcher). Note, the size of the economic compensation does not need to be specified.*

## List of used acronyms and abbreviations

*List all abbreviations used in the CIP. Each term should be written out fully the first time it is used in the CIP, with the abbreviation in parentheses. Examples of common abbreviations are shown below but this list should be adapted to your clinical investigation; add and/or remove rows as needed.*

|  |  |
| --- | --- |
| **Abbreviation** | **Term/Explanation** |
| ADE | Adverse Device Effect  |
| AE | Adverse Event |
| CIP | Clinical Investigation Plan |
| CRF | Case Report Form  |
| DD | Device Deficiency |
| DMC | Data Monitoring Committee |
| GCP | Good Clinical Practice |
| IB | Investigator’s Brochure |
| IFU | Instructions for Use |
| SS-EN ISO | Swedish Standard - European standard International Organization for Standardization  |
| ITT | Intention-to-treat = including all data from all subjects who have participated in the clinical investigation |
| MDCG  | Medical Device Coordination Group |
| PMCF | Post-Market Clinical Follow Up  |
| PP | Per Protocol analysis = including only data from subjects who have completed the clinical investigation completely in accordance with the CIP, with no deviations from the CIP |
| SADE | Serious Adverse Device Effect  |
| SAE  | Serious Adverse Event |
| USADE | Unanticipated Serious Adverse Device Effect |

## Synopsis

*Give an overall summary or overview of the clinical investigation that includes all the relevant information regarding the clinical investigation design. Ensure the information in the synopsis is consistent with the final version of the CIP body text and other clinical investigation documents. Additionally, a synopsis in Swedish shall be included in the notification/application, it can be included in the CIP (e.g., in connection with the Synopsis below) or be provided separately from the CIP. If it is provided separately, this should be noted in the CIP.*

|  |  |
| --- | --- |
| Background and rationale: | *Include a short background and rationale for the clinical investigation.* |
| Investigational device: |  |
| Number of subjects: |  |
| Inclusion criteria: |  |
| Exclusion criteria: |  |
| Study objectives: | Primary objective:Secondary objective(s):Safety objective(s): *if applicable* |
| Study endpoints: | Primary endpoint:Secondary endpoint(s):Safety endpoint(s): *if applicable* |
| Planned duration of the clinical investigation: | *Ex Q2 2022 – Q1 2023* |

## Identification and description of the investigational device

*In this section, add information that is applicable regarding the below topics. For each of the below sections, provide references to the Investigator’s brochure and the Instructions for Use (IFU) when applicable.*

### Description of the investigational device

*Provide a summary description of the investigational device. It is recommended to include schematic and/or photo illustrations to describe device design and system components.*

### Intended purpose

*Describe the intended purpose of the investigational device in the proposed clinical investigation. Note that the intended purpose in the clinical investigation might be different from the planned intended purpose of the final product to be marketed later, or outside the intended purpose of an already CE marked product. It is necessary to clearly describe the difference between the intended purpose of the final device compared to the intended purpose in the clinical investigation.*

### Manufacturer of the investigational device

*Provide details concerning the manufacturer of the device.*Name:
Address:
Contact, phone number:

### Model/type

*Provide the name or number of the model/type, including software version and accessories, if any, to permit full identification.*

### Target population

*Provide a description of the population(s) and indication(s) for which the investigational device is intended.*

Detailed description of the investigational device and materials coming into contact with the human body

*Give a detailed description of the investigational device and include the technical and functional features of the device. For some devices where this list is extensive, this can be placed in an appendix. If the summary given in section 2.1 is covering the detailed description of the investigational device this part of section 2.6 is can be deleted.*

*Describe any materials that will be in contact with tissues or body fluids. Include details of any medicinal substances, human or animal tissues or their derivatives, or other biologically active substances. Provide references to compliance with relevant general safety and performance requirements (GSPR) in MDR Annex I.*

### Medical or surgical procedures

*Give a description of the specific medical or surgical procedures involved in the use of the investigational device.*

### Summary of required training/experience needed

*Give a summary of the necessary training and experience required to use the investigational device. The requirements shall be based on the risk assessment (**SS-EN ISO 14971:2020).*

## Background and justification for the design of the clinical investigation

*This section shall be based on the conclusions of the clinical evaluation (MDR VI, article 61 and part A, annex XIV).*

### Background

*Provide a background literature review.*

*Present the current state of the art in clinical care in the relevant field of application and describe the proposed benefits of the new device.*

### Evaluation of results of prior testing, assessments and clinical investigations

*Justify the use of the investigational device in human subjects by an evaluation of the results of the relevant pre-clinical testing/assessment and, if applicable, clinical investigations previously carried out.*

### Evaluation of clinical data

*Present an evaluation of clinical data of the investigational device that are relevant to the clinical investigation.*

### Description of the clinical development stage

*If applicable, provide the clinical development stage, for example pre-market clinical investigation (involving stages as pilot and pivotal) or post-market clinical investigation (post-market stage) (SS-EN ISO 14155:2020 Annex I).*

## Risks and clinical benefits of the investigational device and clinical investigation

### Expected clinical benefits

*Describe the expected clinical benefits. Also include other expected benefits, e.g., health economics benefits.*

### Anticipated adverse device effects

*Describe the anticipated adverse device effects as identified in the* *risk analysis report (SS-EN ISO 14971:2020). For a definition of an adverse device effect see Section 14.1.2.*

### Risks associated with participation in the clinical investigation

*Describe the risks associated with participation in the clinical investigation, as identified in the risk analysis report (MDR 6.2.3 and SS-EN ISO 14971:2020).*

### Possible interactions with concomitant medical treatments

*Describe possible interactions with concomitant medical treatments as identified in the* *risk analysis report (SS-EN ISO 14971:2020).*

### Steps to be taken to control or mitigate risks

*Describe the steps that will be taken to control or mitigate the risks. List what steps are to be completed to reduce anticipated adverse device effects. List what steps are to be completed to reduce any risks to subjects prior/during/after the procedures in the clinical investigation.*

### Rationale for benefit-risk ratio

*The benefits of the study shall be weighed against the risks for the subjects. Give the benefit-risk rationale and demonstrate that the benefits justify the risks.*

## Objectives and hypotheses of the clinical investigation

### The purpose of the clinical investigation

*Describe the purpose of the clinical investigation and provide the claims for clinical performance, effectiveness or safety of the investigational device that are to be verified. Claims shall be linked to eligibility criteria for subjects and users. Provide scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits, where applicable.*

*The objective(s) shall serve the purpose of the clinical investigation and shall relate to the hypotheses (where applicable) and corresponding endpoints relevant to the target population.*

### Objectives

*Describe the objectives in terms of superiority, non-inferiority, or equivalence, if applicable.*

#### Primary objective

#### Secondary objective(s)

#### Safety objectives

*Include the risks and anticipated adverse devise effect to be assessed in the clinical investigation. If safety is the primary objective, this section can be removed.*

### Hypotheses

*Describe the primary and secondary hypotheses, if applicable, to be accepted or rejected by statistical data from the clinical investigation.*

#### Primary hypothesis

#### Secondary hypothesis(es)

## Design of the clinical investigation

### General information

*Describe the design type of the clinical investigation to be performed (e.g., randomized, comparative double-blind or open label, parallel groups or crossover) and the use of control group and comparator. Provide details about multicenter or international clinical investigation.*

*Provide the rationale for the choice of clinical investigation as set out in the clinical evaluation plan (MDR 6.3 and MDCG 2020-5).* *If no control(s) is to be used this shall be justified.*

*It can be useful to include a figure of the clinical investigation design.*

***Figure*** *X* ***Clinical investigation design***



### Endpoints

*Provide a rational for the selection and measurements of endpoint(s) and variables as set out in the clinical evaluation plan. This is also applicable to composite endpoints.*

#### Primary endpoint

*The primary endpoint shall be appropriate for the investigational device and shall be clinically relevant.*

#### Secondary endpoint (s)

#### Safety endpoint(s)

Exposure to the investigational device, comparator *(remove comparator if not applicable to your investigation)* and supporting treatment

*Provide a description of the exposure to the investigational device(s) or comparator(s), if used. If the comparator is a medical device, include information about this medical device, as applicable (see section 6.3.1). List any other medical device or medication to be used during the clinical investigation. Include the number of investigational devices to be used, together with a justification.*

#### Description of the comparator (applicable if the comparator is a medical device)

 *Provide a detailed description of the comparator. Specify details concerning the manufacturer of the device. Provide the name or number of the model/type, including software version and accessories, if any, to permit full identification. State the intended purpose and enclose the instructions for use for a CE marked device.*

### Subjects

#### Inclusion criteria

*List the Inclusion criteria for subject selection.*

#### Exclusion criteria

*List the exclusion criteria for subject selection.*

#### Investigation population

*Provide the size of the investigation population. State the representativeness of investigation population in relation to target population (see section 2.5). If applicable, provide information on vulnerable subjects involved such as children, pregnant or breastfeeding women, immune-compromised or, elderly subjects.*

#### Criteria and procedures for subject withdrawal or discontinuation.

*Describe when and how to withdraw a subject from the clinical investigation or stop the use of the investigational device. In particular, subject safety aspects related to withdrawal should be considered. For example, if an implantable device, describe how this will be handled. Describe any procedures for the replacement of subjects, and describe plans for documentation of efforts to be made to trace subjects that are lost to follow-up and possible reasons.*

### Methods to minimize bias

*Describe the measures to be taken to minimize or avoid bias, including randomization and the use of blinding/masking. Describe any known or foreseeable factors that can compromise the outcome of the clinical investigation or the interpretation of results. Provide details on the management of potential confounding factors for example subject selection, clinical investigation design (such as stratified randomization) or by statistical analysis.*

*If applicable, describe any differences in* *clinical investigation site environment.*

### Unblinding

*The CIP must describe how the code is broken in emergency situations and who should be informed in connection with this. A clear definition of situations where the code may need to be broken helps prevent unnecessary unblinding. It is important that the code in emergency situations can be broken by the investigator, without the involvement of the sponsor. Describe how possible code break envelopes are stored and who will have access to this as well as how these persons can be reached in case of an emergency.*

*If an electronic system is used, it must be clear how to break the code if the system does not work.*

*If this is not relevant, remove this section.*

*Text suggestion:* The list for breaking the code can be found…

### Description of the clinical procedures and diagnostic methods relating to the clinical investigation

*If applicable, add a flow chart or overview of the* *clinical investigation. Provide a review of each visit describing clinical investigation-related procedure(s) the subject undergoes during each visit.*

*Example table (modify as applicable):*

*Table X* Flow chart

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Procedure | *Screening* *Day/Week x Inclusion visit* | *Visit 1**Baseline* | *Visit 2**Day/Week x (±10 days)* | *Visit 3**Day/Week x (±10 days)* |
| *Incl/exclusion criteria* | √ |  |  |  |
| *Informed consent*  | √ |  |  |  |
| *Medical history/ concomitant medications* | √ |  |  |  |
| *Randomization* | √\* | √\* |  |  |
| *Instuctions for handling of investigational device* |  | √ |  |  |
| *Filled in EQ-5D* |  | √ | √ | √ |
| *X-ray (CT)* |  |  | √ | √ |
| *Adverse Events*  |  | √ | √ | √ |
| *Clinical investigation end* |  |  |  | √ |
|  |  |  |  |  |

*\*Randomization can be done at, e.g., the screening visit or visit 1; adjust the table for the clinical investigation.*

*Describe any pre-screening procedures planned for the* *clinical investigation.*

*Describe the methods and timing for assessing, recording, and analyzing variables. Describe all of the clinical investigation related procedures and diagnostic methods that subjects undergo during the clinical investigation. Highlight any deviation from normal practice.*

*Issues that can be addressed; point of enrolment, total expected duration of the clinical investigation, expected duration of each subject's participation. Include the estimated time needed to select this number (i.e. enrolment period).*

*Describe the equipment to be used for assessing the clinical investigation variables and how to monitor maintenance and calibration.*

*Description of those activities performed by sponsor representatives (excluding monitoring). This can be for example involvement of technical personnel from the sponsor in handling of the device. Also describe that these personnel will not have access to the identity of the subjects or affect the clinical decisions taken.*

*The clinical investigation should include a follow-up period that is sufficient to represent a realistic test of the performance of the investigational device and allow any risks associated with adverse device effects over that period to be identified and assessed.*

*If applicable, address what specific medical care is appropriate to be provided for the subjects after the* *clinical investigation has been completed.*

*Describe the recommended follow-up, if any, that will be provided for the subjects after the clinical investigation has been completed.*

### End of the clinical investigation

*Define the completion of the clinical investigation. This is usually the last visit of the last subject and when the follow-up is complete for the clinical investigation.*

*Describe the follow-up after end of clinical investigation, if applicable. For implantable devices these procedures shall cover traceability as a minimum. If the follow-up of the patient after the clinical investigation does not differ from the clinical practice, this shall be stated.*

*Describe that the sponsor will notify the Swedish Medical Products Agency within 15 days after end of the clinical investigation.*

*Text suggestion:* The clinical investigation ends when the last subject has completed the last follow-up. The sponsor will notify the Swedish Medical Products Agency within 15 days after the end of the clinical investigation and send the clinical investigation report within 1 year after the end of the clinical investigation including an easily understandable summary.

*If for some reason the report cannot be submitted within the general time frames, describe when the results of the* *clinical investigation will be available, and include a justification.*

*For multinational clinical investigations, please see the additional information to this template provided on page 2.*

### Biological sampling procedure (if applicable)

#### Handling, storage, and destruction of biological samples

*Specify sampling, sampling volumes, analytical methods (including information about method validation) and where the analyses will be performed.*

*Detailed sampling and handling procedures can be described in a separate document.*

#### Total volume of blood per subject

*Text suggestion:* The total volume of blood taken from each subject during the clinical investigation is maximum *<<volume>>* ml.

#### Biobank

*If a sample is taken within the healthcare system for research purposes, it is covered by the Swedish Biobank Act, see exemptions below.*

*From 1 January 2019, an exemption was introduced for samples that are taken for research and will not be saved in the biobank: The Swedish Biobank Act is not applicable to samples which are intended for research and which are analyzed within six months after sampling date and destroyed immediately after analysis. Both conditions must be met. For more information see link (in Swedish): <http://biobanksverige.se/forandring-i-biobankslagen-januari-2019>.*

*Researchers who are uncertain about whether a sample in the* *clinical investigation is covered by the exemption rule are advised to contact the region’s biobank coordinator or a regional biobank center for advice.*

*Text suggestion:* All samples taken in this clinical investigation are registered in a biobank at <<Name of biobank>> and handled according to the current biobank laws and regulations. The samples are coded/pseudonymized to protect the subject´s identification. All samples and the identification/code list are stored securely and separately to prevent unauthorized persons from having access to them.

### Monitoring plan

*The monitoring plan shall be developed using a risk-based approach (SS-EN ISO 14155:2020 6.7) based on the nature of the clinical investigation (objective, design, complexity, size, critical data points etc.). Provide the general outline of the monitoring plan, including access to source data and the extent of source data verification planned.*

*Text suggestion:* The clinical investigation will be monitored by an independent monitor before the clinical investigation begins, during the clinical investigation conduct, and after the clinical investigation has been completed, so as to ensure that the clinical investigation is carried out according to the CIP and that data is collected, documented, and reported according to SS-EN ISO 14155:2020 and applicable ethical and regulatory requirements. Monitoring is performed as per the investigation’s monitoring plan and is intended to ensure that the subject’s rights, safety, and well-being are met as well as data in the CRF are complete, correct, and consistent with the source data.

*It is possible to provide a detailed monitoring plan separately from the CIP.*

## Statistical considerations

*With reference to objectives and hypotheses of the clinical investigation and the design of the clinical investigation, the description of and justification for statistical design and analysis of the clinical investigation should cover all relevant topics given in each sub-section below, to the extent applicable for the particular investigation. If needed, new sub-sections can be added.*

*Exploratory clinical investigations might not require pre-specified statistical hypotheses, although the design of the clinical investigation and the interpretation of the outcome can be more straightforward if statistical considerations are provided.*

### Analysis population

*Define the clinical investigation subjects that will be included in the analyses, e.g., state if the analyses will be applicable to intention-to-treat (ITT) or per protocol (PP).*

*Specify whether sensitivity analyses of the main analyses will be performed, i.e., examining the sensitivity of an ITT analysis with help of a complementary PP analysis.*

### Descriptive statistics

*Provide a general description of the descriptive/summary statistics.*

### Analytical procedures

*Describe the statistical methods that will be used to answer the primary and secondary objectives and clarify the underlying statistical models.*

*State which covariates (and any stratifications) will be adjusted for in the analyses.*

*State any transformations of variables and justification for this.*

*State how the clinical investigation results will be reported, e.g., a relative treatment effect with associated 95% confidence interval and p-value.*

*State if one- or two-sided tests of statistical significance will be used. Justify the use of one-sided tests in particular.*

*If hypothesis testing is not appropriate, an alternative process for arriving at statistical conclusions should be provided.*

### Sample size calculation

*State the total number of subjects needed for the* *clinical investigation. Sample size calculations shall be performed for all primary outcome variables (in the case of several).*

*State and motivate the effect size (e.g., group differences, standard deviations) that the sample size calculation builds, usually the smallest clinically relevant effect.*

*Specify in detail the assumptions on which the sample size is based. Specify in particular:*

* *method by which the sample size is calculated*
* *significance level*
* *desired power*
* *compensation for expected drop-outs taking into account expected drop-out rate, such as withdrawal, lost to follow-up, death (unless death is an endpoint).*

*For exploratory and observational clinical investigations, in which the sample size is not required to be derived by calculation, the scientific rationale for the chosen sample size should be provided.*

### Number of procedures to be performed by a single user

*Give 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 analyzed, if applicable. Discuss extent, influence and management of expected learning curve effects, considering that a user develops an increasing experience with the number of procedures performed.*

### Pass/fail criteria

*Specify specific pass/fail criteria to be applied to the results of the clinical investigation.*

### Interim analysis

*Describe if interim analyses are planned and at which timepoints. State the criteria for clinical investigation termination on a statistical ground and the potential need for recalculation of sample size.*

### Multiplicity control

*Describe the statistical procedures planned to deal with, or to avoid, multiplicity.*

### Subgroup analysis

*Specify subgroups to be used for the analysis, if applicable, or if response to treatment is expected to be different in these groups.*

### Missing data

*Specify how drop-outs and missing values will be handled, with a justification. For planned imputation of missing values, the method for this must be stated.*

### Exploratory analysis and sensitivity analysis

*Describe any exploratory and sensitivity analysis, if applicable. This should be done to explore the robustness of results of primary and secondary analysis depending on the methods used for handling missing data.*

### Reporting deviations

*State how any deviations from the original statistical analysis plan will be reported.*

### Handling of imbalance of subjects per site

*For multicenter clinical investigations, a strategy for handling the potential imbalance of the numbers of subjects across clinical investigation sites, for example can centralized randomization be used.*

## Data management and protection

*Include a description of the subject identification code that allows identification of all the data reported for each subject. This list shall be retained by the principal investigator in a secure location*.

*Text suggestion:* Subjects who participate in the clinical investigation are coded with a specific clinical investigation identification number. All subjects are registered in a subject identification list (subject enrolment and identification list) that connects the subject’s name and personal number with a clinical investigation identification number.

All data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification.

### Case Report Form

*Describe the methods for data entry and collection, including procedures for* *verification, validation, and securing of electronic clinical data systems, if applicable.*

*Specify which data that can be reported directly in the CRF. Include a statement that a source data location list will be present at site. Describe that the CRF will be signed by the principal investigator(s) or authorized designees. Describe that any change or correction to data reported on a CRF shall be dated, initialed and explained if necessary, and shall not obscure the original entry (i.e. an audit trail shall be maintained); this applies to both written and electronic changes or corrections.*

### Data cleaning and database lock

*Describe procedures used for CRF tracking, data review, database cleaning, and issuing and resolving data queries. Describe methods for database lock.*

### Archiving

*Specify that the principal investigator and sponsor shall maintain the essential clinical investigation documents in the investigation site and sponsor files, respectively.*

*Specify that the sponsor shall keep the documentation for at least 10 years after the clinical investigation has ended, or, if the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market. In the case of implantable medical devices, the period shall be at least 15 years. Describe for how long the principal investigator will archive the investigation documentation. As a minimum, the principal investigator must follow the requirements set up at the local institution. The sponsor and investigator can also agree that the documents should be archived for longer time. Also, the Swedish Archives Act (Arkivlagen) applies to archiving of research material.*

*Text suggestion:* The PI and sponsor will maintain the essential clinical investigation documents in the investigation site files archive and sponsor files archive, respectively. The sponsor shall keep all documentation and data for at least <<10/15>> years after the clinical investigation has ended *or* <<10/15>> years after the last device has been placed on the market. The PI will archive all local investigation documentation for at least 10 years or as long as stipulated by the local institution.

### Data protection

*Describe the arrangements to comply with the applicable rules on the protection and confidentiality of personal data. Include information about organizational and technical arrangements that will be implemented to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and personal data processed. Describe the measures that will be implemented to ensure confidentiality of records and personal data of subjects and a description of measures that will be implemented in case of a data security breach in order to mitigate the possible adverse effects.*

*Text suggestion:* If any part of the data is handled by any other organization, inside or outside the European Union, appropriate agreements and/or other documentation will be established, to ensure that the data processing is performed in accordance with the provisions of the General Data Protection Regulation (EU ordinance 2016/679, GDPR) and other relevant legislation, before any data transfer takes place.

The content of the informed consent form shall comply with relevant integrity and data protection legislation. In the subject information and the informed consent form, the subject will be given complete information about how collection, use and publication of their clinical investigation data will take place. The subject information and the informed consent form will explain how clinical investigation data are stored to maintain confidentiality in accordance with national data legislation (please describe how data is stored and which data security measures are taken).

All information processed by the sponsor will be pseudonymized and identified with <<Study code/Study ID/Initials>>.

The informed consent form will also explain that for verification of the data, authorized representatives of the sponsor, as well as relevant authority, may require access to parts of medical records or study records that are relevant to the clinical investigation, including the subject’s medical history.

## Amendments to the CIP

*Describe the procedures to amend the CIP.*

*Text suggestion:* Amendments to the CIP will be agreed upon between the coordinating investigator (principle investigator if a single center study) and the sponsor. Substantial modifications must be approved by the Swedish Ethical Review Authority and/or the Swedish Medical Products Agency (as applicable) before implementation.

## Deviations from the CIP

*Describe procedures for recording, reporting, and analyzing CIP deviations.*

*Text suggestion:* Investigator(s) are not allowed to deviate from the CIP except if it is for the protection of the subject´s rights, safety, or well-being under emergency circumstances.
All such deviations shall be documented and reported to the sponsor, the Swedish Medical Products Agency and/or the Swedish Ethical Review Authority (as applicable) as soon as possible.

All deviations shall be documented with an explanation and reported to the sponsor. Deviations will be reviewed by the sponsor and reported to the appropriate regulatory bodies as required.

## Device traceability and accountability

*Describe the clinical investigation specific labelling of each device.*

*Describe how the access to the investigational device will be controlled.*

*Describe the traceability of the device, for example, how it should be achieved during and after the clinical investigation.*

*Describe the process and documentation that the sponsor will use to keep records of the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal.
Describe the procedures and particular materials and instructions for the safe return of investigational devices, including those that are potentially hazardous. The sponsor should have instructions in place and make packaging materials available.*

*Text suggestion:* The investigational device(s) will only be used in the clinical investigation and according to the clinical investigation plan. All investigational device(s) will be labelled *«For clinical investigation use only»* on the packaging as well as on the device. The sponsor provides the site with written instructions and technical support *(if applicable, otherwise remove)*.

The investigator will keep records to document the physical location of all investigational devices from shipment to return/disposal. This record should include: name(s) of clinical investigation personnel who received, used, returned, or disposed the device, the date of receipt, identification and quantity of each investigational device (batch number/serial number or unique code), the expiry date *(if applicable),* the date or dates of use, subject study-ID, date on which the investigational device was returned/explanted from subject *(if applicable),* the date of return of unused, expired or malfunctioning investigational devices *(if applicable),* and the date and documentation of disposal of the investigational devices as per instructions of the sponsor *(if applicable). Describe how these records will be kept.*

## Statements of compliance

### Compliance to the investigational plan, good clinical practice, and regulations

*Text suggestion*: The clinical investigation will be conducted in accordance with the clinical investigation plan, the ethical principles of the Declaration of Helsinki, the principles of SS-EN ISO 14155:2020 and current national and international regulations governing this clinical investigation. This is to ensure the safety and integrity of the subjects as well as the quality of the data collected.

### Ethical review of the clinical investigation

*Text suggestion (**application for a clinical investigation of a class III device or an invasive class IIa or IIb device*: The clinical investigation will not commence until written approval/favourable opinion from the Swedish Medical Products Agency have been received*.*

*Alternative text suggestion (application for a clinical investigation of a class I device or a non-invasive class IIa or class IIb device):* The clinical investigation will commence when written approval/favorable opinion from the Swedish Ethical Review Authority has been received and confirmation of validity has been received from the Swedish Medical Products Agency.

*Alternative text suggestion (in the case of a CE marked device to be assessed within the scope of its intended purpose):* The clinical investigation will commence when written approval/favorable opinion from the Swedish Ethical Review Authority has been received and at least 30 days has passed since the notification was confirmed by the Swedish Medical Products Agency.

The final version of the informed consent form and other information provided to subjects, must be approved or given a written positive opinion by the Swedish Ethical Review Authority and/or the Swedish Medical Products Agency *(as applicable)*. The Swedish Ethical Review Authority and the Swedish Medical Products Agency must be informed of any changes in the CIP in accordance with the current requirements.

### Insurance

*Explain how subjects are insured.*

*Swedish Patient Insurance (Patientskadeförsäkring): The Swedish healthcare regions have signed a patient insurance with Landstingens Ömsesidiga Försäkringsbolag, Löf. Check what applies to medical research at the Löf homepage.*

*The sponsor shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in the clinical investigation are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk.*

## Informed consent process

### General process for informed consent

*Describe the procedure for how information is given to the subjects and how consent is obtained.*

*Informed consent shall be obtained in writing from the subject and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject.*

*The principal investigator (or the person to whom the task has been delegated) must provide both oral and written information to the intended subject regarding what participation in the clinical investigation entails. The investigator must avoid any coercion or undue improper influence on, or inducement of, the subject to participate. The qualification of a principal investigator’s authorized designee can be subject to national regulation.*

*A copy of the subject information as well as a copy of the signed informed consent form shall be provided to the subject.*

*If the subject information changes during the clinical investigation conduct, the subject has the right to once again decide on whether he/she would like to continue their participation. This by allowing the subject to sign a revised subject information and informed consent form.*

*Text suggestion*: The principal investigator shall ensure that the subject is given full and adequate oral and written information about the clinical investigation, its purpose, any risks and benefits as well as inclusion and exclusion criteria. Subjects must also be informed that they are free to discontinue their participation in the clinical investigation at any time without having to provide a reason. Subjects shall be given the opportunity to ask questions and be allowed time to consider the provided information and participation in the clinical investigation. If the person chooses to participate, both the subject and the investigator shall sign the informed consent form. A copy of the subject information as well as a copy of the informed consent form shall be provided to the subject. The subject’s signed and dated informed consent must be obtained before performing any activity specific to the clinical investigation. The process shall be documented in the subject’s source documents and the signed informed consents shall be maintained with the essential documents. If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form. If new information is added to the clinical investigation, the subject has the right to reconsider whether he/she will continue their participation.

*For clinical investigations involving emergency treatments refer to Regulation (EU) 2017/745, article 68 and SS-EN ISO 14155:2020, 5.8.3.*

### Informed consent process for vulnerable populations

*Describe the specific informed consent process, if applicable, for vulnerable populations. Remember to adapt and describe the procedure based on whether the subject is a child. In clinical investigations where minors participate, the consent of both parents (legal representatives of the minor) must be obtained. See MDR Article 64-66, Lag (2021:600) med kompletterande bestämmelser till EU:s förordning om medicintekniska produkter (in Swedish).*

## Adverse events, adverse device effects and device deficiencies

*Note that this section applies for clinical investigations covered by Article 62, 74(2), and clinical investigations article 82 + 3 chapter §1 HSLF-FS 2021:32. The safety reporting in these clinical investigations shall follow article 80(1)-80(4) MDR. In situations where a clinical investigation has started using a non-CE marked device, and the right to bear the CE marking has been obtained before the end of the clinical investigation, the SAE reporting continues until completion of the* *clinical investigation.*

*For pre-market clinical investigations involving CE marked comparator devices used within their intended purpose, SAEs occurring in or to subjects that are in the comparator arm of an investigation shall also be reported.*

*Also, note that SAEs concerning CE marked devices (for examples used as part of the procedures in the clinical investigation) which meet the vigilance reporting criteria also need to be handled under the post-market surveillance/vigilance system.*

*For Post Market Clinical Follow Up (PMCF) studies covered by article 74(1) the safety reporting differs, please see the additional information to this template provided on page 2.*

### Definitions

#### Adverse Event

An Adverse Event (AE) is 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.

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

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

#### Adverse Device Effect

An Adverse Device Effect (ADE) is any AE related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

This includes ‘comparator’ if the comparator is a medical device.

#### Serious Adverse Event

A Serious Adverse Event (SAE) is any AE that led to any of the following:

* 1. death,
	2. serious deterioration in the health of the subject, that resulted in any of the following:
		1. life-threatening illness or injury,
		2. permanent impairment of a body structure or a body function,
		3. hospitalization or prolongation of patient hospitalization,
		4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
		5. chronic disease,
	3. fetal distress, fetal death or a congenital physical or mental impairment or birth defect

#### Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a serious adverse event.

SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device shall not be considered Serious Adverse Device Effects.

#### Unanticipated Serious Adverse Device Effect

An Unanticipated SADE is an 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 shall 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 shall not be considered Serious Adverse Device Effects.

For the anticipated adverse device effects, se section 4.2 above.

#### Device Deficiency

A Device Deficiency (DD) is 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.

### Recording and Reporting

#### Recording

*There may be situations where not all AEs have to be recorded. If applicable to this clinical investigation, include* *a list of adverse events that will not be recorded including the rationale. The selection of AEs to be recorded should be based on what is critical to the evaluation of the results of the clinical investigation.*

The principal investigator or an authorized designee will record:

* <all AEs>/ <all AEs except the events specified not to be recorded>;
* all SAEs;
* all DDs;
* any new finding in relation to any of the above-mentioned events.

#### Reporting

*Text suggestion:* The investigators will report all SAEs and DDs *(can be adjusted)* to the sponsor, immediately but not later than 3 calendar days after investigation site study personnel’s awareness of the event.

*Specify if the collection of events from the principal investigator(s) to the sponsor will be done in the Summary Reporting form or in a form designed specifically for the clinical investigation. If the second option is used, make sure all information is covered. Include contact details to the sponsor for SAE reporting.*

*Text suggestion:* The sponsor will report to the Swedish Medical Products Agency all of the following reportable events:

* any SAE that has a causal relationship with the investigational device, the comparator *(remove comparator if not applicable to your investigation)* or the investigation procedure, or where such causal relationship is reasonably possible;
* any DD that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; and
* any new findings in relation to any event referred to above.

Reporting by the sponsor will be done by filling out the “Summary Reporting Form” (MDCG 2020-10/2). The form will be filled in/updated for each reportable event or for new findings/updates to already reported events. The form will be transmitted to the Swedish Medical Products Agency. For events that 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 sponsor of a new reportable event or of new information in relation with an already reported event. Any other reportable events or a new finding/update to it will be reported immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

*Note that a different periodic reporting than above can be agreed between the Swedish Medical Products Agency and the sponsor according to the design of the investigation and the pathology studied, for example where SAE frequency is expected to be high.*

*For multinational* *clinical investigations, please see the additional information to this template provided on page 2.*

#### Assessment of Causality

The relationship between each adverse event and the investigational device, the comparator and the investigation procedure will be assessed and recorded by the investigator and sponsor. For assessment of causality, the IB and the risk analysis report will be consulted *(adjust according to your clinical investigation).* The sponsor and investigator will distinguish between SAEs related to the investigational device and those related to the procedures, relatedness to both is possible.

Each SAE will be classified according to four different levels of causality:

1. Not related

Relationship to the device, comparator 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 SAE 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 SAE 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 diagnosis, 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 SAE.

1. 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 where relatedness cannot be assessed, or no information has been obtained shall also be classified as possible.

1. Probable

The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

1. Causal relationship

The SAE 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 adverse 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 SAE (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 SAE.

### List of foreseeable Adverse events

*List the foreseeable adverse events in this clinical investigation* *together with their likely incidence, mitigation, or treatment. Note the difference compared to anticipated adverse device effects that are listed in section 4.2. Also, refer to section 4.2 in this section. The foreseeable adverse events that shall be described in this section are for example events related to the investigational procedures.*

### Data Monitoring Committee

*Describe the involvement of a DMC, and its structure, operational objectives and responsibilities, if applicable.*

## Premature termination of the clinical investigation

*Text suggestion:* The sponsor may suspend or prematurely terminate either the clinical investigation at an individual investigation site or the entire clinical investigation for significant and documented reasons, such as when recommended by the DMC *(remove DMC if non applicable to this investigation).* The Swedish Medical Products Agency may suspend or prematurely terminate the clinical investigation at the applicable investigation sites.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the Medical Products Agency, the sponsor will suspend the clinical investigation while the risk is assessed. The sponsor will terminate the clinical investigation if an unacceptable risk is confirmed. The sponsor will inform all investigators.

The sponsor shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other principal investigators.

If, in the opinion of the investigator, the clinical observations in the clinical investigation suggest that it may be unsafe to continue the investigation at the site, the investigator may terminate participation in the investigation after consultation with the sponsor. A written statement fully documenting the reasons for such termination will be provided to the sponsor. If the clinical investigation is prematurely terminated, the investigators shall promptly inform the subjects and take necessary steps to finalize their engagement in the clinical investigation. All relevant investigation material must be collected, and accountability completed.

If the clinical investigation is interrupted or terminated prematurely the sponsor will report to the Medical Products Agency within 15 days together with a justification. If the sponsor has temporarily halted or prematurely terminated the clinical investigation on safety grounds, the Medical Products Agency will be informed within 24 hours. A clinical investigation report will be prepared within three months of the early termination or temporary halt, irrespective of the results. In the event that the clinical investigation is restarted within three months of the temporary halt, the sponsor does not have to submit a clinical investigation report until the clinical investigation has been completed.

The final clinical investigation report shall include detail with respect to the temporary halt.

*Describe the procedures for follow-up of subjects after temporary halt or early termination of the investigation.*

## Publication policy

*Text suggestion:* The clinical investigation will be registered in a publicly accessible database before the start of recruitment activities and the content will be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation.

*Include a statement indicating the conditions and time frames under which the results of the clinical investigation will be offered for publication in scientific journals including the role of the sponsor and criteria for authorship.*

## Bibliography

*Include a list of bibliographic references*

## Appendix