Font
• Red Font: Provides instructions for the body of the section. Remove all text in red font before finalizing document.
• Blue Font: Provides suggested text or text content that may be helpful for the author(s). Remove all text in blue font before finalizing document.
• Black Font: Text that should be included. This language should be read, understood, used if possible, and changed only if necessary or if not applicable.
• Yellow Highlight Text: Text that needs to be inserted. Remove highlighting before finalizing document.

[Full Protocol Title]

List the Amendment Number if applicable, or, identify as the Original Protocol.

Remove row that is not applicable.

Amendment [X] or Original Protocol

**Sponsor Name**

Protocol Summary**:**

Make sure that any changes in the body are reflected in this Protocol Summary.

**PROTOCOL SUMMARY**

|  |  |
| --- | --- |
| Study Title | [Insert Full Protocol Title] |
| Original ProtocolAmendment [X]: | Remove row that is not applicable. |
| Sponsor |  [Insert address]  |
| Study Design | Provide an overview of the study design. May include description of study type, study arms, randomization scheme if applicable, etc. |
| Study Objective | Present the study objective statement. May be broken into primary and secondary. Language regarding hypothesis may be included. |
| Study Endpoint(s) | Present the study endpoints. May be separated into Primary and Secondary. Not necessary to include all secondary endpoints. May separate into Safety and Efficacy. |
| Subject Population | Describe eligible population and total expected enrollment. Include descriptions of test and control groups if applicable, and include the number in each group or ratio |
| Number of Sites | Include number of sites, and include potential for geographic distribution. Sample language: Up to XX Sites in the U.S., Europe and Asia. |
| Expected Time to Complete Enrollment  | *e.g.*, Number of months |
| Schedule of Events | Include screening, treatment, and follow up schedule |
| Additional Information | Information regarding name of CRO contracted to do monitoring, Core Lab, DSMB, CEC, etc |

**List of Abbreviations**:

Add all abbreviations used in the Protocol.

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##

# **Introduction**

## Disease

Provide the disease background (etiology, symptoms, prevalence, etc).

## Historical Treatments

Provide a review of historical treatments. Include any pharmaceutical, medical, and interventional device treatments. Provide literature and data references. Include bibliography in reference section of Protocol.

## Study Device Description

Name and describe the device(s) being studied, including intended purpose. Compare and contrast, as applicable, to historical treatments (how is this device similar or improved in design from existing devices).

# **Study Objectives**

## Primary Objective(s)

State the primary study objective(s).

Single Arm Study Example:

The primary objective of [Insert Study Name] is to evaluate the safety and efficacy of [Insert Device Name] for the treatment of [Insert condition] in patients with [Insert patient population].

## Secondary Objective(s)

State the secondary objectives(s) if applicable. Secondary objectives should only be stated when there are endpoints defined to evaluate the secondary objective and statistical hypotheses.

The secondary objective(s) of [Insert Study Name] is / are:

* To evaluate …
* To compare ...

# **Study Design**

## Study Design Schema

Include a picture/flowchart, if applicable.

## Description of Study Design

Include the type of study and rationale:

* Randomized / Non-randomized
* Single / Multicenter
* Prospective / Retrospective
* Single arm / Multi-arm

As well, provide relevant information on the following design details:

* Number of Sites
* Minimization of Bias
* Number of Devices to be used in the study and justification
* Control Group
* The geographical regions / countries in which the study is being conducted
* Number of Subjects (per arm if applicable).
* Follow-Up Schedule
* Total expected duration of the study, expected duration of each Subject’s participation, and the estimated time needed to enroll the total number of Subjects.

This study is a prospective, multicenter, non-randomized single-arm study to evaluate the safety and efficacy of the [Inset Device Name] for the treatment of [Insert condition] in patients with [Insert patient population].

A maximum of [##] Clinical Sites (referred to as “Sites” in the remainder of this document) in the U.S, Europe, South America, and Asia will participate in this study. [##] patients will be enrolled in this study with a limit of [##] of Subjects enrolled per Site. The anticipated accrual rate is approximately [##] Subjects per month for a total accrual period of approximately [##] – [##] months.

Patients may be enrolled into the study provided all inclusion and no exclusion criteria are met as specified in Section 4. Subjects will be evaluated through hospital discharge and return for follow-up visits at [##] days, [#] months, [#] months, and annually through [#] years post treatment. Total estimated duration of the study is [##] months.

## Study Endpoint(s)

### Primary Endpoint(s)

Define endpoint and rationale. The definition of the endpoint should be unambiguous.

Describe methodology and timing for assessing variable(s).

If applicable describe primary safety endpoint and primary efficacy endpoint.

### Secondary Endpoint(s)

Define endpoint(s) and rationale. The definition of the endpoint should be unambiguous.

Describe methodology and timing for assessing variable(s).

# **Study Population**

## Description of Population

Provide a general description / categorization of the patients targeted for this study.

Patients with [Insert disease state] are eligible for screening for participation in the study.

Only patients who meet all of the Inclusion Criteria and none of the Exclusion Criteria will be enrolled.

## Inclusion Criteria

Describe Inclusion Criteria in a numbered list. Include timeframes for each if applicable (*e.g.*, at the time of ICF signature, at the time of implant, etc.).

Include opening statement based on scope of entry criteria if appropriate.

The patient is / has:

1. Age ≥18 at the time of informed consent signature.
2. Capable of complying with Protocol requirements, including follow-up.
3. An Informed Consent Form signed by Subject or legal representative.

## Exclusion Criteria

Describe Exclusion Criteria in a numbered list. Include timeframes for each if applicable. (*e.g.*, at time of ICF signature, at time of implant, etc).

Include opening statement based on scope of entry criteria if appropriate

The patient is / has:

1. Been treated in another drug or medical device study within 1 year of study enrollment.
2. Pregnant female at the time of informed consent signature.
3. Life expectancy < 1 year

# **Study Procedures/Evaluations**

Throughout this section, as applicable, describe any equipment to be used for assessing the study variables and arrangements for monitoring the maintenance and calibration of the equipment. Sample language: Sites are required to use a duplex ultrasound to assess blood flow. Each Site will be responsible for maintaining and calibrating the equipment used.

Throughout this section, address any known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results.

## Schedule of Events

Insert a quick reference table that indicates visit procedures.

Confirm that the table is updated as Protocol is modified over time.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Screening/Baseline** | **Pre-Procedure** | **Procedure** | **Discharge** | **Follow-up (specify time period)** | **Follow-up (specify time period)** |
| Informed Consent | X |  |  |  |  |  |
| Demographics and Medical History | X |  |  |  |  |  |
| Physical Exam | X |  |  | X |  | x |
| NIH Stroke Scale |  | X |  | X |  |  |
| Anti-Platelet Therapy  | X | X | X | X | x | x |
| Duplex Ultrasound  | X |  |  |  | x | x |

## Informed Consent Process

Only include the references for vulnerable populations and legally authorized representatives if the Clinical Study Team has decided that this is permissible and justified for the study.

All patients must provide informed consent prior to any study related procedures being performed. The case history (*i.e.*, source documents/Subject chart) for each Subject shall document that such informed consent was obtained. The [IRB/EC] approved consent form will be signed and personally dated by the Subject and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the Subject records. A copy of the informed consent document will be given to the Subject for their records.

Include a description of the specific informed consent process for any vulnerable populations identified in the Study Population section.

## Pre-Screening / Screening

Define screening procedures. Include description of existing health information from standard of care which can be used for screening purposes, and the acceptable time frame of the existing health information. Differentiate the existing health information from procedures which are study related procedures that require informed consent. Include specific qualifications/requirements of personnel conducting evaluations if required. Describe the documentation requirements of a screened patient (*e.g.*, screening log).

## Enrollment

Define when a patient is considered enrolled into the study. Include description of screen failure(s), including documentation requirements. Refer to patients as “Subjects” after enrollment. Describe randomization and or blinding procedures.

The patient is considered enrolled when:

Randomized or the device enters the patient’s vasculature

## Procedure

Describe the procedure. Describe adjunct therapy and treatments including medication(s), treatment(s) and or medical devices which are required, permitted or not permitted Include detailed requirements for all procedures including imaging.

## Repeat Interventions

If there is the potential for repeat interventions to the initial procedure, describe here. Include instructions if there are any requirements for use of additional investigational devices, and any specific criteria. Include any specific additional imaging requirements.

## Follow-Up

Describe procedures, evaluations, exams, etc. Describe acceptable windows for each follow up interval, as applicable. Describe adjunct therapy and treatments including medication(s), treatment(s) and or medical devices which are required, permitted or not permitted during the follow-up period of the study. Include detailed requirements for all procedures including imaging.

Repeat Interventions: If there is potential for interventions to occur during the follow up period, describe the criteria necessitating the additional procedures (*e.g.*, when and what needs to be done). If additional devices may be used during the procedure, describe and justify

## Subject Withdrawal from the Study

Describe process if a subject withdraws from the study or the Investigator withdraws a Subject from the study. This includes documentation of withdrawal, the type and timing of the data to be collected for withdrawn Subjects, and the follow-up for Subjects withdrawn from the study. If there are study-specific criteria for withdrawing or discontinuing a Subject those should be explained.

A Subject may withdraw from the study at any time and should notify the Investigator in this event. The Investigator may also withdraw the Subject from the study at any time based on his / her medical judgment.

## Subject Lost to Follow-Up

Define what is considered lost to follow-up, and the documentation and contact attempts required.

A Subject will be considered lost to follow-up and withdrawn from the study once they have missed two consecutive follow-up visits and three documented attempts have been made by the Investigator or designee to contact the Subject or next of kin.

## Subject Study Completion

Describe what constitutes Subject study completion at the Site level. If applicable, include primary endpoint completion vs. long-term follow-up completion. Include a description of what medical care, if any, will be provided for the Subjects after the study is completed.

A Subject has completed the study when [Insert final completion procedures/follow up visits description]. Any Subject that does not complete these requirements due to voluntary withdrawal, physician withdrawal, death, or any other reason will be considered a withdrawal. Subjects will not be provided with any medical care by the Sponsor after study completion or withdrawal.

## Device Deficiencies

Include a definition of device deficiencies after review of applicable regulations in the regions where the study is conducted (particularly for EU). Device deficiencies are defined by ISO 14155 as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Describe the process for reporting device deficiencies. If the device is not investigational, state that reporting should be done through normal product surveillance mechanisms.

# **Study Administration**

## Monitoring

If the name of the monitoring organization is known, insert the name. Otherwise, state the Sponsor or designee.

Site monitoring for this study will be provided by [CRO name] or [the Sponsor or designee]. Monitoring oversight will be provided by the Sponsor.

The Site monitors are qualified by training and experience to oversee the progress of the study at the Site and will verify that the Investigators and their staff understand and adhere to both the applicable regulatory requirements and the study Protocol. In addition, they may assist in resolution of any problems that may arise during the study.

Describe the monitoring activities that will occur for a study,

## Core Lab

Describe all Core Labs which will be used during the study and their specific services. If the name of the Core Lab(s) is / are known, insert the name. Otherwise, state the Sponsor or designee.

Include detailed requirements for all imaging and training. If the section requires lengthy detailed instructions, consider creating a separate Imaging Guideline. Cross reference the Imaging Guideline if applicable.

Core Lab services for this study will be provided by [Insert Core Lab name and address] or [the Sponsor or designee] for [type of service].

## Protocol Deviations

Identify country specific requirements and provide communication of the requirements to the Site.

A Protocol deviation is defined as any change, divergence, or departure from the study design or procedures of a research protocol. The Investigator is responsible for promptly recording and reporting Protocol Deviations to the Sponsor and the reviewing [IRB/EC] per [IRB/EC] policy. The Sponsor will determine the effect of the protocol deviation on the scientific soundness of the study and Subject safety and determine if additional reports or actions are required. Additional action may include Site retraining or Site termination.

The Investigator will not implement any changes to the protocol without first obtaining written agreement from the Sponsor and documented approval from the [IRB/EC], except in the event of an immediate hazard(s) to a Subject. The Investigator will report the Protocol Deviation in accordance with the applicable regulations.

## Protocol Amendments

The Investigator will obtain [IRB/EC] approval on all amendments in a timely manner.

## Access to Source Data/Documents

Source data are defined as all information necessary for the reconstruction and evaluation of the Clinical Investigation.

The Investigator will keep all study records, source data available for inspection by the Sponsor, Sponsor’s monitors, [IRB/EC], and regulatory authorities.

## Study Records Retention

Describe record retention requirements per applicable regulations. Consider the regulatory framework and IRB/EC requirements for the study in different countries, as applicable.

The Investigator will maintain complete, accurate and current study records as required by applicable regulatory requirements. Records will be maintained during the study and for a minimum of …

## Publication Plan

A statement indicating whether the results will be submitted for publication is required. Address the conditions under which the results of the study will be offered for publication.

It is the intent of the Sponsor that the multicenter results of this study will be submitted for publication (in a peer reviewed journal). A publications committee will be established to review the multicenter results and develop publications at the completion of the study.

# **Data Collection and Submission**

This section is written with electronic data capture systems in mind.

The electronic data capture system (EDC system) for this study will be provided by [Insert Clinical Vendor name and address].

## Data Collection Methods

## Data Clarification and Correction

## CRF Completion Schedule

Describe if there are specific timeline requirements for data collection.

Describe if there are specific timeline requirements for CRF completion.

# **Risk Assessment**

List all anticipated Adverse Events and/or additional risks in this section along with their likely incidence, mitigation or treatment, if applicable.

The Risk Assessment section must be consistent with the Risk-Benefit Analysis section of the Clinical Evaluation Plan, the Instructions for Use (see Hazards and Adverse Events section in IFU) and align with the Informed Consent Form.

Describe possible interactions with concomitant medical treatments, any prohibited and restricted therapies during the study, or, any precautions which should be taken during the study for any therapies, if applicable.

## Risk-to-Benefit Rationale

This section is required for studies conducted in EU

# **Adverse Events and Safety Monitoring**

This section addresses what Adverse Events to report and how to report them. Do not simply repeat the list from the Risk Assessment section. Adverse Events (AEs) are defined as any untoward medical occurrences in a Subject whether device-related or not.

## Anticipated Adverse Events

Anticipated Adverse Events are complications that are known to be associated with [insert therapeutic area] patients undergoing [insert procedure name]. See Section 8, Risk Assessment.

### Adverse Event Relationship

Each reported AE will be assessed by the Investigator for its primary suspected relationship to the [device, procedure, disease, and / or insert other relationships as appropriate for the therapeutic area].

**Study Device-related**

The functioning or characteristics of the device caused or contributed to the Adverse Event.

**Study Procedure-related**

The procedure (and not the device) caused or significantly contributed to the Adverse Event.

Include the section below if it is necessary to distinguish Adverse Events related to the underlying disease being treated from other diseases or conditions.

**Disease-related**

The Adverse Event was a result of the underlying disease progression for which the study procedure is being performed, and not the device or procedure.

**Not-related**

An Adverse Event which cannot be attributed to the device, procedure, or disease.

**Unknown relationship**

The relationship of the Adverse Event to the device, procedure, or disease insert other categories as appropriate cannot be determined.

Other possible relationship categories: Include if appropriate

**Medication-related**

The Adverse Event was a result of medical therapy prescribed by the study protocol and not the device or procedure [insert other relationships as appropriate].

### Adverse Event Classification

Serious / Non-serious

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, E2A. 1994.

Global Harmonization Task Force. Medical Devices Post-Market Surveillance: Global Guidance for Adverse Event Reporting. November 30, 2006.

ISO 14155, Clinical Investigation of Medical Devices for Human Subjects-Good Clinical Practice. Second edition 2011-02-01.

Each AE will be assessed by the Investigator to determine if it is Serious or Non-Serious.

**Serious Adverse Event (ISO 14155 Definition)**

A Serious Adverse Event is an Adverse Event that

* led to death
* led to serious deterioration in the health of the Subject that either resulted in
* a life threatening illness or injury, or
* a permanent impairment of a body structure or body function, or
* inpatient or prolonged hospitalization, or
* medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
* led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

**Adverse Event (ISO 14155 Definition)**

An Adverse Event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical

### Adverse Event Reporting and Coding

Customize this section to incorporate local AE reporting requirements and timelines, per local SAE Guideline Documents.

Describe when Adverse Event reporting begins, *i.e.*, after randomization, after implant of device, etc.

If applicable, describe when Adverse Event reporting ends.

Example: a study has a final study visit at 12 months + / - 2 weeks. The Subject returns at 12 months for collection of endpoint data; however, one week later (still in window) a new Adverse Event emerges. Is that a reportable event because it is still within the 12 month window or is it not reportable since the Subject completed the 12 month (final visit)?

Describe the reporting requirement for any condition reported in the medical history and / or present at baseline or index procedure, *e.g.*, do not report as an adverse event unless it becomes serious or increase in intensity, or if a worsening of a baseline condition is reported. Recommend instructing Sites to report the event only if it increases in severity or frequency from baseline. Prospectively establish criteria for assessing increases in severity or frequency that would trigger an Adverse Event report.

Describe the process for an adverse event that changes from nonserious to serious.

AEs will be reported on the appropriate case report form (CRF) and documented in the Subject’s permanent medical record.

The following information on each reported Adverse Event will be collected:

* Adverse Event Name
* Adverse Event Onset Date
* Relationship
* Classification [Serious or Major / Minor]
* Treatment
* Outcome
* Resolution Date

Adverse Event submission guidelines:

* Adverse Event reporting begins once the patient is enrolled in the study. All Adverse Events should be reported from enrollment through study completion / discontinuation.
* Provide a diagnosis if possible. If unable to provide a diagnosis, report the symptoms as separate events. Adverse Events should be reported using the full name without abbreviations or narratives.
* Adverse Events with an outcome status of “Ongoing” should be assessed at each follow-up evaluation to determine if the event has resolved. Adverse Events ongoing at study completion / discontinuation should be left as “Ongoing” on the AE case report form.

### Subject Death

Explicitly state whether death will be considered an Adverse Event or whether only the cause of death is the AE. If death is considered an AE, state whether the cause(s) of death is / are also an AE.

## Unanticipated Adverse Device Effects (UADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

# **Statistical Analysis**

## Study Hypotheses

Break into two sections if there are separate efficacy and safety hypotheses.

## Sample Size Assumptions

Present the assumptions used to calculated sample size. Provide justification for use of comparator and / or historical controls as applicable. If test arm will be compared to a performance goal, provide justification for the performance goal to be used.

## Sample Size Determination

Describe sample size calculation and methods used.

Sample size sensitivity should be included; power under alternative scenarios could be included to demonstrate robustness to assumptions. Discuss expected drop-out rates in the study.

Include plan to replace excluded Subjects from primary analysis, if applicable (*e.g.*, protocol deviations upon DSMB recommendation).

## Data Analysis

### Timing of Analyses

Describe timing of statistical analyses. If no interim analysis is planned, then state so. If interim analysis is planned, state methods employed, stopping rules, who will review data, how will this affect sample size, etc.

### Analysis Populations

Describe the analysis populations and which population is used for primary analysis.

### Statistical Analysis of Primary Endpoint(s)

Describe how the primary study endpoint(s) will be analyzed, including the statistical test and criteria for rejecting null hypothesis. Describe the plan for missing data.

### Statistical Analysis of Secondary Endpoint(s)

Describe how the secondary endpoint(s) will be analyzed, including whether the analyses are planned or exploratory. Describe plan for missing data.

# **Ethical and Regulatory Considerations**

## Statement of Compliance

Provide a statement that the study will be conducted in compliance with applicable regulatory requirements. Include a list of the applicable regulations and requirements depending on study location and regulatory status.

The study will be conducted in compliance with this protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), ISO 14155:2011 and applicable regulatory requirements.

## Compliance Responsibilities

The Sponsor will conduct the study in accordance with all applicable regulations and laws. The Sponsor will be responsible for …

The Investigator will conduct the study in accordance with all applicable regulations and laws, any relevant agreements, the study protocol, and all approval conditions of the reviewing [IRB/EC] and [governing regulatory agencies]. The Investigator will verify [IRB/EC] approval is obtained prior to enrollment, maintained throughout the course of the study, and that all [IRB/EC] reporting requirements are met. The Investigator is responsible for protecting the rights, safety, and welfare of Subjects under the Investigator’s care and for the control of devices under investigation. The Investigator is also responsible for ensuring that informed consent is properly obtained.

The Sponsor will obtain clinical trials insurance as required by the laws of each country in which the study is conducted.

The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

## Informed Consent

The Investigator shall verify that all potential Subjects for this study are provided with a consent form describing this study and sufficient information to make an informed decision about their participation.

The formal consent of a Subject, using the [IRB/EC]-approved consent form, must be obtained by the Investigator before that Subject undergoes any study-related procedure. The consent form will be signed and personally dated by the Subject and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the Subject records. A copy of the informed consent document will be given to the Subject for his or her records. Any significant, new information which emerges while the study is in progress that may influence a Subject’s willingness to continue to take part in the study will be provided to the Subject.

The Investigator shall verify that documentation of the acquisition of informed consent is recorded in each Subject’s records in accordance with applicable regulations.

## Independent Ethical Review

The Investigator shall not enroll any Subjects prior to obtaining approval for the study from a properly constituted independent [IRB/EC].

The Investigator will submit the protocol, informed consent forms, other information to be provided to Subjects such as survey instruments or questionnaires, and any proposed advertising / recruitment materials, to the [IRB/EC] for written approval.

## Conflict of Interest

All Investigators will follow applicable laws and regulations as well as the conflict of interest policies of their Site and the reviewing [IRB/EC].

## Confidentiality

All Subject records will be kept confidential to the extent provided by applicable laws and regulations. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records.

Such records may also be reviewed by the Site’s [IRB/EC] and other regulatory bodies [specify – *e.g.*, FDA, MHRA, PMDA].

The Investigator will inform the Subjects that their records will be reviewed.

## Study Discontinuation or Suspension

Describe the plan for the discontinuation or suspension of the study, if applicable, including ongoing treatment of Subjects.

For studies conducted in EU, include the following: Criteria for suspension or premature termination of the whole study or of the study in one or more investigation sites.

# **References**

Insert references, consecutively numbered. Include references for the Adverse Event Classification system used.

# **Study-Specific Appendices**

Insert appendices here, if applicable, such as Assessment Tools (*e.g.*, Quality of Life).