CLINICAL STUDY PROTOCOL

# Prospective Evaluation to Characterize the Real-World PerFormance of the EMBOVAC™ Aspiration Catheter for Neurothrombectomy: A Post-Market Clinical Follow-up Trial

## PERFECT

**Protocol Number: CNV_2019_01**

**Version: 2.0**

**5 November 2021**

**History of Changes**

| Version Date | Description |
|---|---|
| Version 1.0— 21NOVEMBER2019 | Original Document |
| Version 2.0 – 5 NOVEMBER 2021 | Protocol Revision |

Sponsor: CERENOVUS
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Irvine, CA 92618 USA

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADAPT | A Direct Aspiration First Pass Technique |
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| AIS | Acute Ischemic Stroke |
| ASPECTS | Alberta Stroke program early CT score |
| BA | Basilar Artery |
| CEC | Clinical Events Committee |
| CT | Computed Tomography |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICA | Internal Carotid Artery |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization |
| IFU | Instructions for Use |
| IV | Intravenous |
| IV t-PA | Intravenous tissue Plasminogen Activator |
| LVO | Large Vessel Occlusion |
| MCA | Middle Cerebral Artery |
| mITT | Modified Intent-to-Treat |
| MRI | Magnetic Resonance Imaging |
| mRS | Modified Rankin Scale |
| mTICI | modified Thrombolysis in Cerebrovascular Infarction |
| NIHSS | National Institutes of Health Stroke Scale |
| PHI | Protected Health Information |
| PP | Per Protocol |
| PI | Principal Investigator |
| PMCF | Post-Market Clinical Follow-Up |
| RBC | Red Blood Cell |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis Software |
| SDV | Source Data Verification |
| SOC | Standard of Care |
| SOP | Standard Operating Procedure |
| US | United States |
| USADE | Unanticipated Serious Adverse Device Effect |
| VA | Vertebral Artery |
| WBC | White Blood Cell |

# KEY ROLES AND RESPONSIBILITIES

**Sponsor:**

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**Coordinating Investigator Contact:**

[redacted]

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[redacted]

# PROTOCOL AGREEMENT AND STATEMENT OF COMPLIANCE FORM

**STUDY NAME AND NUMBER:** PERFECT - CNV_2019_01

**STUDY TITLE:** Prospective Evaluation to Characterize the Real-World PerFormance of the EMBOVAC$^{TM}$ Aspiration Catheter for Neurothrombectomy: A Post-Market Clinical Follow-up Trial

**VERSION NUMBER:** 2.0

**VERSION DATE:** 05 November 2021

I have read this protocol and agree to conduct this clinical study in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the study is conducted in accordance with specific provisions of the associated ECs, the current applicable version of ISO 14155, the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable national and regional regulatory requirements, the signed agreement with Cerenovus, and with the protocol outlined herein. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the time period designated by the Sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

I will fulfill the requirements of my Ethics Committee (EC), or other oversight committee, to ensure complete and continual oversight of this clinical investigation. I will use an Informed Consent Document approved by the Sponsor and my reviewing EC (where required).

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any required adverse events as defined in this protocol to the Sponsor, and comply with all adverse event reporting requirements of my reviewing EC. I agree to permit the Sponsor, its authorized representatives, my reviewing EC, and any regulatory authority/body access to all records relating to the clinical investigation.

The below signature confirms I have read and understood this protocol and its associated amendments or attachments, and will accept respective revisions or amendments provided by the Sponsor

| Principal Investigator (PI) Name (PRINT) | Signature | Date |
|---|---|---|

# PROTOCOL SUMMARY

| | | |
|---|---|---|
| **Title of Study** | **P**rospective **E**valuation to Characterize the **R**eal-World Per**F**ormance of the **E**MBOVAC™ Aspiration **C**atheter for Neurothrombectomy: A Post-Market Clinical Follow-up **T**rial. | |
| **Short Title** | PERFECT | |
| **Study Sponsor** | CERENOVUS<br>31 Technology Drive<br>Irvine, CA 92618 USA | |
| **Study Device** | EMBOVAC™ Aspiration Catheter | |
| **Indication** | The EMBOVAC™ Aspiration Catheter is indicated for general intravascular use in the neuro vasculature. The catheter can be used to facilitate introduction of diagnostic or therapeutic agents and is also intended for use in removal/aspiration of emboli and thrombi from selected blood vessels in the neuro vasculature. | |
| **Study Design** | Prospective, multi-center, single arm, post-market clinical follow-up study. | |
| **Sample Size** | Approximately 100 subjects will be enrolled. | |
| **Number of Sites** | Approximately 10 institutions primarily in Europe. | |
| **Study Duration** | Start Date: 2020 | End Date: 2022 |
| **Study Procedures** | EMBOVAC™ Aspiration Catheter is used with ADAPT (A Direct Aspiration, First Pass Technique) as the first attempted device/technique for mechanical thrombectomy in the subject.<br><br>The study evaluation time points follow the site's standard of care and include:<br><br>1. Study Procedure<br>2. 24 Hour follow-up (+/- 12 hrs)<br>3. 7 Day / Discharge follow-up (-1/+7 days) (whichever comes first)<br>4. 90 Day Follow-up (+/- 14 days) | |
| **Primary Objective** | The primary objective of this Post-Market Clinical Follow-Up (PMCF) study is to characterize the performance of the EMBOVAC™ Aspiration Catheter in the treatment of acute ischemic stroke in a real-world clinical setting. | |

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| **Secondary Objective** | The secondary objective is to confirm the benefit of a 'system approach' using Cerenovus products (e.g., distal access catheter, balloon guide catheter) which have been designed for use together in the treatment of acute ischemic stroke. |
| **Primary Endpoint** | Proportion of patients having successful revascularization, defined as number of subjects achieving a modified Thrombolysis in Cerebral Infarction (mTICI) score of ≥ 2b at the end of the procedure, as determined by Core Lab. |
| **Secondary Effectiveness Endpoints** | ✓ Successful Revascularization (final mTICI ≥ 2b) without rescue therapy, as determined by Core Lab<br>✓ Complete Revascularization (final mTICI ≥ 2c), as determined by Core Lab<br>✓ First Pass Effect (mTICI ≥ 2c without rescue), as determined by Core Lab<br>✓ Modified First Pass Effect (mTICI ≥ 2b), as determined by Core Lab<br>✓ Time to recanalization (Time from arterial puncture to complete recanalization mTICI ≥ 2b), as determined by Core Lab<br>✓ Modified Rankin Scale 0-2 at 90 Days |
| **Secondary Safety Endpoints** | ✓ Devices related serious adverse events within 90 days<br>✓ sICH at 24h post procedure specified according to the Heidelberg Bleeding Classification (HBC)<br>✓ NIHSS at 24h post procedure<br>✓ 90 Day All-Cause Mortality |
| **Health Economic Endpoints** | ✓ Hospitalization length of stay for index procedure and unscheduled re-hospitalizations<br>✓ Healthcare resource utilization for index procedure, post-procedure and re-hospitalizations for unscheduled events |
| **Inclusion Criteria** | 1. Subject ≥ 18 years old.<br>2. Subject experiencing acute ischemic stroke with angiographic confirmation of Large Vessel Occlusion (LVO) of the distal |

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| | intracranial internal carotid artery, middle cerebral artery (M1 or M2) or anterior cerebral artery (A1 or A2).<br>3. A clinical decision has been made to use the EMBOVAC™ aspiration catheter prior to enrollment in the research.<br>4. EMBOVAC™ Aspiration Catheter is attempted to be used for the first 3 clot removal passes for the target intracranial occlusion (if 3 passes are needed) using A Direct Aspiration, First Pass Technique (ADAPT).<br>Exception: it is not considered rescue therapy if use of another device is needed to remove distal occlusion in a vessel smaller than 2 mm after the first pass.<br>5. Pre-stroke mRS ≤ 1<br>6. NIHSS ≤ 30<br>7. Informed Consent has been provided by the subject or the subject's legally authorized representative. |
| **Exclusion Criteria** | 1. Potential study candidate has already undergone standard of care assessments or treatment that deviate from the clinical research protocol requirements (e.g., 24 hour imaging conducted outside the protocol specified window).<br>2. All patients with severe hypertension on presentation (SBP > 220 mmHg and/or DBP > 120 mm Hg). All patients, in whom intravenous therapy with blood pressure medications is indicated, with hypertension that remains severe and sustained despite intravenous antihypertensive therapy (SBP >185 mmHg and/ or DBP >110 mmHg).<br>3. Known cerebral vasculitis.<br>4. Known cancer with life expectancy less than 12 months.<br>5. Stenosis, or any occlusion, in a vessel proximal to the target occlusion that requires treatment or prevents access to the site of occlusion.<br>6. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) evidence of recent/ fresh hemorrhage on presentation.<br>7. Baseline computed tomography (CT) or MRI showing mass effect or intracranial tumor (except small meningioma).<br>8. Evidence of dissection in the extra or intracranial cerebral arteries.<br>9. Occlusions in multiple vessels.<br>10. Confirmation of positive pregnancy test according to site specific standard of care (e.g. test, verbal communication).<br>11. Currently participating in an investigational (drug, device, etc.) clinical trial that may confound study endpoints. Patients in observational, natural history, and/or epidemiological studies not involving intervention are eligible. |

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| **Sample Size Justification** | There is no statistical power calculation and no hypothesis testing for this post-market study. 100 subjects are deemed sufficient to characterize the performance of EMBOVAC™ Aspiration Catheter.<br><br>Approximately 100 subjects will be enrolled. With an enrolled sample size of 100 and an attrition rate of no more than 5%, the precision (margin of error) for the primary endpoint is anticipated to be around 8.0% based on 2-sided 95% confidence intervals, where the primary endpoint rate is estimated to be 80%.<br>$$Margin\ of\ error \approx 1.96 \times SE = 1.96 \times \sqrt{\frac{p(1-p)}{n}} =$$<br>$$= 1.96 \times \sqrt{\frac{0.8 \times (1-0.8)}{95}} = 8.0\%$$<br>where SE denotes the standard error and $p$ denotes the proportion of subjects who achieve the primary endpoint. |
| **Statistical Analysis** | Demographics, baseline subject characteristics, procedure characteristics and the primary and secondary endpoints will be presented for each analysis population.<br><br>Descriptive summary statistics will be presented for all endpoints. The number and percentage of subjects will be summarized for categorical variables. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, minimum and maximum. |
| **Interim Analysis** | Interim analyses will be conducted for regional (outside Europe, as well as for European MDR) regulatory submission purposes. Only descriptive statistics will be reported. Results of the interim analyses will not be used as a basis for stopping the trial early. |
| **Laboratories** | Imaging Core Lab<br>[redacted]<br><br>Clot analysis lab<br>[redacted] |

# SCHEDULE OF ASSESSMENTS

**Table 1 Schedule of Assessments**

| | Enrollment | | | | Follow-up | |
|---|---|---|---|---|---|---|
| **Assessments** | Baseline | Procedure | 24hrs post-procedure (+/- 12 hrs) | 7 days/ discharge (-1/+7 days) (whichever comes first) | ☎ 90 Day Follow-up (+/- 14 days) | Unscheduled (6) |
| Eligibility Screening | **X** | **X** | **X** | **X** | | |
| Informed Consent | Patient consent may be obtained up to 45 days post procedure | | | | | |
| Demographics and Medical History | **X** | | | | | |
| IV t-PA administration | **O** | | | | | |
| Imaging (1) | **X** | | **X** | | | **O** |
| NIH Stroke Scale (NIHSS) | **X** (4) | | **X** (4) | **O** | **O** | **O** |
| Modified Rankin Scale (mRS) | **X** (5) | | | **O** | **X**(7) | **O** |
| Angiography (2) | | **X** | | | | |
| Review of Reportable AEs(8) | | **X** | **X** | **X** | **X** | **X** |
| Clot Collection (3) | | **X** | | | | |
| Health Economics Data Collection | | **X** | **X** | **X** | **X** | **X** |

(1) Imaging will be sent to independent Imaging Core Lab for review
(2) Procedural angiography will be sent to Imaging Core Lab for review
(3) Per pass clot collection to be sent to Clot Analysis Lab for processing
(4) If more than one NIHSS was performed during this time period, select the worst (highest) value
(5) To be administered pre-procedure by a qualified evaluator; pre-stroke mRS should reflect the subject's condition just prior to the stroke onset. For example, if the subject was hospitalized during stroke onset, the subject's reason for hospitalization should be taken into account when evaluating the subject's pre-stroke mRS
(6) Assessments should be completed for unscheduled visits from the time of Discharge up to (but not including) the 90-day Follow-up, where imaging, NIHSS or mRS is performed as part of stroke management care for the subject
(7) The 90 day mRS must be performed by a qualified independent evaluator. This may be performed by phone per the site's SOC.
(8) AEs will be reported and recorded (via eCRF) if any of the following apply: (a) The event is neurological in nature (b) The event is a serious adverse event (SAE) (c) AE where causality is related to the device or procedure.

## SCHEMATIC OF STUDY DESIGN

A subject can be enrolled in this study from the angiographic confirmation of an LVO up to 45 days post-procedure. Assessments and imaging performed for this study are part of standard of care (SOC) for stroke treatment and screening can occur without obtaining consent. Informed consent is mandatory and must be obtained before any data is captured in the electronic Case Report Form (eCRF).

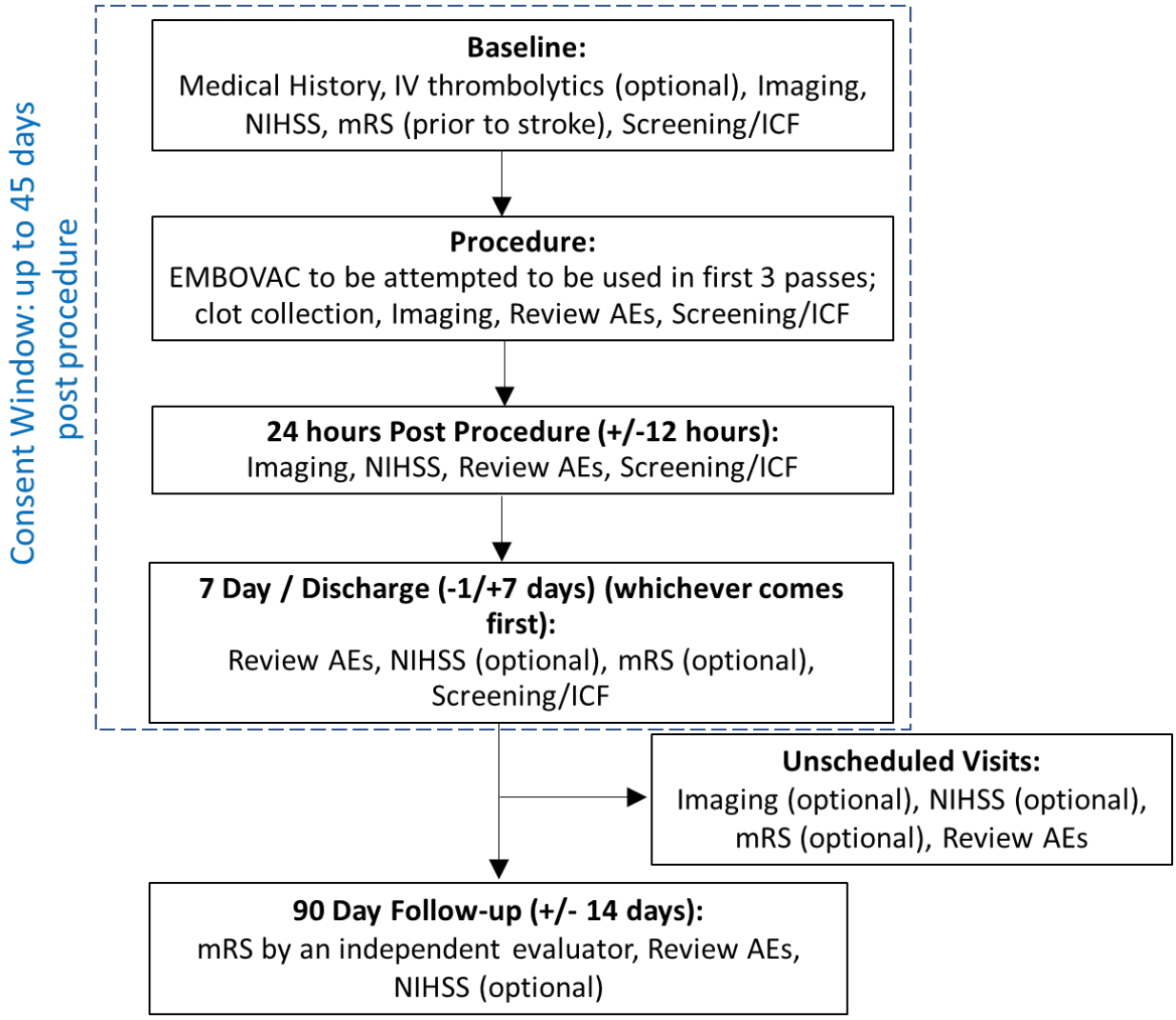


**Figure 1 Schematic of Study Design**

# 1. Background Information and Scientific Rationale

## 1.1. Background Information

According to the World Health Organization, 15 million people suffer from a stroke per year, leaving 5 million dead and 5 million severely disabled[1]. Approximately 90% of all strokes are Acute Ischemic Strokes (AIS), occurring when blood flow to the brain is blocked by a clot / thrombus [2]. The most severe AIS are due to Large Vessel Occlusions (LVO) and are associated with significant disability and mortality due to obstruction of the major vessels in the brain which include – Internal Carotid Artery (ICA), Middle Cerebral Artery (MCA), Vertebral Artery (VA), and the Basilar Artery (BA). Numerous studies have shown that removing the blood clot or occlusion can limit disability and drastically improve the patient's chances of having a good functional outcome.

## 1.2. Current Treatment Options

Intravenous Tissues Plasminogen Activator (IV t-PA) is routinely used to treat patients experiencing AIS in the United States, Europe and other regions. However, many patients do not meet the therapy's eligibility criteria. In the US, the FDA has approved IV t-PA in patients presenting up to 3 hours after symptom onset, while in the EU per ECASS (European Cooperative Acute Stroke Study) criteria, patients are eligible for IV t-PA up to 4.5 hours after symptom onset [3]. In addition to the time constraints, IV t-PA has shown to be less effective in recanalizing proximal LVOs [4]. Due to the limitations of IV t-PA, mechanical thrombectomy surfaced as a valuable alternative to effectively treat patients, regardless of IV t-PA eligibility[5].

Recent randomized controlled trials (SWIFT PRIME, ESCAPE, EXTEND IA, MRCLEAN, THERAPY) were successful in demonstrating the safety and effectiveness of thrombectomy with stent retrievers compared to IV-t-PA alone in treating AIS in patients with LVOs [6-10]. As a result, treatment guidelines have changed to include mechanical thrombectomy as part of standard of care (SOC) [11].

Advancement of catheter design and development has led to "A Direct Aspiration First Pass Technique" (ADAPT) that permits intracranial delivery of large-caliber aspiration catheters to the thrombus interface allowing for direct clot extraction. It was reported that ADAPT therapy is associated with similar reperfusion rates, clinical outcomes and complication rates compared with thrombectomy with stent retrievers [12].

A literature review involving 17 ADAPT studies and 5 Randomized Controlled Trials (ESCAPE, EXTEND, MRCLEAN, REVASCAT, and SWIFT PRIME) were successful in demonstrating higher rates of complete revascularization and reduced time from groin puncture to recanalization compared to standard methods – IV tPA and mechanical thrombectomy with stent retrievers[13].

Further, three randomized control trials compared endovascular approaches of aspiration vs stent retriever – ASTER, Penumbra Separator 3D and COMPASS. ASTER and Penumbra Separator 3D showed successful revascularization rates were similar between both techniques[14, 15]. COMPASS showed aspiration as first pass as non-inferior to stent retriever first line, on an intent to treat basis and showed a faster recanalization time [16]. These studies support the use of direct aspiration as an alternative to stent retriever as first line therapy for stroke thrombectomy[17].

## 1.3. Previous Experience with EMBOVAC™ Aspiration Catheter

No prior clinical investigations have been performed for the EMBOVAC™ Aspiration Catheter. Table 1 below provides an overview of the pre-clinical design verification and validation testing conducted on EMBOVAC™ Aspiration Catheter to demonstrate its safety and performance.

**Table 2 Pre-clinical Design Verification and Validation Testing**

| Title | Description of Section |
|---|---|
| Design Verification Testing | Design Verification testing of the EMBOVAC™ Aspiration Catheter confirmed that the design outputs meet the design inputs. |
| Design Validation | Design Validation testing of the EMBOVAC™ Aspiration Catheter confirmed that the design outputs meet the customer requirements. |
| In-Vivo Animal Testing | Fourteen Yorkshire pigs underwent a single interventional procedure on Day 0 in which selected arteries were treated with the Cerenovus EMBOVAC™ Aspiration Catheter and control device (SOFIA Plus) (16 devices each tested with clot, 12 each without clot). A minimum of 3 passes were performed in all vessels. Acute performance characteristics of the catheters were evaluated, including assessment of the preparation, compatibility between components, trackability, pushability, positioning, radiopacity and withdrawal. On Days 3 and Day 30, histologic evaluation was used to assess local tissue response and downstream organ/tissue effects.<br><br>This study demonstrated that the Cerenovus EMBOVAC™ Aspiration Catheter performed comparably to the control device (SOFIA Plus) with respect to handling, positioning, and pushability; and better with respect to RHV/microcatheter compatibility, and trackability. Clot was retrieved in |

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|---|---|
| | 100% of the Cerenovus Aspiration Catheter arteries and TICI 3 was achieved in 81% of those arteries after the third pass, comparably to SOFIA Plus. There were no dissections or perforations in the treated vessels. Vasospasm was a persistent observation which is typical in the swine model and not specific to the either the test or control devices. There were no health or clinical problems associated with the treatments and all animals survived to their scheduled end point. |
| Biocompatibility | The results of biocompatibility testing of the EMBOVAC™ Aspiration Catheter have demonstrated biocompatibility in compliance with applicable sections of EN ISO 10993. |
| Sterilization | Sterilization/microbiology validation testing of the EMBOVAC™ Aspiration Catheter was completed to demonstrate sterilization to a $10^{-6}$ Sterility Assurance Level (SAL). |
| Packaging | Packaging and labeling, conforms to defined customer requirements and patient needs. |

### 1.3.1. Rationale

This study aims to assess the performance of the EMBOVAC™ Aspiration Catheter when used by multiple interventionalists and centers in a real-world clinical setting, as well as to explore the benefit of a 'system approach' using the Cerenovus products which have been designed for use together in the treatment of acute ischemic stroke (e.g., distal access catheter, balloon guide catheter). This study will also look at association between clot composition and reperfusion in order to gain better insight into the etiology of the disease and means for effective clot removal.

## 1.4. Commercial Product

The EMBOVAC™ Aspiration Catheter is commercially available in the EU since 2019. Please refer to the Instructions for Use (IFU) for instructions on use of the device.

## 1.5. Potential Risks and Benefits

### 1.5.1. Known Potential Risks

Risks that may be associated with the use of the EMBOVAC™ Aspiration Catheter can be found in the commercially available IFUs found with the device.

### 1.5.2. Minimization of Risk

EMBOVAC™ Aspiration Catheter must only be used by investigators who have received appropriate training in interventional neuroradiology and the treatment of ischemic stroke.

Efforts will be made to minimize the potential risks of the study through the following:

1. Investigators who participate in the study will be experienced with EMBOVAC™ Aspiration Catheter and will have performed a minimum of 2 cases with the device using ADAPT prior to study enrollment.
2. The site will have adequate resources to conduct the clinical study.
3. The study has been designed to ensure treatment and follow-up of subjects are consistent with current SOC.
4. The investigator and study personnel will be trained on the study protocol.
5. Each investigator will ensure oversight and approval of the study by the EC prior to activation of the study at the investigation site. Subject status will be monitored by the investigator or designee throughout the follow-up period as defined in the study protocol.
6. A CEC will review and adjudicate safety endpoints, as defined in CEC charter, throughout the course of the study.

### 1.5.3. Known Potential Benefits

Although there may be no direct benefits of study participation, subject participants records will undergo an enhanced level of clinical scrutiny compared to routine SOC, which may provide some indirect health benefits. The potential benefits in this study of the commercially approved device outweigh any anticipated risks.

The results of the study may be beneficial to the research and medical community. The information learnt from this study may improve treatment to patients who require treatment for acute ischemic stroke in the future.

## 2. Objectives and Purpose

### 2.1. Objectives

The primary objective of this post-market clinical follow-up (PMCF) study is to characterize the performance of the EMBOVAC™ Aspiration Catheter in the treatment of acute ischemic stroke in a real-world clinical setting, as well as to confirm the benefits of a “system approach” using the Cerenovus products which have been designed for the use together in the treatment of acute ischemic stroke (e.g., distal access catheter, balloon guide catheter).

# 3. Study Design and Endpoints

## 3.1. Description of the Study Design

This is a prospective, multi-center, single-arm, post-market clinical follow-up study that will enroll approximately 100 subjects at approximately 10 sites primarily in Europe, with clot collection for follow-on histopathological analysis. Subjects will be included in the study for a period of 3 months after the procedure, including follow up visits at 24 hours, 7 days (or discharge) and 90 days after the procedure.

## 3.2. Study Endpoints

### 3.2.1. Primary Endpoint

**Successful Revascularization (final mTICI ≥ 2b)** – Proportion of subjects with substantial angiographic reperfusion assessed using the modified Thrombolysis in Cerebrovascular Infarction (mTICI) scale at the end of the procedure. Successful achievement of the endpoint is defined as achieving a final mTICI score of 2b or greater in the target vessel as determined by the independent Imaging Core Lab.

### 3.2.2. Secondary Effectiveness Endpoints

1. **Successful Revascularization (final mTICI ≥ 2b) without rescue therapy, as determined by Core Lab** – Successful achievement of the endpoint is defined as achieving a final mTICI score of 2b or greater in the target vessel as determined by the independent Imaging Core Lab without use of rescue therapy.
2. **Complete Revascularization (final mTICI ≥ 2c), as determined by Core Lab -** Successful achievement of the endpoint is defined as achieving a final mTICI score of 2c or greater in the target vessel as determined by the independent Imaging Core Lab.
3. **First Pass Effect (mTICI ≥ 2c without rescue), as determined by Core Lab –** Subjects with complete angiographic reperfusion defined as mTICI of 2c or greater after the first pass with the EMBOVAC™ Aspiration Catheter as determined by the independent Imaging Core Lab without use of recue therapy.
4. **Modified First Pass Effect (mTICI ≥ 2b), as determined by Core Lab –** Subjects with complete angiographic reperfusion defined as mTICI of 2b or greater after the first pass with the EMBOVAC™ Aspiration Catheter as determined by the independent Imaging Core Lab.

5. **Time to recanalization (Time from arterial puncture to complete recanalization mTICI ≥ 2b), as determined by Core Lab –** as the time from arterial puncture to achievement of the first mTICI score of 2b or greater, or visualization of final angiographic result if an mTICI score of 2b or greater is not achieved, as determined by the independent Imaging Core Lab.
6. **Modified Rankin Scale (mRS) of 0 - 2 at 90 days** - Must be performed by a qualified independent evaluator. Whenever possible, mRS should be recorded at the follow-up clinic visit. If not possible, then a telephone assessment may be used.

### 3.2.3. Safety Endpoints

1. **Device related serious adverse events within 90 days –**where the EMBOVAC™ Aspiration Catheter caused, or cannot be ruled out as having caused, an event that has resulted in any of the consequences characteristic of an SAE. Device relatedness will be adjudicated by an independent CEC.
2. **Symptomatic Intracerebral Hemorrhage (sICH) at 24 hours specified according to the Heidelberg Bleeding Classification** – adjudicated by an independent CEC - defined as a new intracranial hemorrhage as detected by brain imaging, measured 24 hours after intervention [18], associated with any of the following:

    - ≥4 points total NIHSS at the time of diagnosis compared to immediately before worsening. Note that a 4 points change is not compared with the baseline admission NIHSS score but instead to the immediate pre-deterioration neurological status

    - ≥2 point in one NIHSS category. The rationale for this is to capture new hemorrhages that produce new neurological symptoms, making them clearly symptomatic but not causing worsening in the original stroke territory. For example, a new remote hemorrhage in the contralateral occipital lobe may cause new hemianopia that is clearly symptomatic, but the subject will not have worsening of ≥4 points on the NIHSS score

    - Leading to intubation/hemicraniectomy/EVD placement or other major medical/surgical intervention

    - Absence of alternative explanation for deterioration

3. **NIHSS at 24 hours post procedure** – NIHSS will be measured at 24 hours and compared to the baseline score.
4. **90 Day All-Cause Mortality –** All mortality regardless of cause at 90 days post-procedure.

### 3.2.4. Health Economic Endpoints

Medical Resource Utilization and Health Economics related data including:

1. Hospitalization length of stay for index procedure and unscheduled re-hospitalizations
2. Healthcare resource utilization for index procedure, post procedure and rehospitalizations for unscheduled events

## 3.3. Rescue Therapy

In order to provide an evaluation of the device, rescue therapy should not be used prior to completion of the first three passes with the EMBOVAC™ Aspiration Catheter.

Rescue therapy is defined as:

- Any change in frontline device therapy to remove the target occlusion in a vessel at least 2mm in size.
- Use of intra cranial stenting during the procedure
- Use of an intra-arterial thrombolytic agent during the procedure (e.g., tissue plasminogen activator, urokinase, prourokinase)

Progression in therapy to address thrombus/occlusion that is no longer appropriate for treatment with EMBOVAC™ (e.g., use of another device to remove distal occlusion in a vessel smaller than 2mm) will be considered an appropriate evolution in the standard of care and NOT considered rescue therapy.

# 4. Study Population

## 4.1. Participant Inclusion Criteria

Investigators will assess potential subjects who are candidates for the study. Candidates who meet the protocol inclusion / exclusion criteria may be enrolled. The subject selection criteria are in place for protection of participants and to address factors that may compromise the outcome of the investigation or interpretation of the results.

Candidates for this study must meet ALL of the following criteria:

1. Subject ≥ 18 years old.
2. Subject experiencing acute ischemic stroke with angiographic confirmation of Large Vessel Occlusion (LVO) of the distal intracranial internal carotid artery, middle cerebral artery (M1 or M2) or anterior cerebral artery (A1 or A2).
3. A clinical decision has been made to use the EMBOVAC™ aspiration catheter prior to enrollment in the research.
4. EMBOVAC™ Aspiration Catheter is attempted to be used for the first 3 clot removal passes for the target intracranial occlusion (if 3 passes are needed) using A

Direct Aspiration First Pass Technique (ADAPT). Exception: it is not considered rescue therapy if use of another device is needed to remove distal occlusion in a vessel smaller than 2mm after the first pass.

5. Pre-stroke mRS ≤ 1
6. NIHSS ≤ 30
7. Informed consent has been provided by the subject or the subject's legally authorized representative.

## 4.2. Exclusion Criteria

Candidates will be excluded from participation if ANY of the following apply:

1. Potential study candidate has already undergone standard of care assessments or treatment that deviate from the clinical research protocol requirements (e.g., 24 hour imaging conducted outside the protocol specified window).
2. All patients with severe hypertension on presentation (SBP > 220 mmHg and/or DBP > 120 mm Hg). All patients, in whom intravenous therapy with blood pressure medications is indicated, with hypertension that remains severe and sustained despite intravenous antihypertensive therapy (SBP >185 mmHg and/ or DBP >110 mmHg).
3. Known cerebral vasculitis.
4. Known cancer with life expectancy less than 12 months.
5. Stenosis, or any occlusion, in a vessel proximal to the target occlusion that requires treatment or prevents access to the site of occlusion.
6. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) evidence of recent/ fresh hemorrhage on presentation.
7. Baseline computed tomography (CT) or MRI showing mass effect or intracranial tumor (except small meningioma).
8. Evidence of dissection in the extra or intracranial cerebral arteries.
9. Occlusions in multiple vessels
10. Confirmation of positive pregnancy test according to site specific standard of care (e.g. test, verbal communication).
11. Currently participating in an investigational (drug, device, etc.) clinical trial that may confound study endpoints. Patients in observational, natural history, and/or epidemiological studies not involving intervention are eligible.

## 4.3. Strategies for Recruitment and Retention

The study will enroll approximately 100 subjects across approximately 10 clinical sites in Europe. Once enrolled, each subject will participate in the study for up to 90 days post-procedure per the hospital's Standard of Care and the protocol schedule of assessments.

Principal investigators and clinical sites will be evaluated based upon the following factors:

- Previous experience with thrombectomy using large bore aspiration catheters: Each treating investigator must have performed at least 20 thrombectomy procedures using ADAPT, of which at least 2 cases are with the EMBOVAC™ device.
- Experience in conducting clinical studies.
- Currently treating subjects who meet the inclusion / exclusion criteria.
- Ability to enroll an adequate number of subjects.
- Ability to perform required clinical testing, including: angiography, CT, and/or MRI.
- Ability and willingness to provide the sponsor's representatives and local regulatory authorities access to the hospital records, study files, and subject files as they pertain to the study.
- Willingness to participate, including compliance with all aspects of the study.

Adequate staffing to conduct the study includes:

- Principal Investigator (PI): Responsible for overall clinical management of subjects enrolled at his/her institution. Assumes overall responsibility and accountability for the clinical team and for data obtained from each subject participating in the study. Ensures compliance with the protocol, applicable laws, and applicable regulations; ensures informed consents are signed, and reviews and signs electronic case report forms eCRFs indicating documents are accurate and complete.
- Sub-Investigator (Sub-I): Any individual member of the clinical trial team designated and supervised by the investigator to perform clinical trial-related procedures and/or make important trial-related decisions. A site is not required to have a Sub-I.
- Study Coordinator: Assists PI with study activities as delegated by the PI, including tracking subjects involved in the study, scheduling testing and follow-up visits, maintaining study records, completing eCRFs to the sponsor in a timely manner. A site is not required to have a Study Coordinator but must have an individual other than the PI dedicated to support the study.

To best capture real-world experience with the EMBOVAC™ Aspiration Catheter, the Sponsor will attempt to include a diversified group of investigational sites by engaging with a variety of institutions. To ensure generalizability of results, sites will be geographically distributed throughout Europe so that multiple countries are represented. Influence from any one site will be minimized by limiting maximum enrollment per site to 20 percent of overall study enrollment or approximately 20 subjects.

### 4.4 Participant Withdrawal or Termination

#### 4.4.1 Reasons for Withdrawal or Termination

Subjects are free to withdraw from participation in the study at any time upon request. The investigator may terminate participation in the study if any adverse event or other medical condition or situation occurs such that continued participation would not be in the best interest of the participant.

#### 4.4.2 Handling of Participant Withdrawals or Termination

Subjects that withdraw consent after treatment are not required to undergo follow-up after withdrawal. They will not be replaced and will be considered part of the subject cohort. The reason for early withdrawal will be documented in the source documents and case report forms.

In the event a subject withdraws from the study, their data will be excluded from the data analysis from the time of withdrawal going forward and any remaining clot sample from that subject will be discarded by the Clot analysis lab if no longer needed for study purposes (i.e., will not be stored for future research purposes). All data collected prior to withdrawal will be included in for data analysis, as permitted per country regulations.

## 5. Study Device

### 5.1 Study Device Description

#### 5.1.1 Device Acquisition

The EMBOVAC™ Aspiration Catheter is CE Marked. As a result, shipments will not be tracked for this study, devices will be fully traceable though the company's 21 CFR 820 and ISO 13485 compliant quality system.

### 5.1.2 Device Returns

Any suspected device malfunction with the EMBOVAC™ Aspiration Catheter should be properly documented on the Electronic Case Report Forms (eCRFs). In the event of a suspected malfunction, the device should be returned to Cerenovus for analysis. Site will retain tracking information. All study devices should be returned to:

[redacted]

## 6. Study Procedures and Evaluations

The medical devices used and all treatment related activities (i.e. the tests and procedures) carried out during this study are in line with Good Clinical Practice and are conducted per standard operating policies at the treating hospital (study site). The conduct of this study does not affect the hospitals standard operating policies and does not impact the patient's standard of care.

Study-related activities exclusively consists of the structured collection and evaluation of data; this includes the patient angiographic imaging and analysis of blood clots retrieved from the patient during the procedure. This data (as outlined in the informed consent form) will only be shared with the Sponsor if a signed informed consent is obtained from the study subject or their legal authorized representative.

### 6.1. Study Specific Procedures

The procedures completed as part of this study are in line with SOC and include relevant medical history, relevant medication history, NIHSS, mRS, imaging (CT/MRI), procedural angiography and review of any reportable AEs. Patients presenting with acute ischemic stroke should be evaluated by the physician, in accordance with their institutional practice, to establish an appropriate treatment plan based on the subject's medical condition and available diagnostic screening procedures prior to enrollment in the study.

Clot samples will be collected on a per pass basis and shipped by the site to the Clot analysis lab for follow on analysis.

### 6.1.1. Imaging

In this study, revascularization will be measured by an independent adjudicating Imaging Core Lab and reported using the eTICI (inclusive of the 2C rating) scale [19]. For purposes of data comparisons, a minimum threshold of mTICI 2b is equal to eTICI 2b50.

**Table 3 eTICI Scale**

| | |
|---|---|
| 0 | No reperfusion; 0% filling of the downstream territory, |
| 1 | Thrombus reduction without any reperfusion of distal arteries |
| 2 | • 2a Reperfusion in less than half (1-49%) of the territory<br>• 2b50 Reperfusion in (50-66%) of downstream territory<br>• 2b67 Reperfusion in (67-89%) of downstream territory<br>• 2c Reperfusion in (90-99%) of downstream territory |
| 3 | Complete or 100% reperfusion |

All imaging should be in line with SOC. This includes CT or MR at baseline and 24 hours post procedure to assess any presence of hemorrhage, recanalization of the occluded artery, reperfusion, and infarct growth. Angiographic images obtained during the study should consist of (1) Baseline angiogram - prior to device advancement to assess clot location, (2) Post device angiogram - after each reperfusion attempt/pass of the device (a pass being defined as use of aspiration followed by evaluation of revascularization with angiography), (3) Final Angiogram – after all treatment has been completed. Any other imaging of the head or neck performed per SOC (for example as a result of clinical deterioration) must also be provided.

### 6.1.2. Independent Imaging Core Lab for Image Evaluation

All imaging collected will be SOC, no additional imaging will be requested for this study. An independent Imaging Core Lab will be utilized to provide an unbiased and standardized assessment of all collected imaging. All subject PHI will be removed before an image is uploaded and evaluated by the Imaging Core Lab.

The objective of the Imaging Core Lab will be to:

- Review all angiograms obtained
- Provide an unbiased assessment of the rate of revascularization defined by mTICI score based on angiographic imaging from the study sites
- Evaluate CT/MRI examinations to detect and assess hemorrhages.

This study will be collecting the following imaging data to be assessed by Imaging Core Lab:

Baseline - CT/ MR imaging

- ASPECTS (Alberta Stroke program early CT score)
- Infarct volume
- Clot location
- Clot length
- Clot density
- Clot enhancement

Procedural Angiography

- eTICI score for every pass
- Emboli to new territories
- Collateral score

Post Procedure - CT/ MR imaging

- Infarct volume
- Intracranial Hemorrhage

Hemorrhages will be classified according to the following categories [18]:

- HI 1 – Scattered small petechiae, no mass effect
- HI 2 – Confluent petechiae, no mass effect
- PH1 – Hematoma within infarcted tissue, occupying <30%, no substantive mass effect
- PH2 – Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect
- RIH – Parenchymal hematoma remote from infarcted brain tissue
- IVH – Intraventricular Hemorrhage
- SAH – Subarachnoid Hemorrhage
- SDH – Sub Dural Hemorrhage

The Imaging Core Lab assessor will be blinded to subjects' chart/clinical records. Each angiogram will be read independently by an experienced Imaging Core Lab Neurology reviewer.

### 6.1.3. Procedural Angiogram Shipment

A copy of the angiograms collected during the study will be submitted to the independent Imaging Core Lab electronically via batch upload through the Imaging Core Lab website or through shipping pseudonymized imaging discs. All personally identifying information (e.g., name, date of birth, etc.) will be removed from images.

### 6.1.4. Clot Collection and Processing

Normally, following thrombectomy, the retrieved clot may be discarded, sent to internal departments, or retained for other purposes. However, for subjects in this study, clot samples will be collected for follow-on analysis.

Sites collecting clot for analysis will place the clot collected for each pass in a container of neutral buffered formalin solution for preservation. If more than one clot fragment is retrieved during a retrieval attempt/pass with the device, these fragments will be placed together in one container. Each container will have a unique subject identifier noting the retrieval attempt/pass number on the label. This unique identifier will be entered in the eCRF by the site along with other relevant data and linked to subject ID. Samples will subsequently be shipped by the site to the Central Lab for follow on analysis (Section 6.1.5).

All materials for collecting, processing and shipping samples to the Central Labs will be provided by the Sponsor or the Sponsor's selected vendor. For additional details on sample processing refer to Clot Collection and Processing Manual provided by Cerenovus.

### 6.1.5. Independent Central Lab for Clot Evaluation

Clot materials collected for this study will be processed by an independent Clot analysis lab. Standardized procedures and techniques have been established by the Core Lab for the analysis of AIS clots. These techniques comprise of morphological, histological and immunohistochemistry testing, which will help in defining clot features and in clot compositional analysis for this study.

These samples will be securely stored by the independent core lab in a study specific storage cabinet at the lab.

Samples will be sent to the core lab by the hospital in a vial with a generated "vial accession number". This number will be generated by the site and will contain no patient information. The clots will be stored in containers containing this number for identification for research purposes.

The purpose of collecting and analyzing these clots is to determine the composition of different clot types to better understand the etiology of stroke and clot types successfully removed by direct aspiration.

The following parameters of the clot will be measured/analyzed:

- Histology of the retrieved clot (including the red blood cell and fibrin content) will be measured using MSB (Martius Scarlett Blue) stain and H&E (Hematoxylin and Eosin) stain
- Immunohistochemistry to determine Platelets and Von Willebrand Factor
- Geometry of clot by measuring total weight and clot area

Additionally, samples may be tested for the presence of novel biomarkers that are associated with difficult clot retrieval by mechanical thrombectomy. Any remaining clot material will be retained and may be used in further scientific testing associated with the PERFECT study.

The Clot analysis lab will not have access to the subjects' chart/clinical records.

### 6.1.6. Neurological Evaluations

The following neurological evaluations will be used in this study and are part of SOC:

**NIHSS Score** - The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a subject's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

**The modified Rankin Scale (mRS)** - The mRS is a scale commonly used to measure the degree of disability or dependence in the daily activities in subjects following stroke or other neurologic event and is conducted by a qualified evaluator. It is a scale with seven categories ranging from no symptoms to severe disability and death. Qualifications of evaluator training will be documented for this study.

## 7. Study Schedule

### 7.1. Pre-Screening / Screening

Subjects presenting with AIS to enrolling medical treatment facilities will be evaluated and treated by the physician according to the institutional practice prior to enrollment in the study. All assessment and imaging performed for this study are part of SOC for stroke treatment. Informed consent is mandatory and must be obtained before any data is captured in the eCRF.

A subject can be consented to participate in this study from the point of imaging confirming a large vessel occlusion up to 45 days post-procedure. During the eligibility screening, the investigator or designee will perform an initial evaluation of potential study subjects according to the inclusion/exclusion criteria. Post-procedure, the eligibility criterion to be confirmed will be the requirement for the EMBOVAC$^{TM}$ aspiration catheter and ADAPT to be attempted to be used in the first 3 passes, if required, unless evolution of care is required to remove a clot in a distal vessel of <2mm in diameter, and confirmation that all assessments were in alignment with the schedule of assessments (See Table 1 Schedule of Assessments).

For subjects in whom consent in sought, the investigator, or designee, will explain the research study to the subject and answer any questions that may arise. The possible risks and possible benefits of participation will be discussed. The subject will be asked to read, review and sign the EC approved informed consent form. The informed consent process is detailed further in Section 11.3.

All subjects screened will be documented on the Screening/Enrolment log, including the reason for non-participation for subjects who do not enroll.

If for any reason the subject does not meet the eligibility criteria when assessed by the investigator for inclusion in the study, the subject will not be considered enrolled in this study or be followed per this clinical protocol.

All subjects who provide informed consent will be entered into eCRF regardless of whether or not they participate in the study.

## 7.2. Baseline

The following baseline data will be collected and entered into the eCRF by the site:

- **Demographics** will be collected from a review of the subject's medical records to include age, gender, ethnicity etc. unless prohibited by local regulations (e.g., France)
- **Relevant medical history** will be collected from a subject interview and a review of the subject's medical records to include blood pressure, height, weight, BMI, History of smoking and diabetes etc.
- **Relevant medication history** will be collected from a subject interview and a review of the subject's medical records if necessary. Specifically, a thrombolytic agent (e.g., tissue plasminogen activator, urokinase, prourokinase) delivered prior to and during the procedure will be the only medication collected.
- CT / MR Imaging
- NIHSS
- Pre-stroke mRS Modified Rankin Scale – must be performed by a qualified evaluator

## 7.3. Procedure

The clinical decision to use the EMBOVAC™ Aspiration Catheter, as well as the revascularization procedure are independent (regardless) of the research. Physicians should follow the most current EMBOVAC™ Aspiration Catheter Instructions for Use (IFU) at all times with regards to the device compatibility, preparation and the recommended retrieval procedure. The research procedures are limited to the collection of data. Data will be collected before, during, and after use of the EMBOVAC™ Aspiration Catheter.

During the procedure, the following data will be collected:

- Total number of passes: A pass is defined as use of aspiration followed by evaluation of revascularization with angiography.
- Procedural angiography – The following will be recorded by the clinical site:
  - mTICI score per each attempted pass
  - Procedure Time defined as time from arterial puncture to complete recanalization (first mTICI ≥ 2b)
- Thrombectomy techniques and devices utilized per pass
- Additional interventions performed (if applicable)
- Record any reportable AEs per this protocol which occur during the procedure and up to the time of the 24hour examination.
- Clot collection per pass: this study aims to collect the clot from all subjects enrolled. However, in consideration of the urgent nature of stroke treatment, if the clot cannot be collected in a study procedure, it will not be considered a protocol deviation.

Once subject eligibility has been confirmed, the subject can be enrolled in the study.

**A subject is considered enrolled in this study once the physician confirms the subject meets all eligibility criteria and the subject or their legal representative has provided informed consent.**

A subject will not meet inclusion criteria and must not be enrolled if the EMBOVAC™ Aspiration Catheter is not used for the first 3 clot removal passes for the target intracranial occlusion (unless use of another device is needed to remove clot in a distal vessel <2mm in diameter).

## 7.4. 24 Hours Post Procedure (±12hours)

The 24-hour follow-up visit includes

- NIHSS examination
- CT or MRI imaging
- Record any reportable AEs and device related SAEs which occur after the procedure and up to the time of the 24hour examination.

### 7.5. Discharge or 7 days (whichever occurs first) (-1/+7 days)

- NIHSS examination (optional)
- mRS evaluation (optional)
- Record any reportable AEs per this protocol which occurred after the 24hour time examination and up to the time of the discharge or 7-day examination.

### 7.6. 90 Day (±14 Days) Follow-up

- NIHSS (optional - to be collected only if performed per SOC)
- An mRS assessment must be conducted. This mRS assessment **must be performed by a qualified evaluator who is independent of the interventional treating team and the subject's direct clinical care (e.g., neurologist, CRNC).**
- Record any reportable AEs per this protocol which occurred after 7 day / discharge time point and up to the time of the 90-day examination.

Any study subject who does not attend a scheduled follow-up visit should be contacted by site personnel to determine the reason for the missed appointment and rescheduled. The 90-day assessments may be done via telephone (reportable AEs, mRS).

### 7.7. Unscheduled Visit

Subjects returning for an unscheduled visit to the study center that is related to the stroke treatment recorded in the study or indicating new or unresolved signs and/or symptoms will be documented as an unscheduled follow-up. Assessments should be completed from the time of discharge up to (but not including) the 90-day follow-up, where imaging or NIHSS or mRS may be performed as part of stroke management care for the subject. Corresponding data to be collected includes those listed below. Any imaging performed as SOC for unscheduled visit will be documented and sent to the Core Lab.

- NIHSS examination
- mRS
- Any imaging (CT, MRI, DSA, etc)
- Review of SAEs

### 7.8. Early Termination

During the study, it is possible that subjects will be withdrawn from the study. Factors leading to subject early termination may include, but are not limited to the following:

- Subject withdraws consent prior to study completion of all study follow up requirements
- The Investigator decides to discontinue subject's or site's participation in the study
- The subject is lost to follow-up
- Death
- The study is terminated at a site or as a whole

The study can be discontinued at the discretion of the investigator or study Sponsor for reasons including, but not limited to, the following:

- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of subjects
- Persistent non-compliance of a site with the protocol, or EC regulatory requirements

If the study is discontinued or suspended prematurely at a single clinical site (e.g. due to non-compliance or lack of enrollment), the Sponsor shall inform the clinical investigator/investigational center of the termination or suspension in enrollment and the reason for this. The Sponsor will also inform site personnel that although enrollment will be halted, the currently enrolled subjects will continue to be followed per protocol through the 90-day follow-up visit and then be exited from the study. The Sponsor's communication to the investigator/investigational center will also include instructions for the investigator to promptly inform the EC regarding the change in study status, along with the reason for termination or suspension by the Sponsor.

If the entire study is discontinued or suspended prematurely, the Sponsor shall promptly inform all clinical investigators/investigational centers of the termination or suspension in enrollment and the reason for this.

## 7.9. Lost to Follow-up

If a subject fails to return for the follow-up visit at 90 days, the subject will be contacted at their last known telephone number. When all reasonable attempts to locate the subject have been exhausted including contacting the subject's general practitioner, the subject will be considered lost to follow-up and their data will be excluded from the data analysis from the time of last contact onward. A subject will not be considered lost to follow-up prior to the 90 day visit. All data collected prior to last contact will be included in for data analysis, as permitted per country regulations.

To prevent and/or reduce loss to follow-up the following measures will be implemented for this study:

- The Informed Consent will provide a clear explanation of the expected duration of the subject's participation in the study and a description of the study follow-up requirements to ensure subjects understand and agree to the study requirements.

- At the time each subject is enrolled in the study, sites will obtain contact information for the subject.
- Site personnel will be encouraged to question the subject about any difficulties with adhering to the study schedule. If underlying conditions are identified, the site will make reasonable efforts to address these conditions on a case by case basis and this may require site arrangements or schedule adjustments to allow the subject to continue study participation.
- For each missed or overdue follow-up visit, site personnel will document the reason for the missed or overdue follow-up visit in the subject's medical record or office chart.
- Site personnel re-training will be conducted by Cerenovus or their representatives, when needed, to reinforce the follow-up visit requirements and the necessity of adhering to the protocol's follow-up schedule.

### 7.10. Study Design

A subject can be enrolled in this study from angiographic confirmation of an LVO up to 45 days post procedure. Assessments and imaging performed for this study are part of standard of care (SOC) for stroke treatment. Informed consent is mandatory and must be obtained before any data is captured in the electronic Case Report Form (eCRF).

A schematic of the study design may be found in *Figure 1 Schematic of Study Design* and *Table 1 Schedule of Assessments.*

## 8. Assessment of Safety

For purposes of obtaining long-term safety surveillance in this study, **AEs will be reported and recorded (via eCRF) if any of the following apply:**

- The event is neurological in nature
- The event is a serious adverse event (SAE)
- Causality is related to:
    - The device
    - The procedure

## 8.1. Specific Safety Parameters

### 8.1.1. Adverse Event (AE)

An adverse event (AE) is defined as 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 device and whether anticipated or unanticipated (ISO 14155:2020).

- Note 1: This definition includes events related to the investigational medical device or the comparator
- Note 2: This definition includes events related to the procedures involved
- Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Any medical condition that is present at the time the participant is screened or prior to the start of the study procedure will be considered as baseline. Such conditions should be added to medical history, if not previously reported.

### 8.1.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined (ISO 14155:2020) as an adverse event that led to any of the following:

- Death
- Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function including chronic diseases, or
  - in-patient 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
- Fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment

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

### 8.1.3. Adverse Device Effect (ADE)

An adverse device effect is defined as an adverse event related to the use of an investigational medical device (ISO 14155:2020).

- Note 1: 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
- Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device
- Note 3: This includes 'comparator' if the comparator is a medical device.

### 8.1.4. Serious Adverse Device Effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of an SAE (ISO 14155:2020).

### 8.1.5. Unanticipated Serious Adverse Device Effect (USADE)

Per ISO 14155:2020, an unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

- Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

### 8.1.6. Device Deficiency, Device Malfunction, and Use Error

All study device deficiencies shall be documented in the eCRF throughout the clinical investigation and appropriately managed by the Sponsor.

A **device deficiency** is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance (ISO 14155:2020).

- Note 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.
- Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

If a study device deficiency is detected or suspected that could have led to a SADE, it must be documented on the appropriate eCRF, and the device failure must be reported to the Sponsor within 72 hours upon study site staff awareness. All non-study device malfunctions should be reported via the manufacturer's complaints handling process.

Device deficiencies that did not lead to an adverse event but could have led to a serious adverse device effect:

- if either suitable action had not been taken,
- if intervention had not been made, or
- if circumstances had been less fortunate,

shall be reported as specified in Section 8.2.5. Where applicable, the analysis of used or explanted investigational devices shall be included as supportive information.

**Device malfunction** is defined as a failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan (ISO 14155:2020).

**Use error** is defined as user action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user.

- Note 1: Use error includes the inability of the user to complete a task
- Note 2: Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment
- Note 3: Users might be aware or unaware that a use error has occurred
- Note 4: An unexpected physiological response of the patient is not by itself considered a use error
- Note 5: A malfunction of a medical device that causes an unexpected result is not considered a use error (ISO 14155:2020)

## 8.2. Classification of an Adverse Event

### 8.2.1. Severity of Event

The intensity or severity of each AE must be assessed according to the following classifications:

**Table 4 Intensity or Severity Definitions**

| | |
|---|---|
| **Mild** | Awareness of signs, symptoms, or events that are otherwise easily tolerated that may result in minimal transient impairment of a body function or damage to a body structure, but do not require intervention other than monitoring. |
| **Moderate** | Any event that results in moderate transient impairment of a body function or damage to a body structure that causes interference with usual activities, or that warrants possible intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure. |
| **Severe** | Any event that is incapacitating (an inability to do usual activities) or is life-threatening and results in permanent impairment of a body function or damage to a body structure, or requires intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure. |

### 8.2.2. Relationship to Study Device

The clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

**Table 5 Adverse Event Causality Classifications**

| Caused By | Relation | Definition of Relation |
|---|---|---|
| **Device** | Causal relationship | The event is associated with the investigational device beyond reasonable doubt |
| | Probable | The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained |
| | Possible | The relationship with the use of the investigational device is weak but cannot be ruled out completely |
| | Not related | Relationship to the investigational device can be excluded |
| **Study Procedure** | Causal relationship | The event is associated with the study procedure beyond reasonable doubt |
| | Probable | The relationship with the study procedure seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained |
| | Possible | The relationship with the study procedure is weak but cannot be ruled out completely |
| | Not related | Relationship to the study procedure can be excluded |

### 8.2.3. Outcome

The outcome of each AE must be assessed according to the following classifications:

**Table 6 Adverse Event Outcome Classifications**

| Classification | Definition |
|---|---|
| **Recovered/Resolved** | Subject fully recovered with no observable residual effects |
| **Recovering/Resolving** | Subject's condition is improving, but residual effects remain |
| **Recovered/Resolved with sequelae** | Subject recovered with observable residual effects |
| **Not Recovered/Not Resolved** | AE is ongoing without improvement in the overall condition |
| **Fatal** | Subject died as a result of the AE (whether or not the AE is related to the device or procedure) |
| **Unknown** | AE outcome is unknown (e.g., subject is lost to follow-up) |

### 8.2.4. Time Period and Frequency for Adverse Event Assessment and Follow-up

Adverse events shall be assessed and documented for enrolled subjects starting at the point of procedure and at all study follow-up visits.

A subject is considered enrolled, once the physician confirms the subject meets all eligibility criteria and the subject signs the ICF.Adverse events that occur during this study should be treated by established standards of care which will protect the life and safety of the subject. Each investigator shall provide source documentation as requested by the Sponsor to facilitate reporting and adjudication of these events.

### 8.2.5. Adverse Event and Device Deficiency Documentation and Reporting Requirements

Reportable adverse events and device deficiencies will be recorded and reported on the eCRFs throughout the study and provided to the Sponsor. In the event EDC is unavailable, adverse events can be notified via email to the EMBOVAC study mailbox: [redacted]

If an adverse event occurs, all sections of the Adverse Event eCRF must be completed.

In the case of serious device effects and device deficiencies that could have led to serious adverse device effects, the Sponsor will determine whether the risk analysis needs to be updated and whether corrective or preventative action is required.

Copies of all relevant source documentation (i.e. procedure reports, physician/nursing notes, discharge summary, etc.) should be compiled and provided to the Sponsor for the adjudication process for all AEs recorded in the study.

Timing for reporting the different types of adverse events and device deficiencies is described in Table below.

If sites become aware of an AE prior to the subject providing informed consent, the awareness data will be considered the date of consent.

**Table 7 Adverse Event Reporting Requirements**

| Type of Adverse Event | Reporting Requirements |
|---|---|
| • SAE<br>• Any study device deficiency or malfunctions that could have led to a SADE* | Report to Sponsor immediately upon study site staff awareness of event but no later than 72 hours |
| • All other AEs reportable in this study<br>• All other study device deficiencies* | Report to Sponsor immediately upon study site staff awareness but no later than 14 calendar days |

* Non-study device deficiencies should be reported via the manufacturer's complaints handling process.

There are specifics for safety reporting that would be applied for each country, reporting timelines will comply with country regulations. The investigator is responsible for informing the EC of adverse events as required by local reporting requirements. The Sponsor will submit on regular basis (unless otherwise indicated by the EC or recommended by the Sponsor's medical safety officer) to all participating investigators an update of reported events and device deficiencies occurred at the participating study site. The Sponsor will ensure that all events and device deficiencies are reported to the relevant authorities per country specific regulations.

A licensed medical doctor employed by the Sponsor will review all reported adverse events on an ongoing basis. The site reported event term will be reviewed to assess if the event should remain as reported or be re-classified using a term based on the applicable event definition. Recorded AEs will be evaluated by the Sponsor for significance and relevance with respect to trends that may represent a previously unknown or unanticipated risk that may relate to the study device or treatment.

## 9. Clinical Monitoring

The study will be conducted in accordance with GCP, ISO 14155 requirements, local regulations, the signed clinical study contract with the Sponsor, the protocol outlined herein, as well as with the principals of the Declaration of Helsinki. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that study data are accurate, complete, and verifiable, and that study conduct is in compliance with the country regulations, and the currently approved protocol. Each site will undergo

periodic monitoring visits, and subject medical records shall be made available during the visits.

Monitoring visits may include but are not limited to the following:

- Protocol adherence
- Source documentation verification and accuracy of the eCRFs as specified in the monitoring plan
- Verification that informed consent are being obtained for all subjects participating in the study in accordance with requirements described in the study protocol
- Verification of completeness of the Regulatory Binder
- Verification of accuracy of all study logs such as the Delegation of Responsibility Log, etc.
- Compliance with applicable regulations
- Identification and action to resolve any issues or problems with the study.

Data are to be submitted promptly via eCRF after collection. Missing or unclear data will be queried to be corrected as necessary throughout the study. Cerenovus will request further documentation such as physician notes, outside hospital records, etc. when further documentation is required to understand any adverse events. Monitoring will be conducted in accordance with the monitoring plan.

# 10. Statistical Methods

## 10.1. Statistical Methodology

The sponsor will be responsible for the overall analysis of data from this protocol. A separate Statistical Analysis Plan (SAP) will be written and approved prior to the database lock. The SAP will describe all planned analyses based on the statistical design of this study and subsequent data collected. A brief statistical overview of key statistical analyses is provided below.

## 10.2. Analysis Sets

For the analysis of study endpoints, the analysis populations defined in the following will be used:

- Modified Intent-To-Treat (mITT) Population: The mITT population will consist of enrolled subjects who have received treatment (at least one pass) with the study device. The mITT population will be used to analyze the effectiveness endpoints.

- Safety Population (SP): The SP will consist of all enrolled subjects in whom the treatment was attempted, defined by the advancement of the EMBOVAC™ Aspiration Catheter inside of the patient. The SP will be used to analyze safety endpoints.

## 10.3. Levels of Significance

There are no formal hypothesis tests for this study. 95% confidence intervals may be constructed around the mean percentages if not otherwise specified.

## 10.4. Sample Size Justification

There is no statistical power calculation and no hypothesis tests for this post-market study. 100 subjects are deemed sufficient to characterize the performance of EMBOVAC™ Aspiration Catheter.

Approximately 100 subjects will be enrolled. With an enrolled sample size of 100 and an attrition rate of no more than 5%, the precision (margin of error) for the primary endpoint is anticipated to be around 8.0% based on 2-sided 95% confidence intervals, where the primary endpoint rate is estimated to be 80%.

$$Margin\ of\ error \approx 1.96 \times SE = 1.96 \times \sqrt{\frac{p(1-p)}{n}} = 1.96 \times \sqrt{\frac{0.8 \times (1-0.8)}{95}} = 8.0\%$$

where *SE* denotes the standard error and *p* denotes the proportion of subjects who achieve the primary endpoint.

## 10.5. Analyses to be Conducted

### 10.5.1. General Conventions

Standard descriptive summaries for continuous data include the number of subjects and events with non-missing outcome, mean, standard deviation, median, minimum, and maximum values. For categorical data, the count and percentage will be provided. Percentages will be based on the number of subjects without missing data.

### 10.5.2. Disposition of Study Subjects

Subject disposition (e.g. completed, lost-to-follow-up, early termination/withdrawal) as well as analysis populations will be summarized for all enrolled subjects.

### 10.5.3. Demographic, Baseline and Procedural Characteristics

All demographic, baseline characteristics and procedural data will be summarized.

### 10.5.4. Primary and Secondary Endpoint Analyses

#### 10.5.4.1. Primary Endpoint Analysis

The analysis of the performance endpoints will be conducted in the mITT population.

- **Successful revascularization (final mTICI ≥ 2b)**

  The number and percentage of subjects achieving a final mTICI score ≥ 2b, as determined by Imaging Core Lab, will be summarized. Two-sided 95% confidence intervals using the normal approximation method will be constructed around the percentage.

#### 10.5.4.2. Secondary Endpoint Analyses

All secondary effectiveness endpoints will be analyzed in the mITT population; and secondary safety endpoints will be analyzed in the safety population.

##### 10.5.4.2.1. Secondary Effectiveness Endpoints

- **Successful Revascularization (final mTICI ≥ 2b) without rescue therapy, as determined by Core Lab**

  The number and percentage of subjects achieving a final mTICI score ≥ 2b as determined by Imaging Core Lab without use of rescue therapy, will be summarized. Two-sided exact 95% confidence intervals will be constructed around the percentage.

- **Complete revascularization (final mTICI ≥ 2c), as determined by Core Lab**

  The number and percentage of subjects achieving a final mTICI score ≥ 2c, as determined by Imaging Core Lab, will be summarized. Two-sided exact 95% confidence intervals will be constructed around the percentage.

- **First Pass Effect (mTICI ≥ 2c without rescue), as determined by Core Lab**

  The number and percentage of subjects with complete angiographic reperfusion defined as mTICI score of ≥ 2c after first pass with the EMBOVAC™ Aspiration Catheter as determined by Imaging Core Lab without use of rescue therapy, will be summarized. Two-sided exact 95% confidence intervals will be constructed around the percentage.

- **Modified First Pass Effect (mTICI ≥ 2b), as determined by Core Lab**

  The number and percentage of subjects with complete angiographic reperfusion defined as mTICI score of ≥ 2b after first pass with the EMBOVAC™ Aspiration Catheter as determined by Imaging Core Lab, will be summarized. Two-sided exact 95% confidence intervals will be constructed around the percentage.

- **Time to recanalization (Time from arterial puncture to complete recanalization mTICI ≥ 2b), as determined by Core Lab**

  The procedure time from arterial puncture to complete recanalization (achievement of the first mTICI score of at least 2b or greater), as determined by Imaging Core Lab, will be summarized. If a subject was not able to achieve an mTICI score of 2b or greater, the time from arterial puncture to visualization of the final angiogram will be summarized.

- **Modified Rankin Scale (mRS) 0-2 at 90 days**

  The number and percentage of subjects achieving mRS 0-2 at 90 days will be summarized. Subjects with missing mRS scores due to all-cause mortality are considered to have an mRS score of 6 in the analysis, all other data will be summarized using observed data. Two-sided exact 95% confidence intervals will be constructed around the percentage.

**10.5.4.2.2. Secondary Safety Endpoints**

- **Devices related serious adverse events within 90 days of follow up**

  The number and percentage of subjects with device related SAEs will be summarized. The number of events will also be summarized. Device relatedness will be adjudicated by an independent CEC.

- **sICH at 24h post procedure specified according to the Heidelberg Bleeding Classification (HBC)**

  sICH at 24 hours post procedure as specified by HBC will be assessed by an independent CEC. The number and percentage as well as the two-sided 95% confidence intervals around the percentage will be summarized.

- **NIHSS at 24h post procedure**

  The observed NIHSS total score at 24 hours post-procedure and changes from the baseline score will be summarized.

- **90 Day All-Cause Mortality**

  All-cause mortality at 90 days post-procedure will be summarized. Two-sided exact 95% confidence intervals will be constructed around the percentage.

**10.5.5. Health Economic Endpoints**

Hospitalization data will be analyzed using the mITT population:

- **Hospitalization length of stay for index procedure and unscheduled re-hospitalizations**

The mean, median, minimum and maximum duration of hospitalization length of stay will be summarized for subjects who have been treated with study device during index procedure. The number and percentage of subjects with hospitalization length of stay in the 0-1 day, 1-2 days and >2 days categories will be summarized for the index procedure.

- **Healthcare resource utilization for index procedure, post-procedure and re-hospitalizations for unscheduled events**

  The number and proportion of subjects with re-hospitalizations post index procedure, and the number of re-hospitalizations after the index procedure will be summarized for subjects who have been treated with study device.

### 10.5.6. Clot Analysis

Clot data assessed by the independent Clot analysis lab will be summarized using the mITT population.

Composition of clot components to be evaluated includes: Red Blood Cells (RBC), White Blood Cells (WBC), platelets, fibrin and other fibrous proteins. Clot composition along with weight and area data will be summarized per pass and overall.

### 10.5.7. Plans for Interim Analyses

Interim analyses will be conducted for regional (outside Europe, as well as for European MDR) regulatory submission purposes. Only descriptive statistics will be reported. Results of the interim analyses will not be used as a basis for stopping the trial early.

### 10.5.8. Handling of Missing Data

All data will be summarized as observed, no missing data will be imputed in the study unless specified elsewhere.

## 10.6. Measures to Minimize Bias

Cerenovus will be diligent in controlling for bias by utilizing proper study design and implementation of the approved study protocol. EC approval will be obtained at all clinical sites prior to study initiation. Study agreements/contracts will be made with the hospitals/universities and all compensation for conduct of the study will be paid to the hospitals/universities and not to the investigators. Inclusion and exclusion criteria will be implemented to avoid selection bias.

An independent Clinical Events Committee (CEC) will review and adjudicate the safety endpoints, as specified in the CEC charter. CEC members will provide an impartial review and will not hold a financial interest in Cerenovus. An independent core laboratory will perform the angiographic assessments for the primary and secondary effectiveness

endpoints. These evaluations will be performed by an independent reader who does not hold a financial interest in Cerenovus.

Clinical outcomes will be measured in a standardized manner using the National Institutes of Health Stroke Scale, a standardized, objective, clinical assessment tool used to quantify and document the neurological status of patients and to act as a predictor for clinical outcomes. It is used to determine stroke and the severity of stroke.

Clinical outcomes will be measured in a standardized manner using the Modified Rankin Scale, a commonly utilized seven-point scale measuring functional outcome and disability in patients with stroke. The mRS measures independence and dependence related to activities of daily living and can be used over time to determine recovery or regression. In this study, 90 day mRS evaluations will be conducted by an independent evaluator who is not part of the interventional treating team,the patient's direct clinical care or involved in data entry (e.g., neurologist CRNC).
An independent CEC will review and adjudicate safety endpoints to determine whether they meet protocol-specified criteria. CEC members will provide an impartial and standardized review of these safety events.

An independent Imaging Core Lab will perform the angiographic assessments for the primary effectiveness endpoint, as well as the secondary effectiveness endpoints that are based on imaging. The Imaging Core Lab will provide an impartial and standardized review of imaging outcomes.

Study monitors will have clinical research experience and be proficient at study monitoring. Study data will be source data verified (SDV) as specified in the monitoring plan using the subject's medical records, study source worksheets, clinic notes, and radiographic reports as applicable as source documentation.

In order to minimize potential bias, subject screening logs will be maintained at the sites. These will document all first-line aspiration mechanical thrombectomies performed at the site. All cases of EMBOVAC™ being used in stroke treatment, will be taken into account for total screening numbers, noting why the potential subject was not enrolled.

# 11. Ethics and Protection of Human Subjects

## 11.1. Ethical Standard

As the Sponsor of this study, Cerenovus has the overall responsibility for the conduct of the study and, is conducted in accordance with GCP, ISO 14155 requirements, local regulations, the signed clinical study contract with Sponsor, the protocol outlined herein, as well as with the principals of the Declaration of Helsinki.

- **General Responsibilities**

Sponsor's general duties consist of assuring that sites have received EC approvals, selecting investigators, ensuring proper clinical site monitoring and ensuring subject informed consent is obtained. Any additional requirements imposed by an EC or regulatory authority shall be followed, if appropriate.

- **Data Quality and Reporting**

Sponsor is responsible for providing quality data that satisfy applicable regulations and informing proper authorities of unanticipated adverse effects and deviations from the protocol as applicable.

- **Selection of Investigators**

Sponsor will select qualified investigators, obtain a signed Investigator Agreement and provide the investigators with the information necessary to conduct the study.

- **Supplemental Applications—Protocol Amendments**

As appropriate, Sponsor will submit changes in the study protocol to investigators to obtain EC re-approval. A justification for each amendment will be documented.

- **Maintaining Records**

Sponsor will maintain copies of correspondence, device and procedure related Serious Adverse Events and other records related to the study. Sponsor will maintain records related to the signed Investigator Agreements.

## 11.2. Ethics Committee (EC)

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the EC for review and approval. EC approval of both the protocol and the consent form must be obtained before any participant is consented.

Any amendment to the protocol will require review and approval by the EC before the changes are implemented to the study. Cerenovus and the EC must approve in writing any changes to the protocol that affect the rights safety and/or welfare of the subjects or may adversely affect the validity of the study. All changes to the consent form will be EC approved and a determination will be made regarding whether previously consented participants need to be re-consented.

Investigators are responsible for submitting and obtaining initial and continuing review of the study by their EC.

## 11.3. Informed Consent and Data Release Form Process

### 11.3.1. Consent and Other Informational Documents Provided to Participants

Subject's informed consent must be obtained and documented according to the principles of informed consent. Due to the emergent nature of AIS, consent may be obtained up to 45 days post-procedure, as permitted by the local regulations and EC.

The 45-day window of consent is a mid-point in the patient's follow-up and will prevent study bias for the following reasons:

- Due to the nature of AIS and its treatment, subjects may require several weeks to regain the capacity to provide their consent to be part of the study or to physically sign the informed consent form
- Due to precautionary restrictions at hospitals to prevent the spread of infectious disease, it is not always possible for the treating physician to request the subject's LAR/relative to provide informed consent on the subject's behalf. The 45 day consenting window gives the physicians more chances to connect with subject's relatives

In the event that a subject is not capable of giving their informed consent, all reasonable efforts will be made to obtain informed consent from the subject's LAR (for example, relative or caregiver). This includes cases where the subject dies during the intervention or shortly thereafter, before they can provide their informed consent, or when the severity of the subject's condition prohibits them from providing informed consent. This will vary from case to case, depending on the status / mental state of the patient or if the patient is in life threating condition at the time of screening. In this case, the investigators should follow their standard practice to determine if a patient is able to provide their own consent or whether consent should be obtained from a patient's LAR.

The EC must review and approve an informed consent form (ICF) specific to this study. Cerenovus will provide each study center with an example ICF or data release form. The clinical center, to meet specific EC requirements, may modify this example ICF. The original, subject's ICF must be retained by the investigational site for monitoring, and a copy provided to the subject.

If applicable per local regional requirements, a data release form must be obtained prior to releasing subject information. The EC must review and approve the data release form specific to this study and the written data release form must be signed and dated by the subject prior to participation in this study. The original, signed and dated data release form must be retained by the investigational site for monitoring, and a copy provided to the subject.

### 11.3.2. Consent and Data Release Form Procedures and Documentation

Informed consent is a process that is initiated prior to an individual agreeing to participate in a study and continues throughout the individual's study participation. Discussion of risks and possible benefits of participation will be discussed with the patient and their families as requested prior to enrollment in the study and being considered a subject. The investigator, or designee, will explain the research study to the potential subject and answer any questions that may arise. All patients will receive verbal and written information in language at a level of complexity understandable to the patient about the purpose, procedures, and potential risks of the study and of their rights as research participants. Patients will have ample opportunity to review the informed consent form and to ask questions prior to providing their consent. The patients must be allowed additional time as desired to consider the study prior to agreeing to participate. Prior to participation in the study, the Patient Informed Consent Form will be signed and personally dated by the patient or his/her legal representative. Local regulations may allow for alternative approaches to the written informed consent form, such as witnessed phone consent. The site's alternative approach to obtaining informed consent must be approved by the sponsor and the site's EC/regulatory authority (if applicable) prior to implementation. Approval must be documented in the Investigator Site File.

The subject may withdraw consent at any time throughout the course of the study. The rights and welfare of the participants will be protected, and it will be emphasized to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The completed Patient Informed Consent Form must be collected from each enrolled subject and kept in the study subject files. Subjects will be notified in a timely manner of any significant new information that develops over the course of the study that may affect their willingness to participate.

The informed consent will include an authorization for use and disclosure of the subject's protected health information, in accordance with local regulations. Subject confidentiality will be maintained throughout the clinical study in a way that assures that individual subject data can be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject. Data relating to the study may be made available to third parties, provided the data are treated as confidential and that the subject's privacy is guaranteed.

As applicable per local regional requirements, a data release form may also be required and must be obtained prior to releasing patient information, if required. Similar to consenting procedures, the consent discussion must be conducted in non-technical wording understandable for the patient and the patient must have ample time and opportunity to inquire about further details. Once a patient decides to participate in the study, the written data release form must be signed and dated by both the investigator and the patient. The original, signed and dated data release form must be retained by the investigational site for monitoring, and a copy provided to the subject.

## 11.4. Participant and Data Confidentiality

During this clinical investigation, all representatives of the Sponsor will comply with all in-country privacy laws and regulations regarding contact with subjects, their medical record information, copying of information, and protection of the subject identities.

All information and data sent to Cerenovus concerning subjects or their participation in this clinical investigation will be considered confidential. Only authorized Cerenovus personnel or representatives (including contracted service providers, i.e. Imaging Core Lab, Central Clot Lab, Clinical Research Associate etc.), representatives of regulatory agencies will have access to these confidential files upon request (including, but not limited to, admissions/discharge summaries for hospital admission occurring during a subject's study participation and autopsy reports for deaths occurring during the clinical investigation). All data used in the analysis and reporting of this evaluation will exclude identifiable reference to the subject.

### 11.4.1. Research Use of Stored Human Samples, Specimens and data

Clot samples and related data collected under this protocol may be used to further study the etiology of AIS. Any remaining clot material will be retained and may be used in further scientific testing associated with the study. Access to stored samples and data will be limited to study related personnel, to include Cerenovus appointed vendors and not for other researchers or research groups. Samples will not be used as part of genetic research, and will be used for study related research. This material will not be used outside of the study. Samples and data will be stored using de-identified codes assigned to subjects. Results of the testing will remain the property of Cerenovus.

## 11.5. Future Use of Stored Specimens

With the subject's consent and as approved by local EC, de-identified biological samples will be stored at the Clot analysis lab for future analysis associated with the PERFECT study. These samples could be used for research into the causes of AIS and will be used until the Research and Development testing is complete or the sample is completely used. Samples not completely used will be stored for future use in stroke related research for approximately 15 years.

The samples will only be available for researchers working for or delegated by Cerenovus and not for other researchers or research groups. There will be no transfer of the biological samples to third parties not delegated by Cerenovus.

# 12. Quality Assurance and Quality Control

Quality Control (QC) procedures will be implemented beginning with the data entry system and ongoing QC checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written (Standard Operating Procedures) SOPs, monitors will verify that the clinical study is conducted, and data are generated, documented, and reported in compliance with the protocol, ISO 14155, GCP, and the applicable regulatory requirements. If noncompliance is identified, Sponsor will implement measures to secure compliance.

The investigational site will provide direct access to all study related information, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

# 13. Data Handling and Record Keeping

## 13.1. Data Collection and Management Responsibility

Data collection is the responsibility of the site clinical study staff under the supervision of the investigator. The investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data entered. The Sponsor is responsible for all data management activities. These activities include the development of a database, utilizing validated database software, into which all study data will be entered by the clinical sites. The Sponsor will be responsible for ensuring the overall integrity of the database.

Data protection will abide by regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. Data transfer outside the EU and to the US will be performed under adequate levels of protection and inspired by data transfer modalities at least as protective as the data protection laws within Europe.

### 13.1.1. Electronic Case Report Forms

Electronic CRFs have been developed to capture the information outlined in this study protocol. Data on these eCRFs will be monitored, corrected if necessary, and entered into a validated database. All changes made to the data will be tracked in the electronic audit trail, recording the current value, previous value, reason for change, date timestamp of data entry/change, and the name of the person who changed the data. The investigator will electronically sign all subject eCRFs as verification that the data have been reviewed and correctly reflects source documentation. Data from these eCRFs will be used to provide analysis of this study.

### 13.1.2. Source Documentation

Data entered on to the eCRFs will be obtained from source documentation, such as hospital procedure reports, admission and discharge summaries, and other hospital or physician office/clinic documents. If no standard hospital or clinic document exists to capture information required specifically for this clinical investigation, a source worksheet may be developed to record this information. These source documents will serve as the basis for monitoring subject specific information against the eCRFs.

Electronic subject records will be considered source documents on the condition that the hospital's database is a validated system. If this is not the case, certified electronic record copies will have to be printed and added to the subject's paper file. A print-out of a completed eCRF cannot be used as source documentation.

### 13.1.3. Study Records

Regulations require that investigators maintain information in the subject's medical records, which corroborate data collected on the eCRFs. The Investigator is responsible for maintaining medical and study records for every subject participating in the clinical study (including information maintained electronically such as digital imaging). The Investigator will also maintain ***original*** source documents from which study-related data are derived, which include, but are not limited to:

- Clinic progress notes recording subject's medical history and medications
- Medical charts with operative reports and condition of subject upon discharge
- Medical records regarding device and procedure related Serious Adverse Events, including treatment and clinical outcome
- Results of diagnostic examinations
- Imaging (such as x-rays, MRIs), as well as the report of the radiologist's reading/interpretation of diagnostic imaging
- Shipping records and traceability for clots sent for histopathological analysis
- Notes of phone calls and/or correspondences indicating investigational site's attempts to follow study subjects at the required follow-up visits until subject's participation in the study is complete or terminated
- Records relating to subject death (e.g., death certificate, autopsy report)
- Print-outs of source data generated by technical equipment (e.g., x-rays, MRIs) must be filed with the subject's records.

Only authorized Cerenovus personnel or representatives, authorized site personnel, and local government authorities, will have access to these confidential files.

### 13.1.4. Health Economic Data

Subject hospitalization information will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. Subject admission and discharge date will be collected for the index procedure. Re-hospitalization data for unscheduled events will include admission and discharge date.

### 13.1.5. Data Reporting

The investigator, or designated individual, is responsible for timely completion of all data from the study via the eCRFs supplied by Cerenovus. The investigator/delegated individual is required to electronically sign the eCRF on the appropriate pages to verify that he/she has reviewed, and attests to the correctness, of the recorded data. Completed eCRFs will be reviewed and monitored at the investigational site by Cerenovus, personnel or designee at regular intervals throughout the study. The investigator and institution must permit inspection of the study files and subject eCRFs by such representatives and/or responsible government agencies.

Investigators are required to prepare and submit accurate and timely reports on this study to the EC and Cerenovus as applicable.

### 13.1.6. Data Verification and Review

Cerenovus will track the amount of missing data and contact sites as appropriate to instruct them on steps to minimize missing data and remain compliant with protocol required assessments. Missing or unclear data will be queried as necessary throughout the study. Cerenovus will request further documentation such as physician and/or radiology reports when complications or malfunctions are observed and reported. Cerenovus will be responsible for auditing the database and confirming the overall integrity of the data.

### 13.1.7. Final Data Analysis

All exported datasets for analyses will undergo a final data review before final database lock. Once all critical data are monitored and locked, the final analyses of clinical investigation data will be performed.

### 13.1.8. Study Record Retention and Archiving

The sponsor and principal investigator shall maintain the clinical investigation documents as required by the applicable regulatory requirement(s). It is the principal investigator responsibility to retain study essential documents and source documentation that support the data collected on the study subjects for at least two years after the final report. They shall take measures to prevent accidental or premature destruction of these documents. The principal investigator or sponsor may transfer custody of records to another person/party and document the transfer at the investigation site or at the sponsor's facility. These documents may be retained for a longer period if required by local laws and/or an agreement with Cerenovus. Prior to disposal of any records, the Investigator should notify

Cerenovus. The investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. Cerenovus must receive written notification of this custodial change.

Each site must maintain a file of all documents and records relating to the conduct of this study that will include but will not be limited to the following documents:

- A copy of the Protocol and each Amendment (if applicable)
- EC Approval(s) for the Protocol, Protocol Amendment(s) and study ICF(s)
- EC approved ICF(s) template,
- EC and Sponsor Correspondence, including Reports
- Clinical Study Contract, fully executed
- Principal Investigator, Sub-investigator(s), site personal Curriculum Vitae
- Protocol Signature Page (s)
- Site Training Records
- Study Personnel Authorization Form (Site Delegation Log)
- Screening and Enrolment Log
- Subject Identification Log (not to be removed from site)
- IFU
- ICFs for each subject enrolled

Only authorized Cerenovus personnel or representatives, authorized site personnel, and local government authorities, will have access to these confidential files.

## 14. Protocol Deviations

The investigator is responsible for ensuring that the clinical investigation is conducted in accordance with the procedures described in the protocol, and any conditions required by the reviewing EC. A protocol deviation is a failure to comply (intentionally or unintentionally) with the requirements of the clinical study as specified in the protocol. Examples of protocol deviations include late visits, missed visits, required follow-up testing not completed, visit out of window, non-adherence to inclusion/exclusion criteria, etc. and shall be reported to the Sponsor through the eCRFs.

Any standard of care assessments performed outside of the protocol requirements prior to consent/enrollment will be considered an eligibility deviation. Deviations will be reviewed and assessed by the Sponsor.

It is the responsibility of the site to use vigilance to identify and report deviations to the Sponsor and EC per guidelines. The study monitors shall verify that the conduct of the study is in compliance with the approved protocol and applicable regulations and shall identify deviations and any issues of noncompliance. Corrective and preventative actions will be implemented promptly as necessary and significant protocol deviations that raise subject safety concerns or indicate repeat noncompliance may be grounds for investigator disqualification.

The investigator is not allowed to deviate from the protocol except under emergency circumstances to protect the rights, safety and well-being of study participants. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the ethics committee. Such deviations shall be documented and reported to the sponsor and ethics committee as soon as possible.

# 15. Data and Publication Policy

Publications and/or presentation of the clinical investigational results will be coordinated between Cerenovus and the clinical investigation author(s). Authorship will be determined prior to development of any manuscript. All information concerning the study device, Sponsor operations, patent application, manufacturing processes, and basic scientific data supplied by the Sponsor to the investigator and not previously published, are considered confidential and remain the sole property of the Sponsor.

# 16. Study Administration

## 16.1. Study Registration

This study will be registered on the clinical trial registries and results data banks including, but not limited to www.ClinicalTrials.gov.

## 16.2. Steering Committee

A Steering Committee of experts with experience in the areas of neurosurgery, neurology or interventional neuroradiology will be appointed for this study. The responsibilities of the Steering Committee include:

- Consultation on study design, protocol development, subject eligibility inquiries, data to be collected, analyses to be performed and provide oversight of the study
- Review of clinical data and statistical analyses, assist in data interpretation and writing
- Provide oversight of the study

# 17. Conflict of Interest

The term “conflict of interest” refers to situations in which financial or other personal considerations may compromise or have the appearance of compromising a researcher's professional judgment in conducting or reporting research. Cerenovus will make every effort to safeguard against conflicts of interest to assure the integrity of the data, subject safety and investigator objectivity.

## References


1. Organization, W.H. *Stroke, Cerebrovascular Accident*. [cited 2018 16 April]; Available from: http://www.emro.who.int/health-topics/stroke-cerebrovascular-accident/index.html. Accessed 6 July 2021.
2. Prevention, C.f.D.C.a. *Stroke Facts*. 2017 September 6, 2017 [cited 2018 16 April]; Available from: https://www.cdc.gov/stroke/facts.htm. Accessed 6 July 2021.
3. Hacke, W., et al., *Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke.* N Engl J Med, 2008. **359**(13): p. 1317-29.
4. Rangel-Castilla, L., et al., *Endovascular intracranial treatment of acute ischemic strokes.* J Cardiovasc Surg (Torino), 2016. **57**(1): p. 36-47.
5. Powers, W.J., et al., *2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association.* Stroke, 2015. **46**(10): p. 3020-35.
6. Saver, J.L., et al., *Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke.* N Engl J Med, 2015. **372**(24): p. 2285-95.
7. Goyal, M., et al., *Randomized assessment of rapid endovascular treatment of ischemic stroke.* N Engl J Med, 2015. **372**(11): p. 1019-30.
8. Campbell, B.C., et al., *Endovascular therapy for ischemic stroke with perfusion-imaging selection.* N Engl J Med, 2015. **372**(11): p. 1009-18.
9. Berkhemer, O.A., et al., *A randomized trial of intraarterial treatment for acute ischemic stroke.* N Engl J Med, 2015. **372**(1): p. 11-20.
10. Mocco, J., et al., *Aspiration Thrombectomy After Intravenous Alteplase Versus Intravenous Alteplase Alone.* Stroke, 2016. **47**(9): p. 2331-8.
11. Powers, W.J., et al., *2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association.* Stroke, 2018. **49**(3): p. e46-e110.
12. Gory, B., et al., *A direct aspiration first pass technique for acute stroke therapy: a systematic review and meta-analysis.* Eur J Neurol, 2018. **25**(2): p. 284-292.
13. Phan, K., et al., *A Direct Aspiration First Pass Technique vs Standard Endovascular Therapy for Acute Stroke: A Systematic Review and Meta-Analysis.* Neurosurgery, 2018. **83**(1): p. 19-28.
14. Lapergue, B., et al., *Effect of Endovascular Contact Aspiration vs Stent Retriever on Revascularization in Patients With Acute Ischemic Stroke and Large Vessel Occlusion: The ASTER Randomized Clinical Trial.* Jama, 2017. **318**(5): p. 443-452.
15. Nogueira, R.G., et al., *Safety and Efficacy of a 3-Dimensional Stent Retriever With Aspiration-Based Thrombectomy vs Aspiration-Based Thrombectomy Alone in Acute Ischemic Stroke Intervention: A Randomized Clinical Trial.* JAMA Neurol, 2018. **75**(3): p. 304-311.
16. Turk, A.S., et al., *Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion (COMPASS): a multicentre, randomised, open label, blinded outcome, non-inferiority trial.* The Lancet, 2019. **393**(10175): p. 998-1008.

17. Mokin, M., et al., *Indications for thrombectomy in acute ischemic stroke from emergent large vessel occlusion (ELVO): report of the SNIS Standards and Guidelines Committee.* J Neurointerv Surg, 2019. **11**(3): p. 215-220.
18. von Kummer, R., et al., *The Heidelberg Bleeding Classification: Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy.* Stroke, 2015. **46**(10): p. 2981-6.
19. Liebeskind DS, Bracard S, Guillemin F, et al. eTICI reperfusion: defining success in endovascular stroke therapy. J Neurointervent Surg, 2019; 11:433-438