STUDY PROTOCOL

A PROSPECTIVE, MULTI-CENTER, SINGLE ARM STUDY TO OBTAIN "REAL WORLD" CLINICAL DATA AND CHARACTERIZE THE ACUTE AND LONG-TERM PERFORMANCE OF THE MICRUSFRAME AND GALAXY COILS INCLUDING THE PULSERIDER ANEURYSM NECK RECONSTRUCTION DEVICE FOR THE ENDOVASCULAR TREATMENT OF INTRACRANIAL ANEURYSMS

STERLING REGISTRY

Protocol Number: CNV_2017_01

Version: 4.0

August 10, 2021

History of Changes

Version Date	Description
Version 1.0— 13APR2018	Original Document
Version 2.0- 10JUL2019	Amendment 1
Version 3.0 – 28APR2020	Amendment 2
Version 4.0 – 10AUG2021	Amendment 3

Sponsor: Cerenovus
31 Technology Dr.
Irvine, CA 92618 USA

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List of Figures and Tables

LIST OF ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CTA	Computed Tomography Angiography
DAPT	Dual Anti-Platelet Therapy
DSA	Digital Subtraction Angiography
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	Europe, Middle East, Africa
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HECON	Health Economics
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonization
IFU	Instructions for Use
IRB	Institutional Review Board
ISAT	International Subarachnoid Aneurysm Trial
ISO	International Organization for Standardization
LAR	Legal Authorized Representative
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
PHI	Protected Health Information
PP	Per Protocol
PI	Principal Investigator
SAE	Serious Adverse Event
SAH	Subarachnoid Hemorrhage
SC	Surgical Clipping
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDV	Source Data Verification
SOC	Standard of Care
SOP	Standard Operating Procedure

KEY ROLES AND RESPONSIBILITIES

Sponsor:

Cerenovus
31 Technology Dr.
Irvine, CA 92618 USA
Tel: (888) 783-7723

Contacts:

PPD
Associate Director, PPD
PPD
PPD

PPD
Clinical Research Manager, PPD
PPD

Coordinating Investigators:

Reade De Leacy, MD
PPD
PPD
PPD

Osama Zaidat, MD
PPD
PPD
PPD

Medical/Safety Contact:	PPD , MD Medical Safety Officer, PPD

PROTOCOL AGREEMENT AND STATEMENT OF COMPLIANCE FORM

STUDY NAME AND NUMBER: STERLING Registry (CNV_2017_01)

STUDY TITLE: A Prospective, Multi-Center, Single Arm Study to obtain "real world" clinical data and characterize the acute and long term performance of the MICRUSFRAME and GALAXY coils including the PulseRider Aneurysm Neck Reconstruction Device for the endovascular treatment of intracranial aneurysms.

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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 investigation is conducted in accordance with specific provisions of the associated IRB/IECs, and in accordance with 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 requirement(s), the signed clinical study contract with Sponsor and 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 Institutional Review Board (IRB)/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 IRB/EC.

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report all safety events that meet reporting requirements as defined in the protocol to the Sponsor, and comply with all safety reporting requirements of my reviewing IRB/EC and local regulations. I agree to permit the Sponsor, its authorized representatives, my reviewing IRB/EC, the FDA, 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:	A Prospective, Multi-Center, Single Arm Study to obtain "real world" clinical data and characterize the acute and long-term performance of the MICRUSFRAME and GALAXY coils including the PulseRider Aneurysm Neck Reconstruction device for the endovascular treatment of intracranial aneurysms.
Study Name	STERLING Registry
Study Device:	MICRUSFRAME and GALAXY coils
Indication Under Investigation:	The MICRUSFRAME and GALAXY G3 coils are intended for endovascular embolization of intracranial aneurysms.
Study Sponsor:	Cerenovus 31 Technology Dr. Irvine, CA 92618 USA
Study Objectives:	The objective of this study is to obtain "real world" clinical data and characterize the acute and long-term performance of the MICRUSFRAME and GALAXY coils for the endovascular treatment of intracranial aneurysms. The secondary objective of this study is to evaluate "real world" outcomes with the use of the PulseRider Aneurysm Neck Reconstruction device for the endovascular treatment of intracranial aneurysms.
Study Design:	This is a prospective, multi-center, single arm, registry study in which approximately 850 subjects in the US, EMEA and Japan will be enrolled and treated with the MicrusFrame and/or Galaxy G3 coils, then followed at 180 days, and 1-year post-procedure.
Sample Size:	Approximately 850 subjects will be enrolled into the study.
Number of Sites:	Approximately 60 clinical sites in the US, EMEA and Japan

Study Population: Subjects with intracranial saccular, ruptured or unruptured aneurysms (≤24mm) will be eligible for the study.

Study Procedures: The Study evaluation time points include:

1. Screening/Baseline
2. Procedure
3. Hospital Discharge
4. 180 Day Follow-up
5. 1 Year Follow-up (Clinic Visit)

Primary Endpoint: Adequate Occlusion Rate:

Proportion of subjects who achieve Adequate Occlusion (Modified Raymond-Roy I or II Classification) as assessed by the independent core lab report of the target aneurysm at 12 months without retreatment.

Subgroup analyses will be performed with the following groups: coiling alone, stent-assisted coiling, Pulse-Rider assisted coiling, flow diverter assisted coiling, and intrasaccular flow disruptor assisted coiling.

Secondary Endpoints:

- Packing Density: Packing density is defined as the ratio of the volume of coils to the volume of the coiled part of the aneurysm achieved during the procedure and will be calculated via AngioSuite based on the aneurysm volume and the coils used to treat the target aneurysm. This analysis will be conducted using independent core lab data
- Complete occlusion at 1 year as assessed by the core lab (Modified Raymond-Roy I)
- Recanalization Rate at 1 year: A worsening in aneurysm occlusion grading (using the Modified Raymond-Roy Classification)
- The proportion of subjects with mRS 0-2 at 1 year for subjects with unruptured aneurysms
- Retreatment rate at 1 year: Proportion of subjects with any retreatment (surgical or endovascular) of the target aneurysm up to 12 months post procedure
- Device Related Serious Adverse Events

Additional Endpoints:	• Health Economics- Hospitalizations
	  • Length of stay for study procedure hospitalization
	  • Number of re-hospitalizations related to the target aneurysm
	  • Maximum length of stay for re-hospitalizations

Sample Size Justification:	Approximately 850 subjects will be enrolled into the study at approximately 60 clinical sites from the US, EMEA and Japan. Due to heterogeneity in aneurysm characteristics and treatment (e.g., rupture status, aneurysm location, aneurysm neck-size, adjunctive treatment, etc.), multiple subgroup analyses are planned. A sample size of 850 subjects was selected to ensure there are a sufficient number of subjects to allow for subgroup analyses and to emulate "real world" clinical data to characterize the acute and long term performance of the MICRUSFRAME and GALAXY coils including the PulseRider Aneurysm Neck Reconstruction device for the endovascular treatment of intracranial aneurysms
Statistical Analysis:	There will be no formal hypothesis testing on the endpoint data. The baseline and endpoint data will be summarized with descriptive statistics which include number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables and number of subjects, frequency count, and percentage for categorical variables.
Inclusion Criteria:	1. Patient is between 21 and 80 years of age (inclusive) at the time of consent 2. Patient has an intracranial saccular aneurysm $\leq$ 24 mm in maximal diameter, ruptured or unruptured, and planned embolization procedure includes the use of Cerenovus study coils 3. Written Data Release Form or informed consent is obtained and the patient or Legal Authorized Representative (LAR) signs the Institutional Review Board (IRB)/Ethic Committee

(EC) approved consent along with the HIPAA Authorization for the use and release of PHI or applicable privacy protection

4. Patient or designated Legal Authorized Representative (LAR), confirms the patient has the mental capacity, willingness and ability to comply with protocol and follow-up requirements

Exclusion Criteria:

1. Unstable neurological deficit (condition worsening within the last 90 days)

2. Modified Rankin Score (mRS) ≥ 3

3. Patients with a Hunt and Hess score ≥4

4. Pre-planned staged procedure of the unruptured target aneurysm

5. Pre-planned treatment of the target aneurysm in the study procedure that does not include the use of Cerenovus study coils

6. Women who are pregnant, lactating, or who are of child bearing age and plan on becoming pregnant during the course of the clinical investigation

7. Patient has more than one aneurysm requiring treatment during the course of the study

8. Medical or surgical co-morbidity such that life expectancy is less than 1 year

9. Current involvement 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

10. Vessel anatomy or target aneurysm morphology not suitable for pre-planned treatment strategy

Study Duration: The study duration is expected to be approximately 6 years (including enrollment phase). The enrollment phase is expected to take approximately 5 years following enrollment of the first subject.

Participant Duration: It will take each participant approximately 1 year to complete the protocol required follow-up visits.

Schedule of Assessments

Assessments	Screening/Baseline	Immediately Pre-Procedure	Procedure	Immediately Post-procedure	Discharge	180 Day Follow-up (+3 months)	1 Year Follow-up (-3 months to +6 months)	Unscheduled Visit
Informed Consent	X**							
Medical History	X							
Modified Rankin Scale		X##			O	X	X	O
SOC Imaging		DSA				O	DSA or MRA#*	O
Platelet Reactivity Testing		O						
Hunt and Hess		X^			X^^	X^^	X^^	X^^
Concomitant Medications	X	X	X	X	X	X	X	X
Review of reportable adverse events			X	X	X	X	X	X

X- Required, O – Optional data collection if testing is performed per standard of care

* Due to COVID-19, the 1-year clinic visit may be performed remotely and the 1-year angiogram (DSA, MRA with contrast) may be conducted outside of the protocol specified window up to a maximum of 18 months after the 1 year timepoint

**Informed consent is required prior to the study procedure for patients with unruptured aneurysms and allowed up to 72H post procedure for patients with ruptured aneurysms. Due to COVID-19, patients with ruptured aneurysm are allowed to consent up to 7 days post procedure.

#If MRA, it is strongly recommended to be at high intensity and with contrast

For ruptured aneurysms- immediate pre-procedure mRS refers to the subject's pre-rupture mRS and may be assessed post procedure

^For all patients with ruptured aneurysms

^^For all patients who experience a post-procedure rupture

1. Background Information and Scientific Rationale

1.1. Background Information

An intracranial aneurysm is an abnormal dilation that occurs in an artery as the result of a weakening in the wall of the vessel. This balloon like outpouching fills with blood and may enlarge over time; most commonly this occurs at the junctions or bifurcations of major arteries. As the aneurysm increases in size, the vessel wall becomes thinner and more fragile and is at risk of rupture. Many intracranial aneurysms remain silent and are never diagnosed unless they rupture resulting in a subarachnoid hemorrhage (SAH) or gradually enlarge over time and exert pressure on the surrounding brain tissue resulting in a variety of morbidities. These aneurysms are typically diagnosed because of the associated symptoms e.g. cranial neuropathies, visual disturbances, etc. Asymptomatic, unruptured aneurysms may also be discovered incidentally as a result of some other suspected pathology e.g. migraine headache, dizziness, etc. that requires diagnostic imagining. The most common presentation of an intracranial aneurysm however, is SAH, which is a life-threatening event. Even with prompt medical attention there is a high incidence of morbidity and mortality. Between 40% and 67% of ruptured aneurysms result in death within one month and 10% to 20% of the survivors have major morbidities [Woo 2002]. The primary goal of surgery or endovascular treatment of any aneurysm is to reduce the risk of initial or recurrent subarachnoid hemorrhage by excluding the lesion from the cerebral circulation.

Risk factors for the formation of aneurysms include a family history, various inherited disorders such as polycystic kidney disease, age greater than 50 years, female gender, hypertension, trauma, atherosclerosis, abnormal flow at a vessel bifurcation and current cigarette smoking [Vega 2002]. A strong female predilection has been observed in patients with aneurysms, especially those with multiple aneurysms. There are other rare causes of aneurysms such as infections of the artery wall and drug abuse, especially cocaine, which can cause the artery walls to become inflamed and weakened.

The two most common types of intracranial aneurysms are saccular or berry and fusiform. The saccular aneurysm has a general dilation of one side of the artery and accounts for most of the aneurysms. In contrast, a fusiform aneurysm is a ballooning of the entire circumference of an artery. Saccular aneurysms exhibit a variety of sizes and complex shapes; they are categorized according to neck size, location in a sidewall or at a bifurcation, shape, and the absolute size of the dome.

1.2. Current Options

Depending on aneurysm characteristics (ruptured/non-ruptured, size, shape and location) and subject status (medical history, age, gender) management of intracranial aneurysms remains complex.

Prior to the International Subarachnoid Aneurysm Trial (ISAT), which compared endovascular therapy with coils to surgical clipping, the traditional treatment for aneurysms was open surgery. However, open surgery is highly invasive and requires a significant recovery period even for those who are medically stable and can tolerate the procedure. In many cases, surgery may be contraindicated for patients with co-morbidities.

Following the release of the ISAT data, endovascular coil embolization was established as a viable alternative method for treating intracranial aneurysms [ISAT 2003, Molyneux 2005, Fiorella 2004]. Endovascular coil embolization is associated with fewer adverse outcomes (6.6% versus 13.2%) and decreased mortality (0.9% versus 2.5%) compared with open surgery [Higashida 2007]. Patient selection for either surgery or endovascular coil embolization should include the risks weighed against the probability for adequate aneurysm occlusion. Other key factors to consider are aneurysm location and size, patient comorbidities, and relative contraindications e.g. allergy to contrast media, renal disease, etc. [Johnston 2002].

Although endovascular coiling has been shown to be a safe and effective treatment, recanalization remains a limitation of aneurysm coiling. Some of these same subjects require repeat treatment for aneurysm recurrence (Raymond, 2003; Wakhloo, 2007). Some series regarding mid and long-term clinical outcome and follow up angiographic findings confirm that recanalization may occur in up to 33% of treated subjects, which also tends to increase in the aneurysms with wider necks and larger sizes (Murayama, 2003; Raymond, 2003; Byrne, 1999; Gruber et al., 1999). In wide-necked aneurysms, both surgical and endovascular treatments are difficult to undertake (Zubillaga et al., 1994; Yang and Lawton, 2008, Kato et al., 2003; Guglielmi et al., 1992). Surgical clipping may be difficult or impossible if there is no true aneurysm neck present (Hoh et al., 2001). Endovascular coiling, on the other hand, leads to complete angiographic occlusion in less than 16% of wide-necked (≥ 4 mm diameter) aneurysms (Zubillaga et al., 1994). In order to overcome this problem, adjunctive techniques to aid coil occlusion of wide-necked aneurysms, such as balloon-remodeling and stent-assisted coil occlusion, have been developed. Balloon remodeling, or balloon-assisted coiling, has reportedly been useful in securing placement of the initial coils within wide-necked aneurysms, as a "rescue" method in cases of coil prolapse and to allow for more optimal "packing" of the aneurysm fundus and neck region (Moret et al., 1997).

Another option, geometrically complex aneurysms that pose a technical challenge are sometimes treated with endovascular stent assisted coiling [McDougall 1996, van Rooij 2007]. Use of a single stent involves deploying the stent across a vessel lumen at the neck of the lesion to provide mechanical support and prevent potential coil prolapse into the vessel lumen. Y-stenting, involves placing two stents in the adjacent arteries in a Y configuration [Spiotta 2017]. Additionally, for wide neck bifurcation aneurysms, the PulseRider was specifically designed to treat and provide a bridge across the aneurysm neck and support along the vessel wall in wide-neck bifurcation aneurysms. It supports

embolic agents and may allow more dense packing of the aneurysm while preserving luminal patency and hemodynamic flow, minimizes exposed metal to encourage early device endothelialization.

This registry sponsored by Cerenovus will be a prospective, multi-center, single-arm registry of the MICRUSFRAME and GALAXY coils in the minimally invasive treatment of ruptured/unruptured intracranial aneurysms including those with adjunctive treatment (e.g., balloons, stents, PulseRider).

1.3. Rationale

The MICRUSFRAME and GALAXY coils are intended for the endovascular embolization of intracranial aneurysms. The MICRUSFRAME coil portfolio frames the aneurysm for stability and neck mesh coverage while maintaining an open core for concentric filling. The MICRUSFRAME coil follows a pre-determined shape within the aneurysm while the GALAXY coil portfolio has a complex shape and random loop design, not following a predefined shape. The random loops are created with a proprietary manufacturing process that results in a coil that will pursue a different path each time it is deployed. These characteristics help the coil seek and find open space which could potentially allow for better framing, filling and finishing of aneurysms. The intent of the registry is to collect real world data on the performance of both the MICRUSFRAME and GALAXY coils to characterize the acute and long-term performance of the MICRUSFRAME and GALAXY coils including the PulseRider Aneurysm Neck Reconstruction device for the endovascular treatment of intracranial aneurysms.

1.4. Potential Risks and Benefits

1.4.1. Known Potential Risks

Risks that may be associated with the use of the Cerenovus coils can be found in the commercially available IFUs found with the devices.

1.4.2. Minimization of Risk

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

1. Investigators who participate in the study will be experienced with coil embolization and will have adequate resources to conduct the clinical study.
2. The study has been designed to ensure treatment and follow-up of subjects are consistent with current medical practice.
3. Subject status will be monitored by the investigator or designee throughout the follow-up period as defined in the study protocol.

1.4.3. Known Potential Benefits

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

2. Objectives and Purpose

2.1. Objectives

The objective of this study is to obtain "real world" clinical data and characterize the acute and long-term performance of the MICRUSFRAME and GALAXY coils for the endovascular treatment of intracranial aneurysms.

The secondary objective of this study is to evaluate "real world" outcomes with the use of the PulseRider Aneurysm Neck Reconstruction device for the endovascular treatment of intracranial aneurysms.

3. Study Design and Endpoints

3.1. Description of the Study Design

This study is designed as a prospective, multi-center, single-arm investigation of the MICRUSFRAME and/or GALAXY coils in the treatment of ruptured or unruptured intracranial aneurysms. Approximately 850 subjects will be enrolled and treated with the MICRUSFRAME and/or GALAXY G3 coils at approximately 60 clinical sites across the US, EMEA and Japan.

3.2. Study Endpoints

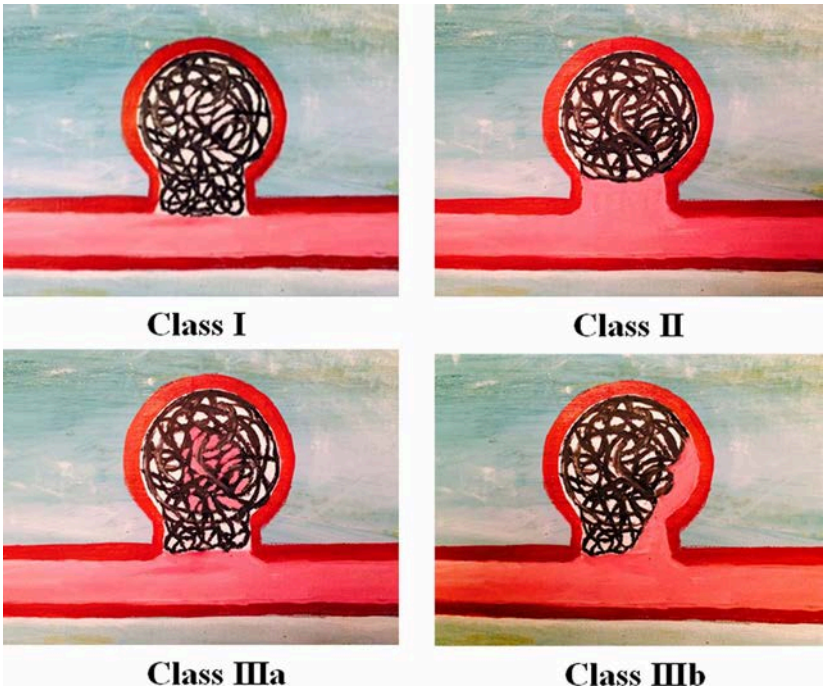
3.2.1. Primary Endpoint

Adequate Occlusion Rate:

Proportion of subjects who achieve Adequate Occlusion (Modified Raymond-Roy I or II Classification) as assessed by the independent core lab report of the target aneurysm at 12 months without retreatment.

Subgroup analyses will be performed with the following groups: coiling alone, stent-assisted coiling, Pulse-Rider assisted coiling, flow diverter assisted coiling and intrasaccular flow disruptor assisted coiling.

Figure 3.2.1A Modified Raymond-Roy Classification (MRRC) [Mascitelli et al. 2014]



- **Class I: Complete** = Complete obliteration
- **Class II: Residual Neck** = Persistence of any portion of the original defect of the arterial wall but without opacification of the aneurysmal sac
- **Class IIIa:** residual aneurysm with contrast within coil interstices
- **Class IIIb:** residual aneurysm with contrast along aneurysm wall

3.2.2. Secondary Endpoints

The secondary endpoints below are to evaluate the effectiveness and safety of the study aneurysm treatment.

- Packing Density: Packing density is defined as the ratio of the volume of coils to the volume of the coiled part of the aneurysm achieved during the procedure. This will be calculated via AngioSuite, based on the aneurysm volume and the coils used to treat the target aneurysm. This analysis will be conducted using independent core lab data

- Complete occlusion at 1 year as assessed by the independent core lab (Modified Raymond-Roy I)
- Recanalization Rate at 1 year: A worsening in aneurysm occlusion grading (using the modified Raymond-Roy Classification Scale)
- The proportion of subjects with mRS 0-2 from baseline at 1 year for subjects with unruptured aneurysms
- Retreatment rate at 1 year: Proportion of subjects with any retreatment (surgical or endovascular) of the target aneurysm up to 12 months post procedure
- Device related Serious Adverse Events

3.2.3. Additional Endpoints

- Health Economics- Hospitalizations
  - Length of stay for study procedure hospitalization
  - Number of re-hospitalizations related to the target aneurysm
    - Maximum length of stay for re-hospitalizations

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. Patient is between 21 and 80 years of age (inclusive) at the time of consent
2. Patient has an intracranial saccular aneurysm ≤ 24 mm in maximal diameter, ruptured or unruptured, and planned embolization procedure includes the use of Cerenovus study coils
3. Written Data Release Form or informed consent is obtained and the patient or Legal Authorized Representative (LAR) signs the Institutional Review Board (IRB)/Ethic Committee (EC) approved consent along with the HIPAA Authorization for the use and release of PHI or applicable privacy protection
4. Patient or designated Legal Authorized Representative (LAR) confirms the patient has the mental capacity, willingness and ability to comply with protocol and follow-up requirements

4.2. Participant Exclusion Criteria

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

1. Unstable neurological deficit (condition worsening within the last 90 days)
2. Modified Rankin Score (mRS) ≥3
3. Patients with a Hunt and Hess score ≥4
4. Pre-planned staged procedure of an unruptured target aneurysm
5. Pre-planned treatment of the target aneurysm in the study procedure does not include the use of Cerenovus study coils
6. Women who are pregnant, lactating, or who are of child bearing age and plan on becoming pregnant during the course of the clinical investigation
7. Patient has more than one aneurysm requiring treatment during the course of the study
8. Medical or surgical co-morbidity such that life expectancy is less than 1 year
9. Current involvement 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
10. Vessel anatomy or target aneurysm morphology not suitable for pre-planned treatment strategy

4.3. Strategies for Recruitment and Retention

The study will enroll approximately 850 subjects across the United States, EMEA and Japan at approximately 60 clinical sites. Once enrolled, each subject will participate in the study for 1-year post-procedure following standard of care and the schedule of assessments outlined in the protocol. Sites are expected to enroll a minimum of 5 subjects with a maximum of 15% of the overall enrollment (128 subjects) per site.

Investigators will be encouraged to evaluate all ruptured and unruptured aneurysm patients for participation in the study, and to offer enrollment to consecutive patients who meet eligibility criteria.

Clinical sites will be selected for participation in the study based on experience with embolic coils, patient population, the capacity to screen and enroll a reasonable number of eligible patients, and the ability to perform the required study procedures, per this protocol. In order to best capture a real-world experience, the Sponsor will attempt to include a diversified group of investigational sites engaging a variety of academic and private institutions geographically located throughout the US, EMEA and Japan. For cases involving the PulseRider device, it is required that the treating physician has previous experience with the implantation of the PulseRider device prior to including these cases in the registry.

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. All data collected prior to withdrawal will be included in the data analysis as allowed per country regulations.

5. Study Device

5.1. Study Device Description

5.1.1. Device Acquisition

The MICRUSFRAME and GALAXY coils are commercially available. The device will be ordered by the sites through standard commercial means. Due to commercial availability, shipments will not be tracked for this registry.

5.1.2. Device Returns

Any suspected device malfunction with the MICRUSFRAME and GALAXY coils 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 if the device was not implanted. Site will retain tracking information. All study devices should be returned to:

ATTN: Cerenovus Complaints

CG Laboratories

1410 Southtown Dr.

Gransbury, TX 76048 USA

6. Study Procedures and Evaluation

6.1. Study Procedures and Evaluations

6.1.1. Study Specific Procedures

All procedures are expected to be standard of care for the sites participating in this study.

6.1.2. Standard Care Procedures

The procedures completed as part of this study are standard practice and include collection of relevant medical history, relevant medication history, mRS, imaging, and if applicable, Hunt and Hess scale for subjects with acute ruptured aneurysms and review of any device related SAEs. This may vary from site to site.

6.1.3. Independent Core Laboratory for Image Evaluation

An independent radiographic core laboratory shall 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. In the event that any PHI remains on the image when it is uploaded from the site, the core lab will ensure PHI is removed prior to assessing the imaging. The core lab assessor will be blinded to subjects' previous medical history. The core lab will evaluate the following for all immediate post-procedure (for ruptured subjects with pre-planned staged procedures, images from part 2 of the staged procedure will be used for analysis) and follow-up imaging:

- Aneurysm occlusion: evaluated per the Modified Raymond– Roy Classification referenced in Figure 3.2.1.

A copy of the angiograms collected during the study will be submitted to the core lab.

6.1.4. Angiogram Shipment

De-identified images may be sent via DICOM format on a CD (that contains the subject ID, study visit, Sponsor name, and protocol number), or electronically to the core lab website, if available.

7. Study Schedule

7.1. Screening

During the initial screening phase, the investigator will perform an initial evaluation of potential study subjects for study eligibility. This initial screening phase may include review of existing patient information (e.g. previously performed angiography, medical history, etc.). For subjects who meet the eligibility criteria and agree to participate, informed consent will be obtained and a written data release form or the informed consent form will be signed per regional requirement. 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. The investigator, or designee, will explain the research study to the patient and answer any questions that may arise. The possible risks and possible benefits of participation will be discussed. The patient will be asked to read, review and

sign the IRB/EC -approved consent form. Informed consent is mandatory and must be obtained from all subjects.

- Subjects with unruptured aneurysms: Informed consent must be obtained prior to participation in the study.
- Subjects with ruptured aneurysms: Due to the emergent nature of acutely ruptured aneurysms, informed consent may be obtained from the point of arrival at the medical treatment facility up to 72 hours after the study procedure. Due to COVID-19, patients with ruptured aneurysm are allowed to consent up to 7 days post procedure. Informed Consent must be obtained before any data is captured in the eCRF.

The informed consent process is detailed further in Section 11.3. Informed consent and/or a written data release form may be signed depending on local regional requirements for sites outside the US.

All patients who provide written informed consent and/or provide a written data release form (per regional requirements) will be entered into EDC regardless of whether or not they participate in the study.

7.2. Enrollment, Baseline Evaluation, and Procedures

7.2.1. Pre-Procedure/Baseline Assessments

The following baseline data will be collected and assessments performed prior to the index procedure.

- **Relevant medical history** will be collected from a subject interview and a review of the subject's medical records with specific attention to neurological deficits/sequelae, bleeding disorders, cardiac conditions that carry a high risk of neurological events, or conditions that may compromise survival or ability to complete follow-up.
- **Relevant medication history** will be collected from a subject interview and a review of the subject's medical records if necessary. Specifically, dual anti-platelet therapy (DAPT) will be the only medication history collected and will be captured within 30 days prior to the index procedure.
- **Hunt and Hess Scale--** The Hunt and Hess Scale is a grading system used to classify the severity of a subarachnoid hemorrhage based on a subject's clinical condition. It is a scale with 5 categories. Will be collected for all patients presenting with a ruptured aneurysm.
- **Modified Rankin Scale – mRS**. The mRS is a scale commonly used to measure the degree of disability or dependence in the daily activities in patients following stroke or other neurologic event and is conducted by qualified personnel. It is a scale with six

categories ranging from no symptoms to severe disability and death. For subjects with ruptured aneurysms, the immediately pre-procedure mRS should reflect the subjects' condition prior to aneurysm rupture and may be assessed post-procedure.

- **Platelet Reactivity Testing-** The platelet function test is used to identify and help diagnose platelet dysfunction in those with a history of excessive bleeding. Where standard of care, conduct the platelet reactivity testing and record the test results in the applicable eCRF.

The schedule of assessments is listed in Table 7.12A. Excluded subjects will undergo routine clinical care for their aneurysm treatment and will be considered a screen failure for the study.

A subject is considered enrolled in this study after the subject is consented and the treating physician confirms the subject continues to meet all eligibility criteria on the day of the study procedure.

7.3. Treatment

The subject should be prepared for the planned interventional procedure according to standard hospital procedures.

Coils: The pre-procedure plan must include at least 75% MICRUSFRAME and GALAXY coils by length. If finishing coils are required, use of GALAXY G3 Mini are recommended. The treatment plan may change during the case and at the physician's discretion to ensure appropriate treatment for the patient.

Staged Procedures:

- Unruptured aneurysms: No pre-planned staged procedures on unruptured target aneurysms will be allowed in the study.
- Ruptured aneurysms: Pre-Planned staged procedures may be performed for ruptured aneurysms at the physician's discretion. In the event of a pre-planned staged procedure, the two procedures will be recorded as part 1 and part 2. The immediately post procedural data will be assessed using the post procedural images from part 2 of the staged procedure. The subject follow-up schedule for subjects undergoing a pre-planned staged procedure for a ruptured aneurysm should start from the date of part 2 of the staged procedure.

Adjunctive devices: Adjunctive devices such as balloon, stents, PulseRider, flow diverters, or intrasaccular flow disruptors may be used in conjunction with the MICRUSFRAME and GALAXY coils as needed. Up to 200 cases with flow diverters and up to 200 cases with intrasaccular flow disruptors used in conjunction with study articles will be allowed. For cases involving the PulseRider device, it is required that the treating physician has previous experience with the implantation of the PulseRider device prior to including these cases in the registry.

Subjects where neither a MICRUSFRAME nor a GALAXY coil is advanced outside of the distal end of the microcatheter inside the subject will only be followed through discharge and then exited from the study.

Peri-procedural heparin will be administered according to the institutional standard of care protocol. Dual anti-platelet therapy will be administered as needed, according to the institutional standard of care.

7.4. Procedure Assessments

Index procedure start/end times will be recorded and the following definitions apply to the index procedure:

- Procedure start time is defined as the point when the guiding catheter is introduced into the subject.
- Procedure end time is defined as the time the last catheter is removed from the subject.

Procedural assessments – pre-treatment, intra-treatment and post-treatment include:

- Procedural medications
- Event assessment
    - Device related Serious Adverse Events
    - Intra-procedural aneurysm ruptures to be reported as AEs
    - Symptomatic Intra-procedural thromboembolic events, along with action taken: Intra-procedural thromboembolic events will be captured as an AE only if symptomatic.
    - Protocol deviations
    - Device malfunctions/deficiency
    - Post-treatment aneurysm occlusion per modified Raymond–Roy classification scale

At a minimum, the following data will also be captured during the procedure:

- Name of the implanting physician
- Aneurysm dimensions - For target aneurysms that have been previously treated, aneurysm measurement will be based on the aneurysm remnant.
- Coils implanted
    - Cerenovus coil lot numbers

- Adjunctive devices used including stents, flow diverters, intrasaccular flow disruptors, balloons, and PulseRider
- Ancillary devices used including the microcatheter
- Microcatheter kick-back- the number of times the microcatheter is re-accessed into the aneurysm during the procedure

The core lab portal should be used to access AngioSuite for the packing density calculation.

Procedural data collected in this study that is not essential to the study endpoints will not be considered a deviation if absent.

7.5. Procedural and Post-Procedural Medications

All anticoagulant and anticoagulation reversal medications that were administered intra-procedurally until the end of the index procedure will be recorded. Post-procedural medication collection will include DAPT, if applicable.

7.6. Post-Procedure Follow-up

The follow-up period begins immediately post-treatment. Site personnel will review the follow-up requirements with the subjects to help ensure compliance with the schedule. Follow up assessments occur at the following timepoints after the index procedure and are listed in Section 7.12:

- At the time of hospital discharge
    - Subjects where a coil is not advanced outside of the distal end of the microcatheter inside the subject will only be followed through discharge and then exited from the study.
- 180 days ($\pm$3 months)
- 1 year (-3 months to +6 months)

The assessments to be completed at each post-procedure follow-up are listed in Section 7.12 and include:

- Modified Rankin Scale – mRS (optional at discharge)
- The 1-year imaging (DSA or MRA) will be used to assess aneurysm occlusion by the investigator and sent to the independent core lab. Any additional imaging performed (DSA, MRA, CTA) per standard of care after the study procedure and prior to the final visit will be sent to the independent core lab.
- Hunt and Hess Scale if acute aneurysm rupture or re-rupture to the target aneurysm occurs post-procedure

- Review of relevant medications
- Review of device related serious adverse events

It is important that the follow-up schedule be adhered as closely as possible for all subjects. Subjects may not be able to return for visits at exactly the date required therefore, a visit window is acceptable and is provided in Section 7.12. Visits not completed within the window will be recorded as protocol deviations. A study visit should be scheduled as close as possible to the earlier side of the visit window to allow for possible re-scheduling thereby minimizing deviations.

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 to reschedule. The reason for the missed visit shall be recorded.

7.6.1. COVID-19

Due to the events of COVID-19, it is understood sites/physicians need to prioritize patient scheduling based on medical necessity. Additionally, subjects may be unable or unwilling to return to the investigation site for completion of the final 1-year follow-up during the mandated COVID-19 restrictions. For this reason, the 1-year clinic visit may be performed remotely and the 1-year angiogram may be conducted outside of the protocol specified window up to a maximum of 18 months after the 1 year timepoint. The completion of the final remote 1-year visit during the COVID-19 restrictions will ensure continued subject safety and completes the collection of clinical data for the study. The final required imaging may occur later than the current protocol window after the COVID-19 mitigations are lifted and investigation sites are able to resume image scheduling, to ensure this important effectiveness imaging data is able to be collected rather than be missing data.

Subjects will be considered exited from the study at the completion of the final imaging. In the event a subject does not return for imaging, that subject will be considered exited at the completion of the 1-year clinic/remote visit.

Additionally during COVID-19, patients who present with a ruptured aneurysm may be consented up to 7 days post procedure.

7.7. Final Study Visit

The final study visit should be done at 1 year (-3 Months to +6 Months) following the coiling procedure. A DSA or MRA should be performed and all other post-procedure assessments will be completed. It is strongly preferred that if an MRA is performed at this timepoint, it is conducted at high intensity and with contrast. Upon exit from the study, the subject will undergo standard follow-up with their doctor and data will not be collected.

7.8. Retreatment

At the discretion of the investigator, a subject may be retreated (e.g. with coils, stent, etc.) at any time. All subjects who are retreated will remain in the study and will continue to receive all follow-up assessments based on the date of the index procedure per the Schedule of Assessments in Section 7.12. Data from the retreatment procedure will be captured in the appropriate eCRF. No pre-planned staged procedures on unruptured target aneurysms will be allowed in the study. Pre-planned staged procedures are not considered as a retreatment for subjects with ruptured aneurysms.

7.9. Early Termination

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 IRB/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 one-year 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 IRB/EC regarding the change in study status, along with the reason for termination or suspension by the Sponsor.

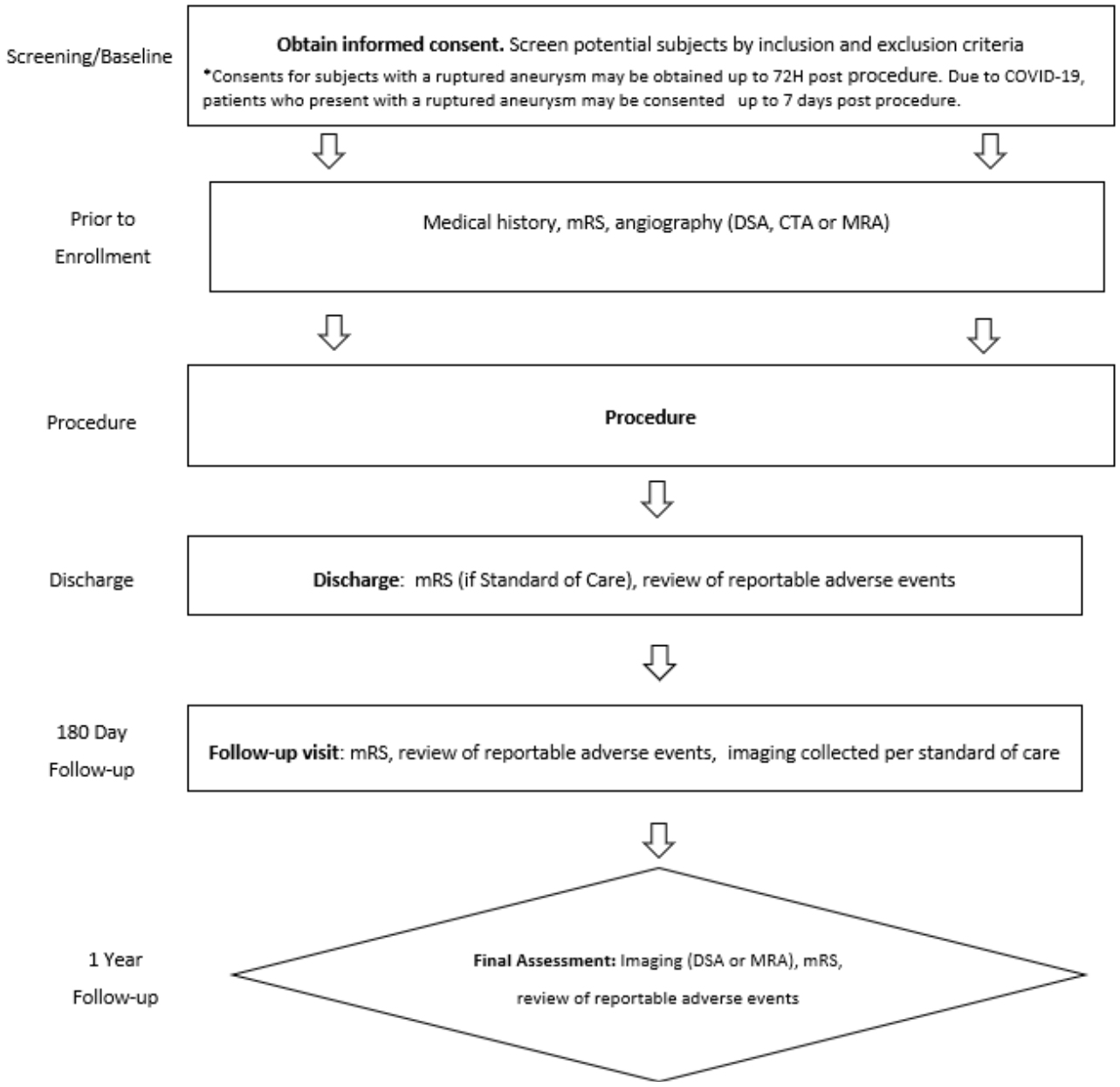
If the entire study is discontinued or suspended prematurely, the Sponsor shall promptly inform all clinical investigators/investigational centers of the termination or suspension in enrollment and the reason for this.

7.10. Lost to Follow-up

Every attempt will be made to have all subjects complete the follow-up visit schedule. A subject will not be considered lost to follow-up until the last study visit and unless efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information will include three attempts to make contact via telephone/email and if unsuccessful, then a letter from the investigator, sent via FedEx or similar traceable method, will be sent to the subject's last known address. Both contact logs and letter contact efforts to obtain follow-up will be recorded in the subject study files.

7.11. Schematic of Study Design – flow chart

Figure 7.11A Schematic of Study Design



7.12. Schedule of Assessments Table

This table provides an overview of the procedures to be performed at each study visit and the visit window.

Table 7.12A Schedule of Assessments

Schedule of Assessments

Assessments	Screening/Baseline	Immediately Pre-Procedure	Procedure	Immediately Post-procedure	Discharge	180 Day Follow-up (±3 months)	1 Year Follow-up (-3 months to +6 months)	Unscheduled Visit
Informed Consent	X**							
Medical History	X							
Modified Rankin Scale		X##			O	X	X	O
SOC Imaging		DSA				O	DSA or MRA#*	O
Platelet Reactivity Testing		O						
Hunt and Hess		X^			X^^	X^^	X^^	X^^
Concomitant Medications	X	X	X	X	X	X	X	X
Review of reportable adverse events			X	X	X	X	X	X

X- Required, O – Optional data collection if testing is performed per standard of care

* Due to COVID-19, the 1-year clinic visit may be performed remotely and the 1-year angiogram (DSA, MRA with contrast) may be conducted outside of the protocol specified window up to a maximum of 18 months after the 1 year timepoint

**Informed consent is required prior to the study procedure for patients with unruptured aneurysms and allowed up to 72H post procedure for patients with ruptured aneurysms. Due to COVID-19, patients with ruptured aneurysm are allowed to consent up to 7 days post procedure

#If MRA, it is strongly recommended to be at high intensity and with contrast

For ruptured aneurysms- immediate pre-procedure mRS refers to the subject's pre-rupture mRS and may be assessed post procedure

^For all patients with ruptured aneurysms

^^For all patients who experience a post-procedure rupture

8. Assessment of Safety

For the purposes of this protocol, the following AEs only will be reported and recorded:

- **Device related serious adverse events**

- **Intra-procedural aneurysm ruptures**
- **Intra-procedural thromboembolic events if symptomatic**

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 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 death
    - Led to serious deterioration in the health of the subject, users, 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
- Led to 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. 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. If a study device deficiency is detected or suspected that could have led to a device related SAE, it should 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 deficiencies should be reported via the manufacturer's complaints handling process.

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: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

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 a medical devices that leads to a different medical result than that intended by the manufacturer or expected by the user (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 8.2.1A 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 8.2.2A 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

8.2.3 Outcome

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

Table 8.2.3A Adverse Event Outcome Classifications

Classification	Definition
Recovered/Resolved	Subject fully recovered with no observable residual effects
Recovered/Resolved with sequelae	Subject recovered with observable residual effects
Recovering/Resolving	Subject's condition improving, but residual effects remain
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)

8.3 Time Period and Frequency for Adverse Event Assessment and Follow-up

Protocol defined adverse events shall be assessed and documented starting at the point the subject is considered enrolled (after the subject is consented and the treating physician confirms the subject continues to meet all eligibility criteria on the day of the study procedure) and at all study follow-up visits. Each investigator shall provide source documentation as requested by the Sponsor to facilitate reporting and adjudication of these events. 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. Events will be followed for outcome information until resolution, stabilization or the subject exits the study, whichever occurs first.

8.4. Reporting Procedures

8.4.1. Adverse Event and Device Deficiency Documentation and Reporting Requirements

Reportable adverse events and study device deficiencies will be recorded and reported on the eCRFs throughout the study and provided to the Sponsor. (In the event EDC is unavailable, these events can be notified via email to the STERLING Registry study mailbox: RA-ASPUS-G3Registry@ITS.JNJ.com. Note: These event(s) will need to be recorded on eCRFs once EDC is functional.)

Timing for reporting the different types of device related serious adverse events and Device Deficiencies is described in Table 8.4.1A.

Table 8.4.1A Adverse Event Reporting Requirements

Type of Adverse Event	Reporting Requirements
Device related Serious Adverse Events	Report to Sponsor immediately upon study site staff awareness of event but no later than 72 hours
All other study adverse events Study device deficiencies*	Report to Sponsor immediately upon study site staff awareness but no later than 14 calendar days

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

The Investigator will report all of the above to the reviewing IRB/EC according to the local reporting requirements. 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 specific provisions of the associated IRB/IECs, and in accordance with 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 requirement(s). 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 21 CFR 50 in the US and with 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 and/or written data release forms (as applicable per regional requirements) 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 Methodology

10.1. Study Design

This is a prospective, multi-center, single arm, clinical study in which approximately 850 subjects in the US,EMEA and Japan will be enrolled and treated with the MicrusFrame and/or Galaxy G3 coils and followed at 180 days, and 1 year post-procedure.

10.2. Treatment Assignment

This registry is a single arm study and all enrolled patients will be implanted with the study device.

10.3. Interval Windows

Refer to section 7.12.

In the event of a pre-planned staged procedure, the two procedures will be recorded as part 1 and part 2. The immediately post procedural data will be assessed using the post procedural images from part 2 of the staged procedure. The subject follow-up schedule for subjects undergoing a pre-planned staged procedure for a ruptured aneurysm should start from the date of part 2 of the staged procedure.

10.4. Primary and Secondary Endpoints, and Associated Hypotheses

Refer to section 3.2. There are no formal hypothesis tests for this study.

10.5. Level of Significance

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

10.6. Analysis Sets

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

- Safety Population (SP): The SP will consist of all enrolled subjects in whom coil treatment is attempted as defined by advancement of a coil outside of the distal end of the microcatheter inside the subject. The SP will be used to analyze safety endpoints.
- Per Protocol (PP) Population: The PP Population will consist of subjects in the Safety population who 1) have met the eligibility criteria, 2) have been treated with at least 75% GALAXY/MICRUSFRAME coils by length and 3) have completed a 1-year (-3/+6mo) DSA/MRA. Effectiveness endpoints will be assessed using this population.

10.7. Sample Size Justification

Approximately 850 subjects will be enrolled into the study at approximately 60 clinical sites from the US, EMEA and Japan. Due to heterogeneity in aneurysm characteristics and treatment (e.g., rupture status, aneurysm location, aneurysm neck-size, adjunctive treatment, etc.), multiple subgroup analyses are planned. A sample size of 850 subjects was selected to ensure there are a sufficient number of subjects to allow for subgroup

analyses and to emulate "real world" clinical data to characterize the acute and long term performance of the MICRUSFRAME and GALAXY coils including the PulseRider Aneurysm Neck Reconstruction device for the endovascular treatment of intracranial aneurysms

With an enrolled sample size of 850 and an attrition rate of no more than 20%, the maximum margin of error for the primary endpoint is anticipated to be 3.8% when the primary endpoint rate is at 50%.

$$Maximum\ Margin\ \approx 2 \times SE = 2\sqrt{\frac{p(1-p)}{680}} = 2\sqrt{\frac{0.5 \times 0.5}{680}} = 3.8\%$$

where *SE* denotes the 2-sided 95% confidence margin of error, and p denotes the proportion of subjects who exhibit adequate occlusion).

10.8. Analyses to be Conducted

10.8.1. General Conventions

Standard descriptive summaries for continuous data include the number of observations with data, number of observations with missing data, 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.

10.8.2. Disposition of Study Subjects

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

10.8.3. Demographics, Baseline, and Procedural Characteristics

All demographic characteristics, procedural, and immediate post-operative data will be summarized in each of the analysis populations including but not limited to: age, sex, medical history, smoking status, prior treatment, aneurysm location, neck and diameter size, pre- and post-procedural DAPT, mRS, Hunt & Hess (for ruptured aneurysms), total number of coils placed, number of GALAXY coils placed, length of procedure, and length of hospital stay.

10.8.4. Primary and Secondary Endpoint Analysis

10.8.4.1. Primary Endpoint Analysis

The primary endpoint is defined as the proportion of subjects who achieve Adequate Occlusion (modified Raymond-Roy I or II) as assessed by the independent core lab report of the target aneurysm at 12 months without retreatment. The primary analysis of Adequate Occlusion Rate will be conducted using the PP population. The number

and percentage of subjects who reached adequate occlusion at 1 year follow-up visit will be summarized. The subjects who failed to reach the endpoint will be listed. The subjects with missing outcomes will be excluded from the primary analysis. The subjects who were considered to have failed the endpoint and received retreatment before reaching the 1 year follow-up visit will be included in the primary analysis and treated as failures. Two-sided 95% confidence interval of the Adequate Occlusion Rate will also be calculated based on the exact binomial distribution**.**

10.8.4.2. Secondary Endpoints Analyses

Secondary endpoints will be summarized using the PP population for the secondary effectiveness endpoints and using the Safety Population for the secondary safety endpoints.

10.8.4.2.1. Analysis of Packing Density Data

- Summary statistics of the packing density will be summarized for subjects with non-missing core lab data.

10.8.4.2.2. Analysis of Secondary Effectiveness Endpoints

The event rates and the two-sided 95% exact confidence intervals around the rates for the following effectiveness endpoints will be provided:

- Complete aneurysm occlusion at 1 year as assessed by the core lab (Modified Raymond-Roy I)
- Recanalization Rate at 1 year: A worsening in aneurysm occlusion grading (using the Modified Raymond-Roy Classification)
- The proportion of subjects with mRS 0-2 at 1 year for subjects with unruptured aneurysms
- Retreatment rate at 1 year: Proportion of subjects with any retreatment (surgical or endovascular) of the target aneurysm up to 12 months post procedure

  The pre-planned part 2 of the staged procedures is not considered as retreatment for subjects with ruptured aneurysms, and pre-planned staged procedure is not allowed for subjects with unruptured aneurysms.

10.8.4.2.3. Analysis of Secondary Safety Endpoint

The number and percentage of subjects with device-related serious adverse events will be summarized.

10.8.4.3 Analysis of Additional Endpoints

Health economics data collected in this study will be summarized descriptively.

- Length of stay for study procedure hospitalization

The mean, median, minimum and maximum duration of hospitalization length of stay will be summarized for the PP population.

- Number of re-hospitalizations related to the target aneurysm
    - Maximum length of stay for re-hospitalizations

The number and proportion of subjects with rehospitalizations, and the number of hospitalizations after the index procedure will be summarized for the PP population. The rate of re-hospitalization per patient year of follow up will also be reported.

10.8.5. Subgroup Analysis

Unless specified otherwise, all subgroup analyses will be performed using the PP population.

To investigate the treatment effect across various subgroups of the study population, subgroup analyses of the primary endpoint will be performed for the following categories including but not limited to :

- Use of coils in combination with other devices (coils alone, coils+ stent, coils + PulseRider, coils + flow diverter, coils + intrasaccular flow disruptor)
- Rupture status (ruptured vs un-ruptured)
- Aneurysm location (anterior circulation vs posterior circulation)
- Aneurysm location relative to artery (bifurcation vs. sidewall)
- Aneurysm neck size (wide-neck vs. narrow-neck)
- Aneurysm size

Other subgroups may be explored as needed.

10.8.6. Plans for Interim Analyses

Interim analysis will be conducted approximately every 200 subjects treated. Only descriptive statistics will be reported.

10.8.7. Handling of Missing Data

No missing data will be imputed for all study endpoints in the above analyses. Sensitivity analyses may be performed to evaluate the impact of missing data on clinical outcomes and will be elaborated in the SAP.

10.9. Measures to Minimize Bias

Cerenovus will be diligent in controlling for bias by utilizing proper study design and implementation of the approved study protocol. IRB/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. Strict inclusion and exclusion criteria will be implemented to avoid selection bias.

An independent core laboratory will perform the angiographic assessments the primary endpoint and several secondary 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 Modified Rankin Scale, a commonly utilized six-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.

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

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, will be conducted in accordance with specific provisions of the associated IRB/IECs, and in accordance with 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 requirement(s).

- General Responsibilities

Sponsor's general duties consist of assuring that sites have received IRB/EC approvals, selecting investigators, ensuring proper clinical site monitoring and ensuring subject informed consent is obtained. Any additional requirements imposed by an IRB/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 IRB/EC re-approval. A justification for each amendment will be documented.

- Maintaining Records

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

11.2. Institutional Review Board (IRB)/Ethics Committees (EC)

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB/EC for review and approval. IRB/EC approval of both the protocol and the consent form must be obtained before any participant is consented. A stamped copy of the IRB/EC approval letter and approved consent form must be submitted to Cerenovus certifying study approval prior to subject consent.

Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. Cerenovus and the IRB/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 IRB/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 IRB/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.

The IRB/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 IRB/EC requirements, may modify this example ICF. Each investigational site will provide Cerenovus with a copy of the IRB/EC approved ICF and renewed approvals and consents as appropriate for the duration of the study. The original, signed and dated ICF should 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 registry. The original, signed and dated data release form should 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 patients and their families as requested by the investigator, or designee. 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 written consent form and to ask questions prior to signing and will be allowed additional time as desired to consider the study prior to agreeing to participate. For elective procedures, 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 as permitted by the governing IRB/EC. Patients who present with a ruptured aneurysm may have up to 72 hours post procedure for the patient, or his/her legal representative to sign consent. During COVID-19, patients who present with a ruptured aneurysm may have up to 7 days post procedure for the patient, or his/her legal representative to sign consent. The subjects 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. A signed and dated copy of the 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 the Health Insurance Portability and Accountability Act (HIPAA) in the US or as required per 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 subject information, if required. Similar to consenting procedures, the consent discussion should be conducted in non-technical wording

understandable for the subject and the subject must have ample time and opportunity to inquire about further details. Once a subject decides to participate in the registry, the written data release form must be signed and dated by both the investigator and the subject. The original, signed and dated data release form should 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, including HIPAA 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. Core Lab, Clinical Research Associate, etc.), representatives of the FDA or other Health Authorities 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.

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, Good Clinical Practice (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.

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, electronic records will have to be printed and added to the subject's paper file. A print-out of an 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 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
- Notes of phone calls and/or correspondence 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 relative to the target aneurysm will be collected for all subjects throughout the study. Subject admission and discharge date will be collected for the index procedure. Re-hospitalization data relative to the target aneurysm including imaging for aneurysm treatment follow-up will also be collected. Unscheduled hospitalizations relative to the target aneurysm will include admission and discharge date, admitting and primary diagnosis, and all procedures performed during re-admission. Sites may opt out of health economics data collection if the data is too onerous to collect, their site policies do not allow for it or if sites do not have access to it.

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. To this end, 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 IRB/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 investigator will maintain all essential study documents and source documentation that support the data collected on the study subjects for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application. 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.

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 IRB/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. 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 IRB/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. In such cases the emergency deviation shall be documented and reported to the Sponsor and IRB/EC as soon as possible, and no later than 5 working days after the emergency occurred.

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 Leadership

The Cerenovus clinical leadership will conduct the registry in accordance with specific provisions of the associated IRB/IECs, and in accordance with 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 requirement(s). Cerenovus will have certain direct responsibilities and will delegate other responsibilities to appropriate consultants. Together, Cerenovus and consultants will ensure that the study is conducted according to all applicable regulations.

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, patient eligibility inquiries, data to be collected and investigator training
- Review of evidence results (assist in data interpretation)

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 take measures to safeguard against conflicts of interest to assure the integrity of the data, subject safety and investigator objectivity.

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