CLINICAL STUDY PROTOCOL

# **M**iddle Meningeal Artery **EM**bolization for the Treatment of Su**B**du**R**al Hem**A**tomas with TRUFILL® **n**-BCA

# MEMBRANE STUDY

**Protocol Number: CNV_2020_01**

**Version: 4.0**

**September 25, 2024**

**History of Changes**

| Version Date | Description |
|---|---|
| Version 1.0— January 25, 2021 | Original Document |
| Version 2.0 – December 12, 2022 | Amendment 1 |
| Version 3.0 – January 17, 2024 | Amendment 2 |
| Version 4.0 – September 25, 2024 | Amendment 3 |

Sponsor: Cerenovus, part of DePuy Synthes Products, Inc.
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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADE | Adverse Device Effect |
| ADP | Adenosine Diphosphate |
| AE | Adverse Event |
| AEDs | Antiepileptic Drugs |
| AI | Artificial Intelligence |
| ASADE | Anticipated Serious Adverse Device Effect |
| AT | As Treated |
| AVMs | Arteriovenous Malformations |
| CEC | Clinical Events Committee |
| CFR | Code of Federal Regulations |
| CMH | Cochran–Mantel–Haenszel |
| cSDH | Chronic Subdural Hematoma |
| CT | Computed Tomography |
| DMC | Data Monitoring Committee |
| DSA | Digital Subtraction Angiography |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Form |
| ECA | External Carotid Artery |
| EDC | Electronic Data Capture |
| eMMA | Middle Meningeal Artery Embolization |
| EVOH | Ethylene-Vinyl Alcohol |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GCS | Glasgow Coma Scale |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | Informed Consent Form |
| ICU | Intensive Care Unit |
| IDE | Investigational Device Exemption |
| IFU | Instructions for Use |
| IRB | Institutional Review Board |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MGS | Markwalder Neurological Grading Scale |
| ITT | Intent-to-Treat |
| MM | Medical Management |
| MMA | Middle Meningeal Artery |
| MMSE | Mini-Mental State Exam |
| MRI | Magnetic Resonance Imaging |
| mRS | Modified Rankin Scale |
| MRU | Medical Resource Utilization |
| n-BCA | n-Butyl Cyanoacrylate |
| NSMM | Non-Surgical Medical Management |
| OUS | Outside of the United States |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PP | Per Protocol |
| PVA | Polyvinyl Alcohol |

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| QA | Quality Assurance |
| QC | Quality Control |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis Software |
| SDH | Subdural Hematoma |
| SDV | Source Data Verification |
| SEPS | Subdural Evacuating Port System |
| SOC | Standard of Care |
| SOP | Standard Operating Procedure |
| UADE | Unanticipated Adverse Device Effect |

# KEY ROLES AND RESPONSIBILITIES

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## PROTOCOL AGREEMENT AND STATEMENT OF COMPLIANCE FORM

**STUDY NAME AND NUMBER:** MEMBRANE – CNV_2020_01

**STUDY TITLE:** A Prospective, Multi-Center, Randomized Controlled Pivotal Study to Evaluate the Safety and Effectiveness of TRUFILL® n-BCA Embolization of the Middle Meningeal Artery for the Treatment of Subdural Hematoma

**VERSION NUMBER:** 4.0

**VERSION DATE:** September 25, 2024

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 Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki, ISO 14155 requirements, applicable FDA regulations (21 CFR Parts 812, 11, 50, 54 and 56), local regulations, the signed clinical study contract with Sponsor, and with the protocol outlined herein. I will conduct this study as outlined herein 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 ensure delegation to qualified individuals.

I will fulfill the requirements of my Institutional Review Board (IRB), 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 I agree to report adverse events as defined in this protocol to the Sponsor, and comply with all adverse event 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 |
|---|---|---|

| Site Name | Address |
|---|---|

# PROTOCOL SUMMARY

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| **Full Title & Protocol Number** | Middle Meningeal Artery EMbolization for the Treatment of SuBduRal HemAtomas with TRUFILL® n-BCA (Protocol #: CNV_2020_01) |
| **Short Title** | MEMBRANE |
| **IDE number** | G200310 |
| **Sponsor** | CERENOVUS, part of DePuy Synthes Products, Inc.<br>31 Technology Drive<br>Irvine, CA 92618 |
| **Study Device** | TRUFILL n-BCA Liquid Embolic System (TRUFILL n-BCA) |
| **Indication** | TRUFILL n-BCA Liquid Embolic System is intended for embolization in the neurovasculature for the treatment of chronic subdural hematoma (cSDH). |
| **Study Device Description** | The TRUFILL n-Butyl Cyanoacrylate Liquid Embolic System is an artificial embolization device, comprised of TRUFILL n-BCA, TRUFILL Ethiodized Oil and TRUFILL Tantalum Powder. The TRUFILL System is used under fluoroscopic guidance via superselective catheter delivery to obstruct or reduce blood flow. Upon contact with body fluids or tissue, the mixture polymerizes into a solid material. The n-BCA is a clear, free- flowing liquid that polymerizes via an anionic mechanism. Ethiodized oil is used as a radiopaque polymerizing retardant. Radiopacity of the n-BCA mixture is accomplished by adding ethiodized oil and tantalum powder to the n-BCA. |
| **Study Design** | This is a prospective, multi-center, open-label, randomized controlled study in which up to 376 subjects will be randomized to receive standard of care (SOC) alone or SOC and TRUFILL n-BCA MMA embolization for the treatment of cSDH. Subjects will be followed at 1 month, 3 months, 6 months, and 1 year post-procedure. The primary endpoint will be evaluated at 6 months post-procedure. The study is designed to evaluate the effectiveness and safety of MMA in two cohorts – a surgical cohort and a non-surgical cohort. |
| **Sample Size** | Up to 376 randomized subjects at up to 35 sites |
| **Study Population** | Patients presenting with a previously untreated symptomatic chronic subdural hematoma not requiring emergent surgery/decompression |
| **Study Duration** | Start date: Q1, 2021 / End date: Q3, 2025 |
| **Procedure(s) description** | Patients presenting with a cSDH will be assessed by the treating neurosurgeon to determine whether the patient will undergo either surgery or non-surgical management. Patients will then be screened for trial enrollment based on the protocol inclusion and exclusion criteria. Patients who meet all eligibility criteria and consent to |

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| | participate in the MEMBRANE trial will be randomized 1:1 to undergo embolization of the MMA plus standard of care vs SOC alone (either surgery or non-surgical management). A computed tomography (CT) scan must be performed within 36 hours prior to the randomization to demonstrate stability of the hematoma. Stability is defined as no worsening of midline shift or increase in the size of the cSDH from the screening image that results in new or worsening clinical symptoms.<br><br>**Surgery Cohort:**<br>All patients will undergo the surgical procedure for SDH decompression prior to randomization. Post the surgical procedure patients will be randomized to MMA embolization (eMMA) or surgery alone.<br><br><u>Surgery + MMA Embolization</u><br>For subjects randomized to surgery and MMA embolization, the MMA embolization will occur using TRUFILL n-BCA. The MMA embolization procedure will occur within 10 days after the surgery and within the same hospital admission*. A CT scan to demonstrate stability of the hematoma must be performed within 36 hours prior to randomization.<br><br><u>Surgery alone</u><br>Subjects randomized to surgery alone will receive no further intervention.<br><br>*Subjects may be transferred within the same hospital network for the study MMA embolization procedure.<br><br>**Non-Surgical Cohort:**<br>Patients assigned to the Non-Surgical cohort will be randomized to non-surgical medical management (NSMM) plus MMA embolization or non-surgical medical management alone.<br><br><u>Non-Surgical Medical Management (NSMM) + MMA Embolization</u><br>For subjects randomized to NSMM and MMA embolization, the MMA embolization will occur using TRUFILL n-BCA. The MMA embolization procedure may occur up to 10 days after randomization. A CT scan must be performed within 36 hours prior to randomization.<br><br><u>Non-Surgical Medical Management</u><br>Subjects randomized to NSMM will be managed per non-surgical medical management SOC including: modifying/stopping oral anticoagulation therapy, initiation of medication i.e. statins (if applicable), observation, repeat imaging, and life-style modification. |

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| | **NOTE:** Subjects randomized to the non-embolization SOC groups, either surgery alone or NSMM, CANNOT undergo MMA embolization during the follow up period (i.e. crossover). |
| **Primary Objective** | The objective of this study is to evaluate the safety and effectiveness of TRUFILL n-BCA for MMA embolization in patients presenting with a cSDH compared to patients treated with standard of care management. |
| **Primary Endpoints** | Primary effectiveness endpoint: Residual or re-accumulation of the cSDH (>10 mm) at 6 months as assessed by an independent core laboratory OR re-operation or surgical procedure on the cSDH within 6 months post randomization.<br><br>Primary safety endpoint: Occurrence of all adverse events (AEs) through 6 months |
| **Secondary Endpoints** | Secondary Effectiveness Endpoints –<br>1. Mean change in hematoma volume at 3 and 12 months compared to baseline, as assessed by an independent core laboratory<br>2. Reduction >50% in hematoma volume at 3, 6 and 12 months as assessed by an independent core laboratory<br>3. Complete resolution of the cSDH at 3, 6 and 12 months as assessed by an independent core laboratory<br>4. Median time to achieve complete resolution of the cSDH<br>5. Subjects that develop an acute component of their existing cSDH or a new cSDH at 3, 6 and 12 months as assessed by an independent core laboratory<br>6. Subjects requiring a surgical procedure on the cSDH within 3 and 6 months post randomization<br>7. Subjects requiring more than one surgery on the cSDH within 3, 6 and 12 months post randomization<br><br>**NOTE:** The following secondary endpoints will be tested for statistical significance for the purpose of supporting labeling claims:<br>- Good functional outcome at 3 months (mRS 0-2 or no worsening from baseline if baseline mRS≥ 3)<br>- Subjects requiring a surgical procedure on the cSDH within 12 months |

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| | - Mean change in hematoma volume at 6 months compared to baseline, as assessed by an independent core laboratory<br><br><u>Secondary Safety Endpoints –</u><br>1. mRS distribution change at 3, 6 and 12 months<br>2. Death, stroke, myocardial infarction or thromboembolic complications within 3, 6 and 12 months as assessed by the Clinical Events Committee (CEC)<br>3. Development of new onset of seizures within 3, 6 and 12 months as assessed by the CEC<br>4. 4. Change in Markwalder Grading Scale at 3, 6 and 12 months compared to baseline<br>5. 5. Change in Mini-Mental State Exam (MMSE) score at 6 months compared to baseline<br><u>Secondary Health Economics Endpoints-</u><br>1. Hospital days and intensive care unit (ICU) days<br>2. Change in EQ-5D-5L score at 6 months compared to baseline |
| **Follow-up Intervals** | • Hospital Discharge<br>• A follow up will occur for Surgery Alone and NSMM groups in the same timeframe as the study embolization procedure occurs in the embolization treatment groups to ensure equal treatment (e.g., number of subject contacts) across study randomization arms<br>• 1 Month Follow-up (Clinic or Phone/Telehealth Visit and CT Scan)<br>• 3 Month Follow-up (Clinic or Phone/Telehealth Visit and CT Scan)<br>• 6 Month Follow-up (Clinic Visit and CT Scan)<br>• 1 Year Follow-up (Clinic or Phone/Telehealth Visit and CT Scan) |
| **Inclusion Criteria** | 1. Subject is between 18 and 90 years of age (inclusive) at the time of consent<br>2. Subject has a diagnosis of chronic subdural hematoma with mass effect determined by brain imaging (CT or MRI) and correlated clinical symptoms<br>3. Pre-randomization modified Rankin Score (mRS) $\leq 3$<br>a. Surgical Cohort: Assessment should reflect the subject's condition just prior to undergoing surgery. Assessment may be performed post-surgery using pre-surgical data. |

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| | 4. Subdural Hematoma Size<br>a. **Non-Surgical Medical Management Cohort:**<br>i. Midline shift < 10mm and hematoma thickness > 10 mm as measured on coronal imaging perpendicular to the skull.<br>ii. No focal deficit related to the chronic subdural hematoma<br>b. **Surgical Cohort:**<br>i. No requirement<br>5. A CT performed within 36 hours prior to randomization that demonstrates stability of the hematoma. Stability is defined as no worsening of midline shift or increase in the size of the cSDH from the screening image that results in new or worsening clinical symptoms<br>6. Patient or designated Legal Authorized Representative, confirms the patient has the mental capacity, willingness and ability to comply with protocol and follow-up requirements<br>7. In the opinion of the treating physician, treatment with TRUFILL n-BCA is technically feasible (e.g., no significant vessel tortuosity, stenosis, occlusion or variation in vascular anatomy to prohibit safe endovascular access) |
| **Exclusion Criteria** | 1. Patients presenting with an acute SDH (e.g. patient presenting with a SDH due to trauma); mixed density is permitted<br>2. Subject has a prior history of craniotomy/burr hole/Subdural Evacuating Port System (SEPS) ipsilateral to the cSDH prior to the baseline procedure treatment<br>3. Subject presents with bilateral cSDHs (contralateral cSDH <5mm and not requiring treatment is permitted)<br>4. Subject presents with Glasgow Coma Scale < 9<br>5. Markwalder assessment $\geq$ 3<br>6. cSDH that developed with underlying conditions such as vascular lesions, brain tumor, arachnoid cyst, spontaneous intracranial hypotension, end stage renal disease (ESRD) on hemodialysis, end stage liver disease or other comorbidities causing a coagulopathy<br>7. Prior carotid stent placement that crosses the origin of the External Carotid Artery (ECA) ipsilateral to the subdural hematoma<br>8. Selective angiography demonstrates opacification of a potentially dangerous anastomosis or dangerous anatomic variation that could lead to increased procedural risk<br>9. Presumed septic embolus, or suspicion of microbial superinfection |

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| | 10. CT or MRI evidence of intra-cranial tumor or mass lesion<br>11. Significant contraindication to angiography (e.g., kidney failure)<br>12. Life expectancy of less than 1 year<br>13. Women who are pregnant, lactating, or of childbearing age and plan on becoming pregnant during the course of the clinical investigation<br>14. Current involvement in an investigational (drug, device, etc.) clinical trial that may confound study endpoints. Subjects in observational, natural history, and/or epidemiological studies not involving intervention are eligible. Sponsor approval is required prior to randomization.<br>15. Patient unwilling to follow SOC recommendations (e.g. refuses surgery or lifestyle modifications) |
| **Safety Assessments** | All adverse events occurring from the time of randomization through the one year follow up visit will be captured. Subjects' follow up assessments will follow the schedule of assessment tables (see below). |
| **Sample Size and Power Calculation** | Cochran–Mantel–Haenszel (CMH) statistic will be used to test superiority in the primary effectiveness endpoint of SOC with eMMA over SOC alone. The CMH test will be performed with stratification of the cohorts (surgery vs. NSMM). Subjects within each cohort will be randomized 1:1 to SOC alone or SOC with eMMA. Assuming a common odds ratio of 0.34, a total sample size of 376 subjects after accounting for 10% attrition will provide at least 80% power for the primary effectiveness endpoint at a one-sided significance level of 0.05.<br><br>For the primary safety endpoint, we expect at least an 80% probability of observing AEs that occur at an incidence of at least 1% within each treatment group. This expectation pertains to approximately 188 participants receiving eMMA (surgery + eMMA and NSMM + eMMA) and 188 participants receiving standard of care (surgery alone and NSMM alone). |
| **Statistical Analysis** | The primary effectiveness endpoint will be evaluated in subjects who are randomized (ITT analysis set). This endpoint will be considered successful if the p-value from the continuity corrected CMH test is less than 0.05. Study success will be based on successful demonstration of the primary effectiveness endpoint.<br><br>Tests of hypotheses of the secondary endpoints will be performed at 0.05 significance level using a gatekeeping strategy for multiplicity control.<br><br>The primary safety endpoint will be evaluated using the As Treated |

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| | analysis set.<br><br>Descriptive summary statistics will be presented for other study endpoints. The number and percentages of subjects will be presented for categorical endpoints. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, minimum and maximum. The study will be deemed a success if the primary effectiveness endpoint criterion is met. |

# Schedule of Assessments

| **Surgical Cohort**<br><br>**Table Legend:**<br>X = Required<br>O = Optional, to be collected if performed during standard of care<br><br>**Assessments** | Screening (0-30 days prior to Randomization ) | Surgical Procedure | Pre-Randomization[1] | Randomization | Day 0 (within 10 days of surgery)<br>**Embolization Arm Only:** Embolization Procedure<br>**Surgery Alone Arm Only:** Phone/In person Follow up | Discharge[5] | 1 Month Follow-up (+/-14 days) Clinic or Phone/Telehealth + CT Exam | 3 Months Follow-up (+/- 14 days) Clinic or Phone/Telehealth + CT Exam | 6 Months Follow-up (+/- 30 days) Clinic Visit | 1 Year Follow-up (+/- 60 days) Clinic Visits or Phone /Telehealth/ + CT exam | Unscheduled Visit | Re-Operation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | |
| Pregnancy Test | X | | | | | | | | | | | |
| CT Exam[2] | X[7] | | X (≤36 hrs before randomization) | | | | X | X | X | X | O | X |
| Surgical Procedure | | X | | | | | | | | | | |
| Randomization | | | | X | | | | | | | | |
| Embolization Procedure (Embolization Arm Only) | | | | | X (DSA for eMMA) | | | | | | | |
| Glasgow Coma Scale (GCS) | | | X | | | | | | | | O | |
| Markwalder Grading Scale (MGS) | X[3] | | | | | X | X | X[4] | X[4,6] | X[4] | O | |
| Modified Rankin Score (mRS) | X[3] | | | | | X | X | X[4] | X[4,6] | X[4] | O | |
| Mini-Mental State Exam (MMSE) | | | X | | | X | | | X | | O | |
| Quality of Life (EQ-5D-5L) | | | X | | | | | | X | X | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X |
| Adherence to SOC | | | | | | X | X | X | X | X | X | X |
| Review of Adverse Events | | | | X | X | X | X | X | X | X | X | X |
| Medical Resource Utilization | | X | X | X | X | X | X | X | X | X | X | X |

[1] Pre-Randomization assessments may occur on the day of randomization, prior to the subject being randomized.
[2] An external CT scan (not performed by the site) is acceptable as long as the scan is provided to the site investigator and the core laboratory.
[3] Assessment should reflect the subject's condition just prior to undergoing surgery. Assessment may be performed post-surgery using pre-surgical data.
[4]Assessment must be performed by a qualified independent evaluator who is not part of the interventional (embolization) treating team, not involved in patient care or data entry, and is blinded to study treatment assignment. The evaluator does not need to be a physician.
[5]Discharge assessments may be performed when subject is medically ready to be discharged OR at the time of discharge.
[6] mRS and MGS may be completed via phone/telehealth by blinded assessor.
[7] MRI at screening is acceptable. Pre-randomization imaging must be CT scan

| **Non-Surgical Cohort**<br><br>**Table Legend:**<br>X = Required<br>O = Optional, to be collected if performed during standard of care<br><br>**Assessments** | Screening (0-30 days prior to Randomization) | Pre-Randomization[1] | Randomization | Day 0 (within 10 days of randomization)<br>**Embolization Arm Only:** Embolization Procedure<br>**NSMM Arm Only:** Phone/In person Follow up | Discharge[4]<br>**Embolization Arm Only** | ☎ 1 Month Follow-up (+/-14 days) Clinic or Phone/Telehealth + CT Exam | ☎ 3 Months Follow-up (+/- 14 days) Clinic or Phone/Telehealth + CT Exam | 6 Months Follow-up (+/- 30 days) Clinic Visit | ☎ 1 Year Follow-up (+/- 60 days) Clinic Visit or Phone/Telehealth + CT Exam | Unscheduled Visit | Surgical Procedure |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | | |
| Medical History | X | | | | | | | | | | |
| Pregnancy Test | X | | | | | | | | | | |
| CT Exam[2] | X[6] | X (≤36 hrs before randomization) | | | | X | X | X | X | O | X |
| Randomization | | | X | | | | | | | | |
| Embolization Procedure (Embolization Arm Only) | | | | X (DSA for eMMA) | | | | | | | |
| Glasgow Coma Scale (GCS) | X | | | | | | | | | O | |
| Markwalder Grading Scale (MGS) | X | | | | X | X | X[3] | X[3,5] | X[3] | O | |
| Modified Rankin Score (mRS) | X | | | | X | X | X[3] | X[3,5] | X[3] | O | |
| Mini-Mental State Exam (MMSE) | | X | | | X | | | X | | O | |
| Quality of Life (EQ-5D-5L) | | X | | | | | | X | X | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X |
| Adherence to SOC | | | | | X | X | X | X | X | X | X |
| Review of Adverse Events | | | X | X | X | X | X | X | X | X | X |
| Medical Resource Utilization | | | X | X | X | X | X | X | X | X | X |

[1] Pre-Randomization assessments may occur on the day of randomization, prior to the subject being randomized.
[2] An external CT scan (not performed by the site) is acceptable as long as the scan is provided to the site investigator and core laboratory.
[3] Assessment must be performed by a qualified independent evaluator who is not part of the interventional (embolization) treating team and not involved in patient care or data entry and is blinded to study treatment assignment. The evaluator does not need to be a physician
[4] The discharge assessments may be performed when subject is medically ready to be discharged OR at the time of discharge.
[5] mRS and MGS may be completed via phone/telehealth by blinded assessor.
[6] MRI at screening is acceptable. Pre-randomization imaging must be CT scan

# 1. Background Information and Scientific Rationale

## 1.1 Background Information

Subdural hematoma is an accumulation of blood between the dura and arachnoid layers of the meninges surrounding the brain that can cause symptoms including headache, seizures, memory or other neurological (including motor) impairment, and confusion. SDH can occur in an acute (emergent) fashion, often becoming symptomatic within 72 hours and requiring immediate surgical intervention, or develop chronically over a period of 3 or more weeks (Sahyouni et al., 2017). The most common cause of chronic SDH is thought to be a combination of direct or indirect head trauma and chronic inflammation. Other known causes or risk factors include alcoholism, liver cirrhosis, chronic renal failure, hematologic disease, and anticoagulant or antiplatelet therapy (Sim et al., 2012). Given these risk factors, cSDH has a predilection towards the elderly: the estimated annual incidence of cSDH is 1-5.3 cases per 100,000 population, but the incidence among individuals > 65 years has been reported as high as 48.0-80.1 per 100,000 per year (Kudo et al., 1992; Karibe et al., 2011; Adhiyaman et al., 2017). Moreover, recent data suggest that cases of cSDH are on the rise due to population aging and the increased use of antithrombotic medications (Sim et al., 2012; Adhiyaman et al., 2017).

The clinical diagnosis of cSDH is based on symptomatic presentation and the presence of risk factors such as recurrent falls, increased confusion, and decreased mobility. cSDH is confirmed on brain imaging with CT without contrast enhancement (Soleman et al., 2014) and typically quantified in terms of hematoma size or volume and the presence or absence of cerebral compression, whereas clinical assessment and treatment response are measured using the Markwalder grading system for the classification of cSDH or non-specific scales such as the modified Rankin Scale and Glasgow Coma Scale.

The primary goal of cSDH treatment is to relieve intracranial pressure and drain accumulated blood and fluids in order to alleviate patient symptoms. The current standard of care is somewhat variable but generally utilizes pharmacological and/or surgical interventions to accomplish this aim.

## 1.2 Current Treatment Options

Current treatments for cSDH can be divided into conservative medical management (MM) and surgical intervention. Of note, there is a dearth of class I evidence supporting the efficacy of any pharmacological treatment for cSDH, such that current MM options are largely based on theoretical efficacy and physician experience.

### 1.2.1. Conservative Medical Management

Conservative MM is indicated in patients who are asymptomatic or have only mild symptoms and none or mild clinical or imaging signs of cerebral compression. MM can include treatment with steroids, ACE inhibitors, statins, or alternatively a “watch and wait”

observation approach (Lee, 2019). Antiplatelet therapy is typically discontinued, and anticoagulant therapy is converted with vitamin K (Soleman et al., 2014). A survey of practice in the United Kingdom and Ireland found that while conservative management was used in less than 25% of cases, more than half of medical management utilized a steroid (Santarius et al., 2009). An international survey that included the United States and Europe similarly found that almost half of respondents used steroid monotherapy with dexamethasone when electing for conservative treatment, whereas ACE inhibitors and statins were rarely (~10% of respondents) prescribed (Laldjising et al., 2020). Unfortunately, few studies have provided rigorous evidence for the efficacy of MM alone for cSDH. Jiang et al. (2018) evaluated atorvastatin monotherapy (8 weeks, 20 mg) versus placebo for cSDH in a Chinese population and reported a reduction in hematoma volume of 12.55 mL compared to the placebo group, as well as a significant improvement in neurological function. Conversion to surgery was necessary in 11.2% in the atorvastatin group compared to 23.5% in the placebo group. Fountas et al. (2019) similarly compared dexamethasone monotherapy to surgical therapy or a combination thereof; in this study, surgery (burr hole craniotomy) plus dexamethasone resulted in the lowest rate of recurrence (4%) followed by a rate of 7.3% in the surgery only group and 30% in the dexamethasone monotherapy group. The recently completed SUCRE trial compared methylprednisolone to placebo in cSDH using a double-blind, randomized controlled design (Hénaux et al., 2017), but the results are not yet available.

### 1.2.2. Surgical Intervention

Surgical evacuation of cSDH is a common neurosurgical procedure that alleviates intracranial pressure and cerebral compression in order to ameliorate patient symptoms. Surgical options typically include single or double burr hole evacuation and craniotomy. The majority of published studies on surgical management of SDH use a threshold of 10 mm for patient inclusion and/or outcome assessment, and refer to the established surgical guidelines (Bullock et al., 2006 "…acute SDH with a thickness greater than 10 mm or a midline shift greater than 5 mm on computed tomographic [CT] scan should be surgically evacuated.."), which are in turn based on the mortality rates associated with increased hematoma thickness (up to 10% for ≤10 mm, 50% for 18 mm and ≥90 % for thickness 30 mm and higher; Bullock et al., 2006; Zumkeller et al, 1996). A prospective observational cohort study in United Kingdom and Ireland found that burr hole craniotomy was the most common procedure for cSDH (89%) and moreover that 96% of all patients underwent some form of surgery (Brennan et al., 2017). Despite the widespread use of surgical evacuation for cSDH, these procedures are associated with important risks in the target population due to advanced age and comorbidities and furthermore do not address the cause of hematoma formation. To this end, surgical evacuation is associated with a recurrence rate of roughly 5-30% depending on the specific surgical technique (Oh et al., 2010). Rovlias et al. (2015) found that age, neurological status on admission, and antiplatelet or anticoagulant therapy were significant predictors of outcome after burr hole evacuation with closed system drainage in a cohort of 986 patients. This study reported a recurrence rate of 11.8% and a postoperative complication rate of 22.7%. Knopman et al. (2018) examined rates of reoperation after craniotomy for isolated nontraumatic SDH in two separate cohorts and reported reoperation rates of 5-10% and mortality of 8-18%.

Several studies indicate that drain insertion (subdural or subperiosteal) may decrease the rate of recurrence and improve patient outcomes. A meta-analysis of 10 studies comparing subdural versus subperiosteal drain placement after burr hole evacuation of cSDH demonstrated that subdural drain placement significantly decreased the rate of recurrence (odds ratio, 0.73; 95% confidence interval, 0.58-0.92). Brennan and colleagues (2017) similarly found that failure to insert a subdural drain significantly predicted reoperation and unfavorable outcome. Sanitarius et al. (2009) reported a recurrence rate of 9.3% with subdural drain placement versus 24.0% without drain placement at 6 months follow-up, indicating a noteworthy benefit.

### 1.3. Neurovascular Embolization

Given the nature of cSDH as a disease of the elderly that can occur secondary to serious comorbidities, there is a need for effective treatment options that minimize or circumvent surgical risk and decrease the probability of recurrence. Endovascular embolization of the MMA with embolic materials including n-BCA, polyvinyl alcohol (PVA) particles, ethylene vinyl alcohol (EVOH) copolymers, and coils/gelatin sponges is an increasingly attractive option. In cSDH, the MMA and neovascular vessels in the outer membrane anastomose via the dura mater, leading to intermittent bleeding of weak or vulnerable blood vessels and an increase in cSDH volume. Theoretically, embolization of the MMA reduces the recurrence of cSDHs by disrupting blood flow to the outer membrane of the hematoma (Saito et al., 2019). On this premise, endovascular embolization of the MMA not only provides a minimally invasive alternative to surgery, but also addresses a root cause of hematoma formation.

Several studies have demonstrated the efficacy of endovascular treatment in cSDH, with early studies focusing on the treatment of recurrent cSDH. Saito et al. performed embolization of the MMA using 12-24% n-BCA for recurrence after single burr hole evacuation with irrigation (cohort recurrence rate, 11.8%) in 8 patients and reported only 1 recurrence 3 months after surgery with no complications (Saito et al., 2019). The authors attributed recurrence after MMA embolization to neovascularization of the inner membrane and septum. In a similar study, Ishihara et al. performed MMA embolization with 20% n-BCA in 7 patients with intractable cSDH after burr hole evacuation and reported no cases of further recurrence at 15 months follow-up (Ishihara et al., 2007). In a case study, MMA embolization with n-BCA was successfully used to treat iatrogenic dural arteriovenous fistula associated with recurrent cSDH in an 82-year-old woman (Mewada et al., 2016). Okuma et al. reported a case series of 17 patients which involved three patients treated with gelatin microspheres and one patient treated with coils alone, resulting in recurrence-free survival in all patients at a mean follow-up of 26.3 ± 17.4 months (Okuma et al., 2019). Another case report involving a 13-year-old male patient treated with coil-based MMA embolization for recurrent cSDH showed no neurological complications or recurrence at 5-year follow-up (Kang et al., 2015). Several studies have demonstrated successful MMA embolization using PVA for recurrent cSDH, typically resulting in low recurrence rate (Mandai et al., 2000;Tsukamoto et al., 2011;Kim, 2017;Ban et al., 2018;Sirh et al., 2018;Link et al., 2019). In addition, Tempaku et al. reported a case series of five patients with repeated recurrence of cSDH that were successfully treated with MMA

embolization using PVA particles, each showing no further recurrence at follow-up ranging from 4 to 60 weeks (Tempaku et al., 2015).

Other studies have proposed the use of embolization as an adjuvant to surgical therapy in high-risk or intractable cases. In a cohort of 17 patients with multiple intractable risk factors to standard treatment, MMA embolization with 20% n-BCA or trisacryl gelatin microspheres followed by burr hole craniotomy and irrigation led to no complications or recurrence during a mean follow-up of 26.3 months (Okuma et al., 2019). A prospective cohort study performed MMA embolization for cSDH using gelatin sponges and Guglielmi detachable coils as an adjunct treatment to closed-system drainage or irrigation with drainage in 4 patients, resulting in no observed recurrence at 6 months (Mino et al., 2010). PVA-based MMA embolization has also been used as a successful adjuvant to surgical therapy in several studies, including case reports, case series, and prospective and retrospective cohort studies (Tempaku et al., 2015;Sirh et al., 2018;Link et al., 2019;Arham and Zaragita, 2020). One pilot study examined MMA embolization with PVA as an adjuvant to surgery for symptomatic cSDH and identified superior volume resorption (mean difference, 17.5 mL) compared to a surgery control group (Ng et al., 2020). An ongoing non-randomized clinical trial also seeks to investigate the efficacy of PVA as adjuvant therapy and PVA as a stand-alone therapy relative to burr hole drainage/craniotomy (NCT04065113).

More recently, MMA embolization has been explored as a stand-alone therapy for cSDH. A case series which included a 63-year-old female at risk of recurrent cSDH that was treated with MMA embolization (16% n-BCA) at the first sign of recurrence demonstrated complete disappearance of the hematoma at 4-months (Hashimoto et al., 2013). Another prospective investigation of MMA embolization with PVA for cSDH achieved spontaneous hematoma resolution in all of 27 asymptomatic patients, whereas 1 of 45 symptomatic patients experienced hematoma re-accumulation after treatment. In this study, a recurrence rate of 1.4% was significantly lower than 27.5% (129/469) in the conventional treatment group (Ban et al., 2018). Similarly, Link et al. (2019) performed MMA embolization with PVA particles (150-250 microns) as new treatment in 42 patients plus treatment for recurrence in 8 patients and reported a recurrence rate of 8.9% (4 patients) (Link et al., 2019). Overall, 91% of patients were stable or showed a decrease in hematoma size and avoided surgery through follow-up. There were no differences in treatment-related complications. Shotar et al. compared 104 MMA embolization procedures (triacryl gelatin microspheres in 81 cases, n-BCA in 5 cases) performed in 89 patients to 174 historic controls and identified recurrence rates of 4% and 14%, respectively (odds ratio, 0.28; 95% confidence interval, 0.07-0.86) (Shotar et al., 2020).

Despite advances and rapid adoption of new devices and techniques, significant unmet clinical needs still exist, creating a demand for innovation and new devices for MMA embolization. The use of PVA particles for MMA embolization is significantly limited by a tendency for particle aggregation (Sharma et al., 2016), which can result in poor penetration, vessel occlusion proximal to the intended target, and concerns for distal embolization. These issues are in part avoidable through sufficient particle dilution and slow infusion, the latter of which increases procedure times. Moreover, the long-term

efficacy of PVA is not well examined in the literature. While EVOH copolymers offer better penetration compared to PVA, these agents also require slow infusion to avoid issues related to DMSO toxicity: EVOH copolymers are prepared in DMSO solvent, which diffuses away on contact with blood to permit EVOH polymerization. Rapid injection of DMSO can lead to vasospasm and necrosis, making slow infusion necessary to limit the rate of DMSO diffusion (Vaidya et al., 2008). These liquid embolic agents commonly require microcatheters that are larger than ideal, which can hamper distal access and put patients at higher risk for other complications (Arafa et al., 1999;Righini et al., 2004).

n-BCA resolves some of the shortcomings of the other embolic agents being used to treat chronic subdural hematomas. Unlike PVA and EVOH, n-BCA is supplied as a clear, free-flowing monomer that undergoes rapid polymerization upon exposure to an anionic environment (e.g. blood, water), the speed of which depends on the concentration of n-BCA (Pollak and White, 2001). n-BCA can be delivered through a smaller microcatheter than other liquid embolic agents to facilitate distal access and decrease likelihood of other complications. Compared to the alternatives, n-BCA may be optimal for procedures performed under conscious sedation because of its quick action, pain-free nature of the injection, and lower associated fluoroscopy exposure (Velat et al., 2008). Accordingly, the use of n-BCA for MMA embolization is expected to maximize the safety and efficacy of a minimally invasive protocol for treatment of cSDH and warrants evaluation against both surgical and MM interventions that represent the current standard of care for cSDH.

## 1.4. Rationale

The use of liquid embolic agents for the minimally invasive treatment of cSDH offers a solution that both circumvents the risk of surgical complications and addresses the source of fluid accumulation, thereby decreasing the likelihood of recurrence. There are currently no endovascular embolic agents approved in the US for treating chronic subdural hematomas. Despite the promising preliminary findings summarized above, there is a need for high-quality evidence from prospective randomized controlled studies to support MMA embolization as a primary treatment option for cSDH. TRUFILL n-BCA provides a minimally invasive option for stand-alone treatment as well as, as an adjunct to surgical treatment of cSDHs and offers several potential advantages to other current embolic agents.

The aim of the present study is to assess the safety and effectiveness of MMA embolization with TRUFILL n-BCA Liquid Embolic System in both non-surgical and surgical patient populations relative to standard management without MMA embolization in a prospective, multicenter, pivotal clinical trial. Data generated will be used to support a Pre-market Approval Application to expand the indication of TRUFILL n-BCA to include treatment of subdural hematomas.

## 1.5. Previous Experience

### 1.5.1. Bench and Animal Validation

The safety and effectiveness of TRUFILL n-BCA Liquid Embolic System for its currently approved use in embolization of cerebrovascular AVMs, is supported by extensive pre-clinical bench and animal testing. The same pre-clinical bench and animal data set also

support the reasonable safety of the use of TRUFILL n-BCA in embolization of MMA in treatment of SDH. Pre-clinical bench and animal testing include the following:

- Polymerization Rate for a range of nBCA and Ethiodized Oil mixture ratios
  - *In vitro* evaluation with pre-determined objective acceptance criteria
  - *In vivo* evaluation by physicians to qualitatively assess polymerization
- Viscosity of individual components: nBCA, Ethiodized Oil
- Tantalum Powder particle size and suspension in ethiodized oil
- Radiopacity of liquid embolic
- Microcatheter Compatibility
- USP Physicochemical Testing – n-BCA, Ta Powder
- Evaluation of Hydrolytic Degradation of implant
- Evaluation of Elution of Ethiodized Oil from implant
- Verification that product meets sterility requirements (SAL $10^{-6}$)
- Package & Sterile Barrier Integrity
- Self Piercing Luer Cap performance testing
- Shelf Life – Real Time Studies confirming minimum 2-year shelf-life
- Biocompatibility of liquid embolic system per ISO 10993
  - *In vitro* evaluations of cytotoxicity, genotoxicity, hemocompatibility per applicable chapters of ISO 10993
  - *In vivo* evaluations of hemolysis, intramuscular implantation for 7 and 30 days, systemic and sub-chronic toxicity, pyrogenicity, intracutaneous reactivity/toxicity, and delayed contact sensitization per applicable chapters of ISO 10993

Cerenovus has undertaken all necessary steps to apply standard techniques in designing, pre-clinically evaluating, and manufacturing the devices to ensure they are safe and perform as intended.

### 1.5.2. Study Product

TRUFILL n-BCA Liquid Embolic System has been commercially available in the US since 2000 and in select countries (Belarus, Russia) globally since 2012. TRUFILL n-BCA Liquid Embolic System may be considered Investigational for certain countries and will be tracked as an investigational product as applicable.

An Investigational Device Exemption (IDE) Instructions for Use (IFU) will be provided to the sites separately for instructions on use of the device for the study.

## 1.6. Potential Risks and Benefits

Risks that may be associated with the use of the TRUFILL n-BCA and the procedure are described in this section.

### 1.6.1. Known Potential Risks

The following AEs associated with endovascular embolization of the MMA have been identified as possible (anticipated) AEs associated with the use of the TRUFILL n-BCA or with the procedure.

Access site injury (including bleeding, bruising, infection, pain)

Allergic reaction / anaphylactic shock

Catheter glued inside vessel

Cerebral infarction

Death

Early polymerization

Embolism, including pulmonary and thromboembolism

Headache

Hematoma

Hemorrhage

Infection/inflammation

Late polymerization

Myocardial infarction

Nausea / vomiting

Neurological deficits

Non-target embolization (passage of embolic material into normal vessels adjacent to the target) which may cause but not limited to blindness, dysesthesias of the face (increased or decreased sensitivity), facial weakness, or deafness

Occluded catheter

Renal failure

Seizure

Stroke

SDH hematoma recurrence

Vasospasm

Vessel dissection, perforation and injury

Use of the device requires fluoroscopy which presents potential risks to physicians and patients associated with x-ray exposure. Possible risks include, but are not limited to, the following:

Alopecia

Burns ranging in severity from skin reddening to ulcers

Cataracts

Delayed neoplasia

### 1.6.2. Minimization of Risks

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

1. Treating investigators who participate in the study will have extensive experience using TRUFILL n-BCA or similar device (e.g., other n-BCA) in neurovascular embolization procedures.
2. Investigators will have experience performing embolizations through the middle meningeal artery.
3. All sites will have a neurosurgical program capable of treating subdural hematomas.
4. All sites will be required to have adequate resources to conduct the clinical study and assure compliance.
5. Each investigator will ensure oversight and approval of the study by the IRB/EC prior to initiation of the study at the investigation site.
6. The investigator and study personnel will be trained on the study protocol.
7. An IDE IFU will be provided to the sites for instructions on use of the device for the study.
8. Subjects will be carefully evaluated against the pre-defined inclusion/exclusion criteria prior to being enrolled in the study to ensure that their diagnosis and medical status are appropriate for participation.
9. Each investigator will be required to commit to follow all subjects per protocol, including preforming the required CT scans.
10. Subjects will be monitored closely as part of the study to allow for detection of adverse events. This should allow for early treatment, if necessary.

11. Data from all investigation sites will be monitored by the sponsor throughout the study to evaluate protocol compliance and identify any issues that may affect the safety and welfare of the subjects.
12. All safety endpoints for the study will be reviewed and adjudicated by an independent CEC.
13. All imaging based endpoints for the study will be assessed by an independent core laboratory.
14. An Independent Data Monitoring Committee (DMC) will be responsible for assessing and monitoring the accumulated AEs and interim data on a periodic basis as the study progresses to ensure subject safety.

### 1.6.3. Potential Benefits

The potential benefits of TRUFILL n-BCA are that it may decrease or stop the blood flow into the MMA and thus decrease or eliminate the outflow of blood that may be contributing to the formation and/or growth of the cSDH, which may help decrease or eliminate the hematoma, potentially reducing symptoms, the need for surgical treatment, as well as the risk of future complications or death. 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.

### 1.6.4. Risk-Benefit Rationale

Extensive commercial experience with TRUFILL n-BCA supports the reasonable safety of the device, and available data on MMA embolization for the treatment of SDH further support the safety of the procedure. Published literature also suggests that the rates of surgical treatment following MMA embolization may be lower than those associated with standard of care alone. Multiple steps will be taken to ensure risks to the subject are minimized including selecting only sites experienced with endovascular MMA treatment, monitoring subject closely thorough follow-up evaluations as required by the protocol and independent oversight of the study through a DMC. Cerenovus considers the potential benefits of MMA embolization with TRUFILL n-BCA to outweigh the potential risks in the defined subject population.

# 2. Objectives and Purpose

## 2.1. Objectives

The objective of this study is to evaluate the safety and effectiveness of TRUFILL n-BCA for MMA embolization in patients presenting with a cSDH compared to patients treated with standard of care management.

# 3. Study Design and Endpoints

### 3.1. Description of the Study Design

This is a prospective, multi-center, open-label, randomized controlled study in which up to 376 subjects will be enrolled and randomized to receive standard of care alone or standard of care and TRUFILL n-BCA MMA embolization for the treatment of cSDH. Pre-planned treatment should be TRUFILL n-BCA as the only liquid embolic agent. The subjects will be followed at 1 month, 3 months, 6 months, and 1 year post-procedure. The primary endpoint will be evaluated at 6 months post-procedure. The study is designed to evaluate the effectiveness and safety of MMA in two cohorts – a surgical cohort and a non-surgical cohort.

#### 3.1.1. Primary Endpoint

- Primary effectiveness endpoint: Residual or re-accumulation of the cSDH (>10 mm) at 6 months as assessed by an independent core laboratory OR re-operation or surgical procedure on the cSDH within 6 months post randomization.

  Re-operation and surgical procedures will be reported by the site. Hematoma size will be assessed by the independent core laboratory.

  Primary safety endpoint: Occurrence of all AEs through 6 month

#### 3.1.2. Secondary Endpoints – Effectiveness

1. Mean change in hematoma volume at 3 and 12 months compared to baseline, as assessed by an independent core laboratory
2. Reduction> 50% in hematoma volume at 3, 6 and 12 months as assessed by an independent core laboratory
3. Complete resolution of the cSDH at 3, 6 and 12 months as assessed by an independent core laboratory
4. Median time to achieve complete resolution of the cSDH
5. Subjects that develop an acute component of their existing cSDH or a new cSDH at 3, 6 and 12 months as assessed by an independent core laboratory
6. Subjects requiring a surgical procedure on the cSDH within 3 and 6 months post randomization
7. Subjects requiring more than one surgical procedure on the cSDH within 3, 6 and 12 months post randomization

Re-operation and surgical procedures will be reported by the site. Hematoma volume and resolution, as well as identification of an acute component of the cSDH or a new cSDH will be assessed by the independent core laboratory.

**NOTE:** The following secondary endpoints will be tested for statistical significance for the purpose of supporting labeling claims:

- Good functional outcome at 3 months (mRS 0-2 or no worsening from baseline if baseline mRS $\geq$ 3)
- Subjects requiring a surgical procedure on the cSDH within 12 months
- Mean change in hematoma volume at 6 months compared to baseline, as assessed by an independent core laboratory

### 3.1.1. Secondary Endpoints – Safety

1. mRS distribution change at 3, 6 and 12 months
2. Death, stroke, myocardial infarction or thromboembolic complications within 3, 6 and 12 months as assessed by the Clinical Events Committee (CEC)
3. Development of new onset of seizures within 3, 6 and 12 months as assessed by the CEC
4. Change in Markwalder Grading Scale at 3, 6 and 12 months compared to baseline
5. Change in Mini-Mental State Exam MMSE score at 6 months compared to baseline

Death, stroke, myocardial infarction, thromboembolic complications and new onset seizures will be adjudicated by the CEC. Markwalder and mRS used in secondary endpoints will be assessed by a qualified independent evaluator who is not part of the interventional (embolization) treating team and not involved in patient care or data entry and is blinded to study treatment assignment.

### 3.1.4. Secondary Endpoints – Health Economics

1. Hospital days and intensive care unit (ICU) days
2. Change in EQ-5D-5L score at 6 months compared to baseline

# 4. Study Population

Study population will be patients presenting with a previously untreated chronic subdural hematoma not requiring emergent surgery/decompression.

Investigators will assess potential subjects who are candidates for the study. Patients will be assessed by the site physicians to determine whether the patient will undergo either surgery or non-surgical management of the hematoma, per standard of care. Patients will then be screened for trial enrollment based on the protocol inclusion and exclusion criteria. Patients who meet all eligibility criteria and consent to participate in the MEMBRANE trial will be randomized 1:1 to undergo embolization of the MMA vs standard of care.

Older age is shown to be a factor in developing cSDH: the estimated annual incidence of cSDH is 1-5.3 cases per 100,000 population, but the incidence among individuals > 65 years has been reported as high as 48.0-80.1 per 100,000 per year (Kudo et al., 1992; Karibe et al., 2011; Adhiyaman et al., 2017). Based on the age profile of cSDH patients, the Medicare population would benefit most from the study treatment. The results of this study are expected to be generalizable to the Medicare population based on age requirement >=65 for enrollment.

## 4.1 Participant Inclusion Criteria

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

1. Subject is between 18 and 90 years of age (inclusive) at the time of consent
2. Subject has a diagnosis of chronic subdural hematoma with mass effect determined by brain imaging (CT or MRI) and correlated clinical symptoms
3. Pre-randomization modified Rankin Score (mRS) ≤ 3
    a. Surgical Cohort: Assessment should reflect the subject's condition just prior to undergoing surgery. Assessment may be performed post-surgery using pre-surgical data.
4. Subdural Hematoma Size

    **Non-Surgical Medical Management Cohort:**

    - Midline shift < 10mm and hematoma thickness > 10 mm as measured on coronal imaging perpendicular to the skull
    - No focal deficit related to the chronic subdural hematoma

    **Surgical Cohort:**

    - No requirement
5. A CT performed within 36 hours prior to randomization demonstrates stability of the hematoma. Stability is defined as no worsening of midline shift or increase in the size of the cSDH from the screening image that results in new or worsening clinical symptoms.
6. Patient or designated Legal Authorized Representative, confirms the patient has the mental capacity, willingness and ability to comply with protocol and follow-up requirements
7. In the opinion of the treating physician, treatment with TRUFILL n-BCA is technically feasible (e.g., no significant vessel tortuosity, stenosis, occlusion or variation in vascular anatomy to prohibit safe endovascular access)

## 4.2. Participant Exclusion Criteria

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

1. Patients presenting with an acute SDH (e.g. patient with presenting with a SDH due to trauma); mixed density is permitted
2. Subject has a prior history of craniotomy/burr hole/SEPs ipsilateral to the cSDH prior to the baseline procedure treatment
3. Subject presents with bilateral cSDHs (contralateral cSDH <5mm and not requiring treatment is permitted)
4. Subject presents with Glasgow Coma Scale < 9
5. Markwalder assessment ≥ 3
6. cSDH that developed with underlying conditions such as vascular lesions, brain tumor, arachnoid cyst, spontaneous intracranial hypotension, end stage renal disease (ESRD) on hemodialysis, end stage liver disease or other comorbidities causing a coagulopathy
7. Prior carotid stent placement that crosses the origin of the External Carotid Artery (ECA) ipsilateral to the subdural hematoma
8. Selective angiography demonstrates opacification of a potentially dangerous anastomosis or dangerous anatomic variation that could lead to increased procedural risk
9. Presumed septic embolus, or suspicion of microbial superinfection
10. CT or MRI evidence of intra-cranial tumor or mass lesion
11. Significant contraindication to angiography (eg. kidney failure).
12. Life expectancy of less than 1-year
13. Women who are pregnant, lactating, or who are of childbearing age and plan on becoming pregnant during the course of the clinical investigation
14. Current involvement in an investigational (drug, device, etc.) clinical trial that may confound study endpoints. Subjects in observational, natural history, and/or epidemiological studies not involving intervention are eligible. Sponsor approval is required prior to randomization
15. Patient unwilling to follow SOC recommendations (e.g. refuses surgery or lifestyle modifications)

### 4.3. Study Duration

The duration of the study is expected to be approximately 3 years. This includes an enrollment period of approximately 2 years and a post-treatment follow-up evaluation of 1 year.

### 4.4. Number of Subjects

A target of 376 subjects will be randomized into this study. Each cohort will have a maximum enrollment of 276 subjects (approximately 70%) and a minimum of 100 subjects. To ensure generalizability of the results and minimize the influence of any single site, no more than approximately 15% of the total 376 randomized subjects will be allowed at a single site, with limits on individual strata (i.e., a maximum of 38 subjects per cohort with a combined limit of 56 subjects randomized across both cohorts per site).

The study will be conducted in up to 475 enrolled (consented) subjects to achieve 376 subjects randomized at up to 35 sites in the United States (US). It may later be determined that approximately 50 of the 376 randomized subjects in approximately 5 of these 35 sites and will be in geographies outside of the US. Randomization will be stratified by site within cohort.

### 4.5. Number of Sites

The study will be conducted at up to 35 sites.

### 4.6. Participant Withdrawal or Termination

#### 4.6.1. Reasons for Withdrawal or Termination

Subjects are free to withdraw from participation in the study at any time by notifying the investigator. 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.

#### 4.6.2. Handling of Participant Withdrawals or Termination

Subjects that withdraw consent after treatment are not required to undergo study-related 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.

## 5. Study Device

### 5.1. Study Device Description

#### 5.1.1. Device Acquisition

The TRUFILL n-BCA System is commercially available in the US, and considered an investigational device in other regions with sites participating in this study. The device is manufactured for Medos International SARL by Cerenovus, Inc. US and CE Marked

catalog codes are identical in all aspects of design, chemical composition, and packaging configuration, and only the labeling is different to account for differences in US and EU medical device labelling requirements. The devices that will be used at US study sites will be the US commercial devices and contain commercial labeling and instructions for use as approved by FDA (PMA# P990040). Devices used at study sites at all regions outside the US (OUS) will be those labeled with the European CE Mark.

Due to commercial availability in the US, shipments and device accountability will not be tracked in the US for this study. However, devices will be fully traceable though the company's 21 CFR 820 and ISO 13485 complaint quality system. Device accountability will be tracked in regions where TRUFILL n-BCA is considered an investigational device.

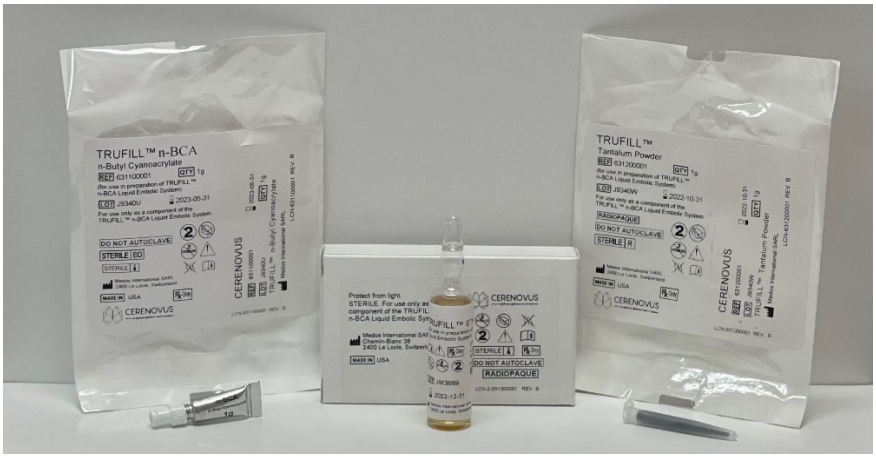
### 5.1.2. Device Appearance, Packaging, and Labeling Description

The TRUFILL n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System is an artificial embolization device, comprised of TRUFILL n-BCA, TRUFILL Ethiodized Oil and TRUFILL Tantalum Powder. These components must be used as a system. They are not intended for use as individual components.

TRUFILL n-BCA is a clear, free- flowing liquid that polymerizes via an anionic mechanism. Ethiodized oil is a straw-to-amber colored, oily fluid containing iodinated poppy seed oil and is used as a radiopaque polymerizing retardant. Tantalum powder is a finely ground, irregularly shaped, dark gray metal that can be used with ethiodized oil to make the n-BCA radiopaque.

The families of compatible microcatheters, and recommended accessories for use with the TRUFILL n-BCA system are listed in the IFU.

**Figure 1 – TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System**



### 5.1.3. Device Training Requirements and Investigator Experience

In addition to the clinical protocol training, all investigators who will be performing procedures for this study will be trained on the study IDE IFU and will be required to undergo didactic training on use of TRUFILL n-BCA for MMA embolization. Treating investigators not already experienced with TRUFILL n-BCA are required to undergo training via a device in-service, which includes detailed reviews of the device (specifications, indications for use, procedural components, etc.).

A physician proctor may be provided to provide support for the first few cases that each investigator uses the TRUFILL n-BCA for MMA embolization. The combination of the didactic and hands-on portions of the device training will be documented and along with any physician proctoring to provide the investigator with the experience necessary to perform the protocol specified procedures for the study.

TRUFILL n-BCA for MMA embolization should only be used by investigators who have endovascular training and thorough knowledge of angiographic techniques and the treatment of cSDH.

There must be at least one physician at each site experienced in standard of care surgical evacuation of SDH via burr hole, craniotomy.

### 5.1.4. Device Storage and Stability, Preparation and Instructions for Use

The TRUFILL n-BCA System device should be stored in a cool, dark, dry place, in accordance with the IFU.

The n-BCA mixture polymerizes into a solid material upon contact with body fluids or tissue. Recommended ratios of n-BCA to ethiodized oil and tantalum powder vary depending on the location, diameters and tortuosity/linearity of the target, and flow rates. Higher concentrations of ethiodized oil increase the polymerization time, which allows the physician to embolize the target more distally. Higher concentrations of n-BCA result in a faster polymerization rate, which will allow the physician to embolize the target more proximally. Radiopacity of the n-BCA mixture is accomplished by adding ethiodized oil and tantalum powder to the n-BCA. These additives will also extend the polymerization time of the n-BCA. Guidelines for recommended mixtures and approximate polymerization times are listed in the IFU.

### 5.1.5. Device Returns

Any suspected device malfunction, treatment failure or device associated with an adverse event will undergo a thorough complaint analysis and must be properly documented on the electronic Case Report Forms (eCRFs). In the event of a suspected malfunction or device observation, the device shall be returned to Cerenovus for analysis if the device was not implanted. All returned devices must be properly decontaminated per hospital policy and

properly labeled with the subject identification number, date of event, identified as a defective return, non-defective return, or adverse event. Retain tracking information. All study devices should be returned to:

C.G. Laboratories,Inc.
2449 Bob White Dr.
Granbury, TX 76049 USA

# 6. Study Procedures

Some of the procedures completed as part of this study are standard of care which may vary from site to site. For the purpose of the MEMBRANE Study, "Standard of Care" is defined as the best care for the individual subject including guideline-based care where clinical guidelines are available. Patients 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.

## 6.1. Independent Imaging Core Lab for Image Evaluation

An independent Imaging Core Lab shall be utilized to provide an unbiased and standardized assessment of study imaging. All subject Protected Health Information (PHI) will be redacted by the site before an image is uploaded to the Core Lab for evaluation. The Imaging Core Lab assessors will be blinded to subjects' previous medical history. The Imaging Core Lab will evaluate all primary and secondary endpoints that are based on imaging, specified in the list below, as well as other parameters of interest specified in the Core Lab Reading Guidelines.

- Subdural hematoma volume
- Subdural hematoma thickness
- Presence of a new cSDH or an acute component

The study endpoints parameters will be independently read by two Imaging Core Lab assessors. In the event of discordance between the two reviewers, a third independent assessor will evaluate the image. This independent assessor will be a blinded evaluator and will not have access to assessments of other reviewers. The interpretation identified by 2 out of the 3 reviewers will be used.

All imaging (DSA and CT) shall be performed in accordance to the Oculus Imaging Guideline recommended protocol provided to the sites. A copy of the study DSA and CT scans will be submitted to the core lab. 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 uploaded electronically to the Imaging Core Lab website. An external CT scan (not performed by the site) is acceptable as long as the scan is provided to the site investigator and the core laboratory.

### 6.2. Concomitant Medications, Treatments, and Procedures

The following will be recorded throughout the study on the eCRF:

- Antithrombotic medications (i.e., antiplatelet, anticoagulant, fibrinolytics)
- Statins
- Steroids
- Antiepileptic drugs (AEDs)
- Medications used during the study embolization procedure, excluding anesthesia
- Medications to treat adverse events
- Any additional surgeries (e.g. Endovascular/Neurovascular Surgery, Percutaneous Endoscopic Gastrostomy, Tracheostomy, Shunt) performed throughout the study period related to the treatment of the cSDH

### 6.3. Neurological and Cognitive Evaluations

The following neurological and cognitive evaluations will be used in this study:

- **Glasgow Coma Scale (GCS)** - The Glasgow Comma Score is a tool used by healthcare providers to objectively quantify the degree of impairment in patients presenting with neurological symptoms. It is composed of 3 categories scored between 3-6 for normal response and 1 for no response. The individual scores from each category are summed in order to calculate a subject's total GCS score. The maximum possible score is 15, indicating normal function, with the minimum score being a 3, indicating unresponsive patient.

- **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 events. It is a scale with seven categories ranging from no symptoms (=0) to severe disability (=5) and death (=6).

  The mRS assessments used in a secondary endpoint will be performed by a qualified independent evaluator who is not part of the interventional (embolization) treating team and not involved in patient care or data entry and is blinded to study treatment assignment. The evaluator does not need to be a physician.

- **Markwalder Neurological Grading Scale (MGS)** - Markwalder Neurological Grading Scale is a grading system developed to evaluate neurological performance in patients presenting with cSDH. It is a 5 point scale ranging from 0

(patient neurologically normal), through 1-3 (mild to severe neurological deficit), to 4 (patient comatose).

The MGS assessment used in a secondary endpoint will be performed by a qualified independent evaluator who is not part of the interventional (embolization) treating team and not involved in patient care or data entry and is blinded to study treatment assignment. The evaluator does not need to be a physician.

- **Mini Mental State Exam (MMSE)** - The Mini Mental State Exam is a standardized tool widely used by healthcare providers to assess mental state in elderly patients or those who may be cognitively impaired. It includes tests of orientation, attention, memory, language, and visual-spatial skills. It is comprised of questions (e.g. "What is the year?") and tasks (e.g. "Make up and write a sentence about anything."). The examiner asks questions and gives directions to perform tasks and scores the response according to MMSE instructions. Scores 0-17 indicate severe cognitive impairment, scores 18-23 indicate mild impairment, and scores 24-30 are considered normal.

  All study personnel assigning the MMSE score will have training available in performing of the MMSE assessment.

### 6.4. Medical Resource Utilization and Health Economics

Medical resource utilization associated with the study procedure will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. Procedure and post-procedure healthcare resource utilization will be assessed at hospital discharge. Healthcare resource utilization will include length of hospitalization and number of ICU days.

The study will also utilize the EQ-5D-5L questionnaire to assess subjects' quality of life. The EQ-5D-5L measures self-assessed health-related quality of life based on 5 categories: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each area is rated on a scale that describes the degree of problems in that area (i.e. I have no problems walking about, slight problems, moderate problems, severe problems, or unable to walk). This tool also has an overall health scale where the rater selects a number between 1-100 to describe the condition of their health, 100 being the best imaginable.

### 6.5 Viz RECRUIT

All MEMBRANE study sites will have the option to utilize the Viz Recruit system. Viz RECRUIT is Viz.ai, Inc.'s commercial software application designed to support subject screening in research studies. Viz RECRUIT can interface with and incorporate commercial products and artificial intelligence (AI)-based algorithms to assist clinicians in identifying potential candidates who may meet study criteria.

## 7. Study Schedule

### 7.1. Screening (0-30 days prior to randomization)

Patients presenting with a chronic subdural hematoma will be assessed by the institution's site physicians to determine the appropriate standard of care treatment regardless of the research study, either surgery or non-surgical management. Patients will then be screened for trial enrollment based on the protocol inclusion and exclusion criteria. 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 CT, laboratory studies, medical history, physical examination, etc.) A Pre-screening Log will be utilized at enrolling centers and will capture all patients with presenting with a diagnosis of cSDH, as well as the reason for non-eligibility, including detailed reasons for cases when eMMA was not deemed technically feasible.

Informed consent must be obtained from all subjects prior to any study-specific evaluations. The informed consent process is detailed further in Section 11.3.

**A patient is considered enrolled in the study upon signing the informed consent form.**

All Subjects who provide written informed consent will be entered into Electronic Data Capture (EDC) regardless of whether or not they undergo randomization.

The following screening data will be collected after subject provides a signed informed consent and is confirmed to meet eligibility criteria, prior to the randomization:

- **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. The following relevant medications taken within 30 days prior to randomization will be recorded.
    - Antithrombotic medications (i.e., antiplatelet, anticoagulant, fibrinolytics)
    - Statins
    - Steroids
    - Antiepileptic drugs (AEDs)
- **A pregnancy test** will be done according to the treating institutions SOC (e.g., blood or urine test). Pregnancy may also be ruled out by documented medical history (e.g. menopause, surgical sterility).
- **CT exam** (MRI allowed only at screening)– a standard CT or MRI exam will be performed as part of the screening process.

All screening tests should be completed within 30 days prior to randomization.

In the event that greater than 30 calendar days has elapsed prior to randomization, screening tests and procedures are to be repeated, as needed to ensure all are performed within 30 days of the randomization.

## 7.2. Pre-randomization through Discharge

This section is presented separately for the surgical and non-surgical cohorts, based on their respective treatments.

### 7.2.1. Surgical Cohort

#### 7.2.1.1. Surgery

Patients assigned to surgery as determined by the institution's site physicians will undergo surgical cSDH decompression, per the institution's standard of care. All patients will undergo surgery prior to randomization. The type of surgery will be captured in the eCRF.

#### 7.2.1.2. Pre-Randomization

After surgery and prior to randomization, the assessments listed below will be performed, and data collected on the eCRF. Pre-randomization assessments may occur post-surgery on the day of randomization, prior to the subject being randomized.

- CT

  The CT scan must demonstrate stability of the hematoma. Stability is defined as no worsening of midline shift or increase in the size of the cSDH from the screening image that result in new or worsening clinical symptoms.

- GCS

  If any worsening of the subject's GCS post the pre-randomization CT is noted, a new CT scan is required to demonstrate stability of the hematoma.

- mRS

  For the surgical cohort, mRS should reflect status prior to surgery

- MGS

  For the surgical cohort, MGS should reflect status prior to surgery.

- MMSE
- Quality of Life (EQ-5D-5L)
- Concomitant medications
- Medical resource utilization

Subjects determined to be ineligible for the study prior to randomization will only require the reason for the eligibility failure and study exit to be recorded in the eCRF. No further follow-up or data collection in the eCRFs are required.

#### 7.2.1.3. Randomization

Post the surgical procedure, patients who meet all eligibility criteria and consent to participate in the MEMBRANE trial will be randomized 1:1 to undergo surgery and embolization of the MMA vs. surgery alone (SOC).

For subjects randomized to surgery and eMMA, the MMA embolization procedure will occur up to 10 days after the surgery (but within the same hospital admission). Embolization is defined as injection of TRUFILL n-BCA into a blood vessel beyond the tip of the microcatheter.

**Subjects randomized to surgery alone will receive no further intervention.**

**NOTE: Subjects randomized to the surgery alone group CANNOT undergo MMA embolization during the follow up period (i.e. no crossover).**

#### 7.2.1.4. Day 0 (within 10 days of surgery):

##### 7.2.1.4.1 eMMA Arm Study Embolization Procedure (within 10 days of surgery)

The subject should be prepared for the planned study embolization procedure according to standard hospital procedures for MMA embolization. Medications appropriate for anesthesia will be administered using standard hospital practice. Immediately prior to TRUFILL n-BCA placement, the physician will perform a digital subtraction angiography (DSA) of the MMA. Selection of the target artery segment and angiography will be done using standard techniques and images will be submitted to the core lab.

Clinical sites will be responsible for providing ancillary devices (e.g., guidewires, guide catheters, sheaths) during the procedure.

Pre-planned treatment should be TRUFILL n-BCA as the only liquid embolic agent. The treating investigator will utilize the TRUFILL n-BCA device to embolize the MMA per the IDE IFU.

The following data should be captured during the procedure and recorded on the eCRF.:

- Procedure date
- Name of the implanting physician
- Ancillary devices used to gain access and deliver the study device (e.g., microcatheters)

- Procedure start and end times (arterial puncture through last catheter withdrawal)
- Total cumulative fluoroscopy time
- Presence of vasospasm (vessel and times of onset/resolution). Vasospasm will be captured as an adverse event only if it leads to a subsequent thrombotic or ischemic event.
- Embolization technique (all that apply):
    - No embolization
    - Proximal ligation
    - Penetration without reaching midline
    - Penetration to midline
    - Penetration beyond midline
- Total number of TRUFILL n-BCA packages opened during the procedure and lot numbers of the packages
- Ratios of TRUFILL n-BCA system component used
- AEs
- Medical Resource Utilization
- All procedure medications except anesthesia
- Device malfunctions/deficiency

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

The timing of all study follow-up visits is relative to the date of the study embolization procedure (Day 0).

In the event that the subject is confirmed eligible for the study and randomized for the eMMA procedure, but the target artery is not treated with the TRUFILL n-BCA (including those subjects who are deemed not to be suitable candidates for eMMA based on pre-procedure angiograms), the subject will be followed-up per study schedule up to 6 months.

#### 7.2.1.4.2. Surgery Alone Arm: Telephone or In-person Visit (within 10 days of surgery)

In order to ensure an equal number of contacts with all subjects, those subjects randomized to surgery alone will undergo a Day 0 follow-up visit. The Day 0 visit should occur within 10 days of surgery. The purpose of the visit is to ask how the subject is feeling after the surgery, review any post-surgery instructions, and to record the following information which will then be entered into the eCRF:

- AEs
- Relevant medications taken
- Medical Resource Utilization

The timing of all study follow-up visits is relative to the date of this Day 0 follow-up visit.

In the event that the subject is not discharged within 10 days of surgery, the Day 0 visit assessments may be performed inpatient, within 10 days of surgery.

In the event the subject cannot be contacted within 10 days of surgery, the Day 0 visit date will be 10 days post surgery and all subsequent follow-up visits will be based on this Day 0 date.

#### 7.2.1.5. Discharge

The following data will be collected upon subject being medically ready for discharge or at discharge and entered into the eCRF by the site:

- MGS
- mRS
- MMSE
- AEs
- Relevant medications taken
- Adherence to SOC recommendations (e.g. MM, lifestyle modifications)
- Medical Resource Utilization

### 7.2.2. Non-Surgical Cohort

#### 7.2.2.1. Pre-Randomization

Prior to randomization, the assessments listed below will be performed, and data collected on the eCRF. Pre-randomization assessments may occur on the day of randomization, prior to the subject being randomized.

- CT

  The CT scan must demonstrate stability of the hematoma. Stability is defined as no worsening of midline shift or increase in the size of the cSDH from the screening image that results in new or worsening clinical symptoms.

- GCS

If any worsening of the subject's GCS post the pre-randomization CT is noted, a new CT scan is required to demonstrate stability of the hematoma.

- mRS
- MGS
- MMSE
- Quality of Life (EQ-5D-5L)
- Concomitant medications
- Medical resource utilization

Subjects determined to be ineligible for the study prior to randomization will only require the reason for the eligibility failure and study exit to be recorded in the eCRF. No further follow-up or data collection in the eCRFs are required.

#### 7.2.2.2. Randomization

Patients who meet all eligibility criteria and consent to participate in the MEMBRANE trial will be randomized 1:1 to undergo NSMM and embolization of the MMA vs. NSMM alone (SOC).

For patients randomized to NSMM and MMA embolization, the MMA embolization will occur using TRUFILL n-BCA. The MMA embolization procedure may occur up to 10 days after randomization. Patients randomized to NSMM alone will NOT undergo the study embolization procedure and will be managed per non-surgical medical management standard of care alone including: modifying/stopping oral anticoagulation therapy, initiation of medication i.e. statins (if applicable), observation, repeat imaging, and life-style modification. NOTE: Subjects in the non-surgical cohort may have only one CT scan as their screening and randomization. If the CT scan is within 36 hours of randomization, an additional CT scan may not be required.

**NOTE: Patients randomized to the NSMM alone group CANNOT undergo MMA embolization during the follow up period (i.e. no crossover).**

#### 7.2.2.3. Day 0: (within 10 days of randomization)

##### 7.2.2.3.1. eMMA Arm Only: Study Embolization Procedure (within 10 days of randomization)

Subjects in the NSMM cohort who are randomized to the eMMA arm undergo the same study embolization procedure and capture the same data on the eCRF as described in Section 7.2.1.4.

#### 7.2.2.3.2. NSMM Arm Only: Follow-up Visit (within 10 days of randomization

In order to ensure an equal number of contacts with all subjects, those subjects randomized to NSMM alone will undergo a follow-up visit (may be performed via telephone) within 10 days of randomization. The purpose of the call is to ask how the subject is feeling, remind the subjects to adhere to NSMM guidelines previously provided, and to record the following information which will then be entered into the eCRF:

- AEs
- Relevant medications taken
- Medical Resource Utilization

The timing of all study follow-up visits is relative to the date of this Day 0 follow-up visit.

In the event that the subject cannot be contacted within 10 days of randomization, the Day 0 visit date will be 10 days post randomization and all subsequent follow-up visits will be based on this Day 0 date.

#### 7.2.2.4. Discharge (eMMA arm only)

The following data will be collected upon subject being medically ready for discharge or at discharge for the eMMA arm and entered into the eCRF by the site:

- MGS
- mRS
- MMSE
- AEs
- Relevant medications taken
- Adherence to SOC recommendations (e.g. MM, lifestyle modifications)
- Medical Resource Utilization

For subjects randomized to receive NSMM only (no eMMA), the pre-randomization assessments outcomes will be carried forward to the discharge timepoint. These assessments do not need to be repeated.

### 7.3. Follow-up – All Subjects

The follow-up period begins immediately post-treatment (i.e., MMA embolization procedure for subjects randomized to receive embolization or telephone visit for subjects randomized to SOC). Site personnel will review the follow-up requirements with the

subjects to help ensure compliance with the schedule. Any imaging related to the target cSDH conducted post-treatment and prior to the final study visit should be sent to the Imaging Core Lab.

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. 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.

In order to maximize patient retention and decrease the potential for missing data, all follow-up visits, **except the 6 month visit**, can be either an in person clinic visit or a phone/telehealth visit (e.g. video conference or a telephone call). However, a CT exam will still be required. An external CT scan (not performed by the site) is acceptable as long as the scan is provided to the site investigator and core laboratory.

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. If the missed visit was due to an AE, an AE eCRF must be completed and any reporting and assessment requirements must be met.

### 7.3.1. 1 Month Follow-up (±14 days) – Clinic or Phone/Telehealth Visit

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

- CT exam **is required** and must be sent to the independent Imaging Core Lab
- MGS
- mRS
- AEs
- Relevant medications taken
- Adherence to SOC recommendations (e.g. MM, lifestyle modifications)
- Medical resource utilization

### 7.3.2. 3 Months Follow-up (±14 days) – Clinic or Phone/Telehealth Visit

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

- CT exam **is required** and must be sent to the independent Imaging Core Lab
- MGS*
- mRS*
- AEs

- Relevant medications taken
- Adherence to SOC recommendations (e.g. MM, lifestyle modifications)
- Medical resource utilization

*NOTE: Must be performed by a qualified independent evaluator who is not part of the interventional (embolization) treating team and not involved in patient care or data entry and is blinded to study treatment assignment. The evaluator does not need to be a physician. Assessments may be completed via phone/telehealth by blinded assessor.

### 7.3.3. 6 Months Follow-up (±30 days) – Clinic Visit

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

- CT exam **is required** and must be sent to the independent Imaging Core Lab
- MGS*
- mRS*
- MMSE
- Quality of Life (EQ-5D-5L)
- AEs
- Relevant medications taken
- Adherence to SOC recommendations (e.g. MM, lifestyle modifications)
- Medical resource utilization

*NOTE: Must be performed by a qualified independent evaluator who is not part of the interventional (embolization) treating team and not involved in patient care or data entry and is blinded to study treatment assignment. The evaluator does not need to be a physician. Assessments may be completed via phone/telehealth by blinded assessor.

### 7.3.4. 1 Year Follow-up (± 60 days) – Clinic or Phone/Telehealth Visit

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

- CT exam **is required** and must be sent to the independent Imaging Core Lab
- MGS*

- mRS*
- Quality of Life (EQ-5D-5L)
- AEs
- Relevant medications taken
- Adherence to SOC recommendations (e.g. MM, lifestyle modifications)
- Medical resource utilization

*NOTE: Must be performed by a qualified independent evaluator who is not part of the interventional (embolization) treating team and not involved in patient care or data entry and is blinded to study treatment assignment. The evaluator does not need to be a physician. Assessments may be completed via phone/telehealth by blinded assessor.

### 7.4. Unscheduled Visit

Subjects returning for an unscheduled visit to the study center that is related to the cSDH treated in the study or indicating new or unresolved signs and/or symptoms will be documented as an unscheduled follow-up. Information to be collected, at a minimum includes:

- AEs
- Relevant medications
- Adherence to SOC recommendations (e.g. MM, lifestyle modifications)
- Medical resource utilization

The following assessments will be optional but if performed per standard of care, should be entered in the eCRF:

- CT exam – if performed, must be sent to the independent Imaging Core Lab
- GCS
- MGS
- mRS
- MMSE

### 7.5. Post-Randomization Surgical Procedure/ Re-Operation

As determined by the treating physician, subjects in both randomization cohorts may require surgical hematoma decompression at any time after randomization. Subjects who

undergo re-operation or surgical procedure on the cSDH within 6 months post randomization will be considered as failing the primary endpoint.

In the event a surgical procedure or re-operation is performed post-randomization, the following data will be collected and entered into the eCRF by the site:

- CT exam **is required** and must be sent to the independent Imaging Core Lab
- AEs
- Relevant medications taken
- Medical resource utilization
- Type of surgery

**NOTE: After the initial study procedure, <u>TRUFILL n-BCA may NOT</u> be used for MMA embolization during the follow up period.**

### 7.6. 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:

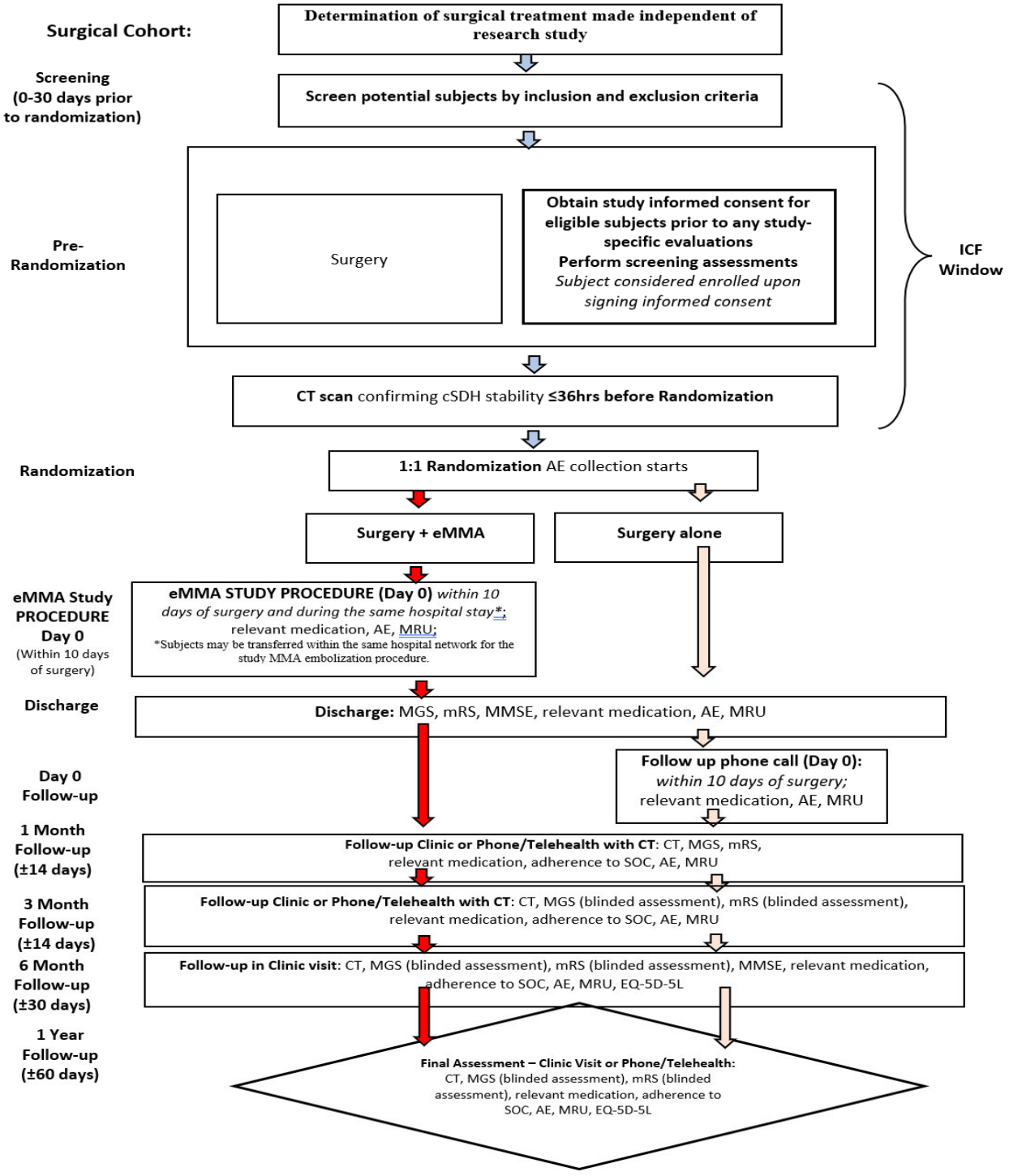
- Per recommendation of the DMC
- Unanticipated adverse device effect (UADE) presenting an unreasonable risk to subjects (Sponsor may terminate the study immediately)
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of subjects
- Persistent non-compliance of a site with the protocol, or IRB/EC regulatory requirements

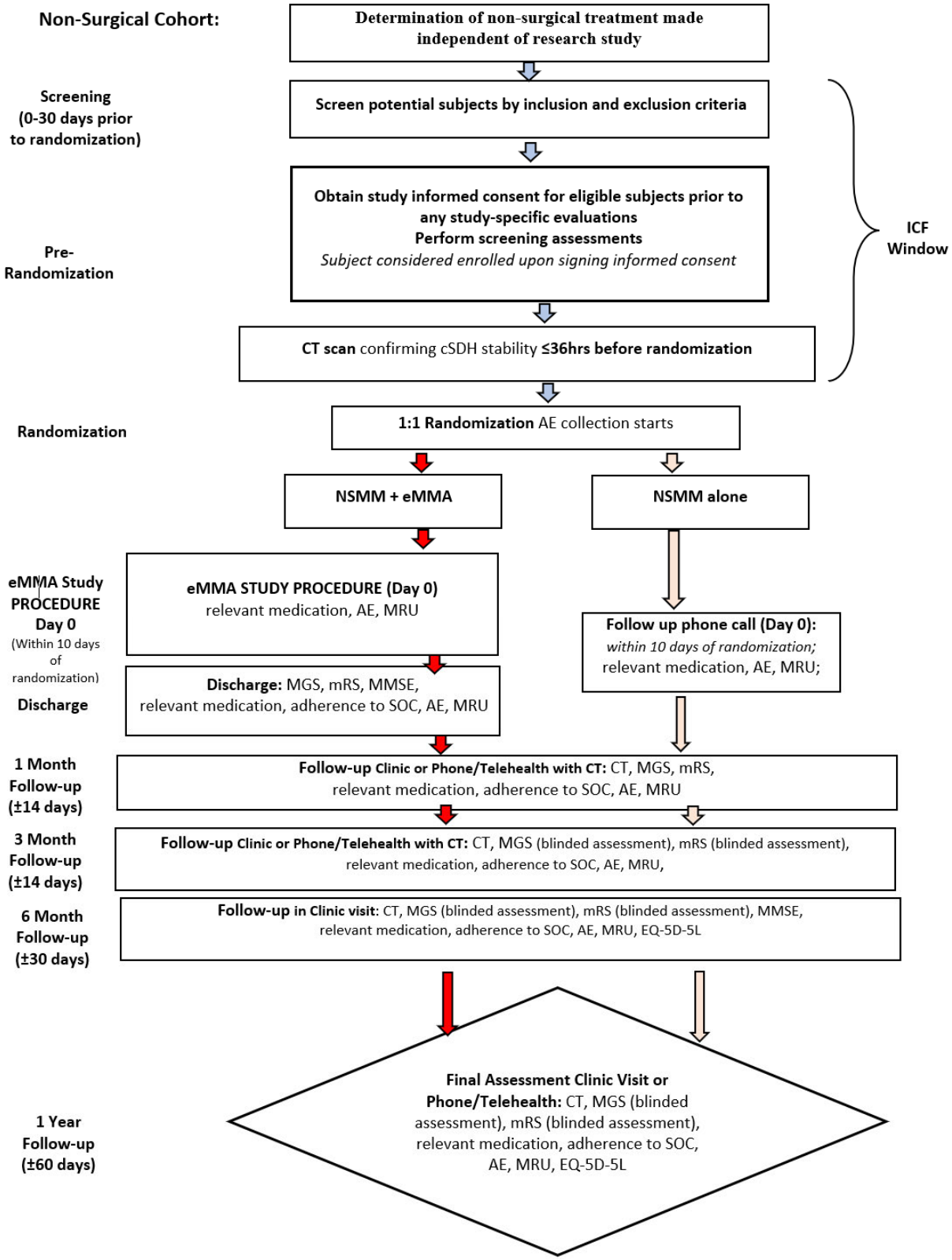
If the study is discontinued or suspended prematurely at a single clinical site (e.g. due to non-compliance or lack of enrollment) or across all study centers, the Sponsor shall inform the clinical investigator(s)/investigational center(s) of the termination or suspension in enrollment, along with the reason. 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 exited from the study. The Sponsor's communication to the investigator(s)/investigational center(s) will also include instructions for the investigator to promptly inform all consented subjects at their center(s), as well as the IRB/EC regarding the change in study status, along with the reason for termination or suspension. The Sponsor will notify regulatory authorities in writing of the action, per regulations. The personal physicians of the subjects may also need to be informed if deemed necessary.

## 7.7. 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 and a return receipt is filed to document delivery of the letter.

## 7.8. Schematic of Study Design




Non-Surgical Cohort:
Determination of non-surgical treatment made independent of research study
Screening (0-30 days prior to randomization)
Screen potential subjects by inclusion and exclusion criteria
Pre-Randomization
Obtain study informed consent for eligible subjects prior to any study-specific evaluations
Perform screening assessments
Subject considered enrolled upon signing informed consent
ICF Window
CT scan confirming cSDH stability ≤36hrs before randomization
Randomization
1:1 Randomization AE collection starts
NSMM + eMMA
NSMM alone
eMMA Study PROCEDURE Day 0
(Within 10 days of randomization)
eMMA STUDY PROCEDURE (Day 0)
relevant medication, AE, MRU
Follow up phone call (Day 0):
within 10 days of randomization;
relevant medication, AE, MRU;
Discharge
Discharge: MGS, mRS, MMSE,
relevant medication, adherence to SOC, AE, MRU
1 Month Follow-up (±14 days)
Follow-up Clinic or Phone/Telehealth with CT: CT, MGS, mRS,
relevant medication, adherence to SOC, AE, MRU
3 Month Follow-up (±14 days)
Follow-up Clinic or Phone/Telehealth with CT: CT, MGS (blinded assessment), mRS (blinded assessment),
relevant medication, adherence to SOC, AE, MRU,
6 Month Follow-up (±30 days)
Follow-up in Clinic visit: CT, MGS (blinded assessment), mRS (blinded assessment), MMSE,
relevant medication, adherence to SOC, AE, MRU, EQ-5D-5L
1 Year Follow-up (±60 days)
Final Assessment Clinic Visit or Phone/Telehealth: CT, MGS (blinded assessment), mRS (blinded assessment), relevant medication, adherence to SOC, AE, MRU, EQ-5D-5L

## 7.9. Schedule of Assessments

| **Surgical Cohort**<br><br>**Table Legend:**<br>X = Required<br>O = Optional, to be collected if performed during standard of care<br><br>**Assessments** | Screening (0-30 days prior to Randomization ) | Surgical Procedure | Pre-Randomization[1] | Randomization | Day 0 (within 10 days of surgery)<br>**Embolization Arm Only:** Embolization Procedure<br>**Surgery Alone Arm Only:** Phone/In person Follow up | Discharge[5] | 1 Month Follow-up (+/-14 days) Clinic or Phone/Telehealth + CT Exam | 3 Months Follow-up (+/- 14 days) Clinic or Phone/Telehealth + CT Exam | 6 Months Follow-up (+/- 30 days) Clinic Visit | 1 Year Follow-up (+/- 60 days) Clinic Visits or Phone /Telehealth/ + CT exam | Unscheduled Visit | Re-Operation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | |
| Pregnancy Test | X | | | | | | | | | | | |
| CT Exam[2] | X[7] | | X (≤36 hrs before randomization) | | | | X | X | X | X | O | X |
| Surgical Procedure | | X | | | | | | | | | | |
| Randomization | | | | X | | | | | | | | |
| Embolization Procedure (Embolization Arm Only) | | | | | X (DSA for eMMA) | | | | | | | |
| Glasgow Coma Scale (GCS) | | | X | | | | | | | | O | |
| Markwalder Grading Scale (MGS) | X[3] | | | | | X | X | X[4] | X[4,6] | X[4] | O | |
| Modified Rankin Score (mRS) | X[3] | | | | | X | X | X[4] | X[4,6] | X[4] | O | |
| Mini-Mental State Exam (MMSE) | | | X | | | X | | | X | | O | |
| Quality of Life (EQ-5D-5L) | | | X | | | | | | X | X | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X |
| Adherence to SOC | | | | | | X | X | X | X | X | X | X |
| Review of Adverse Events | | | | X | X | X | X | X | X | X | X | X |
| Medical Resource Utilization | | X | X | X | X | X | X | X | X | X | X | X |

[1] Pre-Randomization assessments may occur on the day of randomization, prior to the subject being randomized.
[2] An external CT scan (not performed by the site) is acceptable as long as the scan is provided to the site investigator and the core laboratory.
[3] Assessment should reflect the subject's condition just prior to undergoing surgery. Assessment may be performed post-surgery using pre-surgical data.
[4] Assessment must be performed by a qualified independent evaluator who is not part of the interventional (embolization) treating team, not involved in patient care or data entry, and is blinded to study treatment assignment. The evaluator does not need to be a physician.
[5] Discharge assessments may be performed when subject is medically ready to be discharged OR at the time of discharge.
[6] mRS and MGS may be completed via phone/telehealth by blinded assessor.
[7] MRI at screening is acceptable. Pre-randomization imaging must be CT scan

| **Non-Surgical Cohort**<br><br>**Table Legend:**<br>X = Required<br>O = Optional, to be collected if performed during standard of care<br><br>**Assessments** | Screening (0-30 days prior to Randomization) | Pre-Randomization[1] | Randomization | Day 0 (within 10 days of randomization)<br>**Embolization Arm Only:** Embolization Procedure<br>**NSMM Arm Only:** Phone/In person Follow up | Discharge[4]<br>**Embolization Arm Only** | 1 Month Follow-up (+/-14 days) Clinic or Phone/Telehealth + CT Exam | 3 Months Follow-up (+/- 14 days) Clinic or Phone/Telehealth + CT Exam | 6 Months Follow-up (+/- 30 days) Clinic Visit | 1 Year Follow-up (+/- 60 days) Clinic Visit or Phone/Telehealth + CT Exam | Unscheduled Visit | Surgical Procedure |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | | |
| Medical History | X | | | | | | | | | | |
| Pregnancy Test | X | | | | | | | | | | |
| CT Exam[2] | X[6] | X (≤36 hrs before randomization) | | | | X | X | X | X | O | X |
| Randomization | | | X | | | | | | | | |
| Embolization Procedure (Embolization Arm Only) | | | | X (DSA for eMMA) | | | | | | | |
| Glasgow Coma Scale (GCS) | X | | | | | | | | | O | |
| Markwalder Grading Scale (MGS) | X | | | | X | X | X[3] | X[3,5] | X[3] | O | |
| Modified Rankin Score (mRS) | X | | | | X | X | X[3] | X[3,5] | X[3] | O | |
| Mini-Mental State Exam (MMSE) | | X | | | X | | | X | | O | |
| Quality of Life (EQ-5D-5L) | | X | | | | | | X | X | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X |
| Adherence to SOC | | | | | X | X | X | X | X | X | X |
| Review of Adverse Events | | | X | X | X | X | X | X | X | X | X |
| Medical Resource Utilization | | | X | X | X | X | X | X | X | X | X |

[1] Pre-Randomization assessments may occur on the day of randomization, prior to the subject being randomized.
[2] An external CT scan (not performed by the site) is acceptable as long as the scan is provided to the site investigator and core laboratory.
[3] Assessment must be performed by a qualified independent evaluator who is not part of the interventional (embolization) treating team and not involved in patient care or data entry and is blinded to study treatment assignment. The evaluator does not need to be a physician
[4] The discharge assessments may be performed when subject is medically ready to be discharged OR at the time of discharge.
[5] mRS and MGS may be completed via phone/telehealth by blinded assessor.
[6] MRI at screening is acceptable. Pre-randomization imaging must be CT scan

# 8. Assessment of Safety

## 8.1. Specific Safety Parameters

To ensure the safety of the subject and provide a complete picture of the safety of the device so that important safety events are not missed, all adverse events occurring from the time of randomization through the one year follow up visit will be captured at each study visit. Progression of disease or subdural hematoma recurrence (e.g. increase in midline shift or increase in subdural hematoma size) will not be considered an AE, unless symptomatic.

In addition, all mortality will be reported in the study regardless of causality.

The following will be reported by the independent Imaging Core Lab and not reported as AEs unless they are symptomatic.

- Increased midline shift
- Increased subdural hematoma size

### 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 prior to randomization will be considered as baseline and not reported as an AE. 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 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

- Led to fetal distress, fetal death, 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

### 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. Unanticipated Adverse Device Effect (UADE)

Per 21 Code of Federal Regulations (CFR) 812.3(s), an unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

### 8.1.7. 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 SADE, it should be documented on the appropriate eCRF, and the device failure and AE (if applicable) 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.

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 labeling.

Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

**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, or investigator brochure (ISO 14155:2020).

**Use error** is defined as the 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 (ISO 14155:2020).

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.

## 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 1 - 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 and/or Procedure

The investigator 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. Refer to Sections 8.6 and 8.7 regarding CEC adjudication and DMC safety oversight, respectively.

**Table 2 - Adverse Event Causality Classifications**

| Caused By | Relation | Definition of Relation |
|---|---|---|
| **Device** | Causal relationship | The event is associated with the study device beyond reasonable doubt |
| | Probable | The relationship with the use of the study 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 study device is weak but cannot be ruled out completely |
| | Not related | Relationship to the study device can be excluded |
| **Study Procedure (Embolization)** | 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 procedure can be excluded |
| | Causal relationship | The event is associated with the surgical procedure beyond reasonable doubt |

| | | |
|---|---|---|
| **Surgical Procedure to treat the SDH** | Probable | The relationship with the surgical 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 surgical procedure is weak but cannot be ruled out completely |
| | Not related | Relationship to the surgical procedure can be excluded |
| **SDH Medications** | Causal relationship | The event is associated with SDH medication beyond reasonable doubt |
| | Probable | The relationship with the SDH medication seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained |
| | Possible | The relationship with the SDH medication is weak but cannot be ruled out completely |
| | Not related | Relationship to the SDH medication can be excluded |

**Note: Related events are defined as those with causal, probable and possible relationship to the event.**

### 8.2.3. Outcome

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

**Table 3 - 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) |

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

Adverse events shall be assessed and documented starting at the point of randomization. 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. Each investigator shall provide source documentation as requested by the Sponsor to facilitate reporting and adjudication of these events.

## 8.4. Reporting Procedures

### 8.4.1. Adverse Event Documentation and Reporting Requirements

All adverse events 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 MEMBRANE study mailbox: n-BCA_Pivotal_CNV_2020_01@its.jnj.com. Note: the adverse event(s) will still need to be recorded on eCRFs once EDC is functional.

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.

The different types of AEs and Device Deficiencies should be reported within the timeframes noted in Table 4, or per local country requirements, whichever is earlier.

**Table 4 - Adverse Event Reporting Requirements**

| Type of Adverse Event | Reporting Requirements |
|---|---|
| SAE<br>SADE<br>USADE<br>Death<br>Any study device deficiencies that could have led to a SADE* | Report to Sponsor immediately, and no later than 72 hours upon study site staff awareness of event or according to the local reporting requirements if less than 72 hours. |
| UADE | Report to Sponsor immediately, and no later than 72 hours, upon study site staff |

| Type of Adverse Event | Reporting Requirements |
|---|---|
| | awareness of event, followed by a written report within 10 working days after investigator first learns of the effect to Sponsor and IRB/EC or according to the local reporting requirements if less than 72 hours and 10 working days. |
| All other adverse events<br>All other study device deficiencies* | Report to Sponsor immediately, and no later than 14 calendar days, upon study site staff awareness or according to the local reporting requirements if less than 14 calendar days. |

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

The Investigator will report all the above to the reviewing IRB/EC according to the local reporting requirements.

### 8.4.2. Unanticipated Adverse Device Effect Reporting

Sponsor must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs/ECs, and participating investigators within 10 working days after the Sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1) or according to the local county reporting requirements.

A Sponsor who determines that a UADE presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the Sponsor makes this determination and not later than 15 working days after the Sponsor first received notice of the effect. 21 CFR 812.46(b(2)) or according to the local country reporting requirements.

## 8.5. Device Complaints, Failures, Deficiencies, and Malfunctions

All device complaints, failures, deficiencies, malfunctions (with or without an associated AE), and technical complications must be reported to Cerenovus Complaint department within **72 hours** of investigator's/site's knowledge of the event or according to the local reporting requirements if less than 72 hours. This device must remain at the site until Sponsor provides instructions on how to return the device for analysis.

## 8.6. Clinical Events Committee

The independent Clinical Events Committee (CEC) will consist of a minimum of three independent physicians with expertise in neurosurgery, neurology or interventional

neuroradiology and who are not otherwise involved with the study. The CEC will review all adverse events to adjudicate the safety endpoints (e.g. death, stroke, MI, thromboembolic complications, new onset seizure). The CEC will operate under a CEC Charter.

### 8.7. Data Monitoring Committee

An independent DMC will be responsible for assessing and monitoring the accumulated AEs and interim data on a periodic basis as the study progresses to ensure subject safety. The DMC will be comprised of representatives from multiple disciplines including but not limited to neurosurgery, neurology, interventional neuroradiology and biostatistics. The DMC will advise the Sponsor regarding the continuing safety of subjects and those yet to be recruited to the study, as well as the continuing validity and scientific merit of the study. The DMC will provide recommendations to the Sponsor regarding stopping or continuing enrollment in the study. The DMC will operate according to an approved charter.

## 9. Clinical Monitoring

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 complies with 21 CFR Parts 812, 11, 50, 54, and 56, ISO 14155, the currently approved protocol, Good Clinical Practice, and with applicable regulatory requirements. Each site will undergo periodic monitoring visits, and subject source documentation, including medical records, shall be made available during the visits.

The monitors for this study will be:

Johnson and Johnson
31 Technology Drive
Irvine CA, 92618

Johnson & Johnson Medical (Shanghai) Ltd.
Part C F1-3 No 439 Fute West First rd China (Shanghai) Pilot Free Trade Zone, Shanghai, P.R. CHINA

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

- Protocol adherence
- Source data verification and accuracy of the eCRFs
- Verification that informed consent is being obtained for all subjects screened and enrolled 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 Authority Log, Pre-Screening Logs, etc.
- Device accountability for regions in which the study device is investigational
- Compliance with applicable regulations
- Identification and action to resolve any issues or challenges 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. The Sponsor 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.

### 9.1 Site Selection

The sites selected to participate in this study will be required to have:

- Treating investigators who participate in the study will have extensive experience using TRUFILL n-BCA or similar device (e.g., or other n-BCA) in neurovascular embolization procedures.
- All sites will have a neurosurgical program capable of treating subdural hematomas.
- Investigators will have experience performing embolizations through the middle meningeal artery.
- All sites will be required to have adequate resources to conduct the clinical study and assure compliance.
- Each investigator will be required to commit to follow all subjects per protocol, including preforming the required CT scans.

## 10.0 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.

### 10.1 Analysis Sets

The following analysis sets are defined for this study:

- **Intent-to-Treat (ITT) Analysis Set**

The ITT analysis set consists of all enrolled subjects who are randomized in the study. Subjects will be analyzed as randomized regardless of treatment received.

- **Per Protocol (PP) Analysis Set**

The PP analysis set is a subset of the ITT analysis set, excluding the subjects with significant eligibility deviations, as well as those who did not receive treatment as assigned, in addition to other major protocol deviations which will be outlined in the Statistical Analysis Plan.

- **As Treated (AT) Analysis Set**

The As Treated analysis set consists of all randomized in the study who receive study treatment. Subjects will be analyzed by actual treatment they received.

## 10.2 Randomization and Blinding Procedures

This is an open label study. Subjects presenting with a subdural hematoma will be assessed by site physicians to determine the appropriate treatment for each subject: surgery or non-surgical management. Eligible subjects will then be randomized 1:1 to undergo SOC with eMMA vs SOC alone. Randomization will be stratified by site within cohort.

The Sponsor will remain blinded to the summary outcomes by treatment arm until the primary endpoint analyses are complete.

## 10.3 Levels of Significance

The primary effectiveness endpoint will be tested at a one-sided significance level of 0.05. Secondary endpoints will be tested using a gatekeeping strategy only if the primary effectiveness endpoint is successful. The familywise error-rate for hypotheses tests intended for labeling will therefore be controlled at 5%.

## 10.4 Sample Size Justification

Cochran–Mantel–Haenszel (CMH) statistic will be used to test superiority in the primary effectiveness endpoint of SOC with eMMA over SOC alone. The CMH test will be performed with stratification of the cohorts (surgical vs. NSMM). A target of approximately up to 70% of subjects are expected to be allocated to the surgical cohort and the remaining subjects will be allocated to the NSMM cohort. Subjects within each cohort will be randomized 1:1 to SOC alone or SOC with eMMA. Assuming a common odds ratio (Agresti, 1990) of0.34, a total sample size of 376 subjects after accounting for 10% attrition will provide at least 80% power for the primary effectiveness endpoint at a one-sided significance level of 0.05.

Anticipated effectiveness rates for the primary effectiveness endpoint were derived from the literature (key articles include Rovlias et al., 2015; Kim, 2017; Brennan et al., 2017; Ban et al., 2018; Knopman et al., 2018; Fountas et al., 2019; Link et al., 2019; Shotar et al., 2020; Ng et al., 2020). The assumptions in Tables 5 and 6 below reflect the consensus of the Executive Steering Committee for the study.

For the secondary endpoint that evaluates a component of the primary effectiveness endpoint later in time (12 months), it is anticipated that the effect size will be at least as large for the primary effectiveness endpoint assessment.

**Table 5 – Assumptions of event probability of primary effectiveness endpoint in surgical cohort**

| | SOC with eMMA | SOC alone |
|---|---|---|
| Event-free (success) probability | 95.9% | 88.5% |
| Event (failure) probability | 4.1% | 11.5% |
| Odds ratio | 0.33 | |

Note: odds ratio is calculated as the ratio of odds of failure over success in SOC with eMMA versus the odds of SOC alone.

**Table 6 - Assumptions of event probability of primary effectiveness endpoint in non-surgical medical management cohort**

| | SOC with eMMA | SOC alone |
|---|---|---|
| Event-free (success) probability | 90.9% | 78.0% |
| Event (failure) probability | 9.1% | 22.0% |
| Odds ratio | 0.35 | |

Note: odds ratio is calculated as the ratio of odds of failure over success in SOC with eMMA versus the odds of SOC alone.

For the primary safety endpoint, we expect at least an 80% probability of observing AEs that occur at an incidence of at least 1% within each treatment group. This expectation pertains to approximately 188 participants receiving eMMA (surgery + eMMA and NSMM + eMMA) and 188 participants receiving standard of care (surgery alone and NSMM alone).

## 10.5 Analyses to be Conducted

### 10.5.1. General Conventions

Data will be summarized by treatment arm and cohort, unless instructed otherwise.

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 percent will be provided.

In the event a subject withdraws or discontinues from the study without completing full follow-up, unless otherwise specified, observed data up to the date of discontinuation or withdrawal will be included in analyses. Unless specified otherwise, percentages will be based on the number of subjects without missing data.

Endpoints will be analyzed by analysis window in the SAP and may differ from the protocol defined clinical visit window.

### 10.5.2. Disposition of Study Subjects

Subject disposition will be summarized by treatment arm and cohort in the following way:

- With a summary of the number and percentage of subjects enrolled by site/investigator

- With a subject accountability table which indicates the number and percentage of subjects in each analysis set, and a summary of subjects who were randomized, completed the study, who died or were withdrawn or lost-to-follow-up with associated reasons.

### 10.5.3. Demographics and Baseline Characteristics

All demographic and baseline characteristics, will be summarized for each analysis set, including but not limited to: age, sex, medical history, prior treatment etc.

### 10.5.4. Procedural and Post-Procedural Characteristics

Procedural and immediate post-operative characteristics will be summarized for each analysis set.

### 10.5.5. Primary Endpoint and Secondary Endpoint Analyses and Associated Hypotheses

#### 10.5.5.1. Primary Endpoint and Associated Hypotheses

**1. Primary effectiveness endpoint: Residual or re-accumulation of the cSDH (>10 mm) at 6 months as assessed by an independent core laboratory OR re-operation or surgical procedure on the cSDH within 6 months post randomization**

The primary effectiveness endpoint analysis will be conducted on the ITT analysis set as the primary analysis; the same analysis will be repeated using the PP and AT analysis sets as supportive analyses.

The null and alternative hypotheses for this endpoint are

$$H_0: \theta_{CMH} \geq 1$$

$$H_A: \theta_{CMH} < 1$$

Where $\theta_{CMH}$ is the common odds ratio for primary effectiveness endpoint failure. Cochran-Mantel-Haenzel (Agresti 1990) test with continuity correction, and stratification by cohort (surgical or non-surgical) will be used to test the primary effectiveness endpoint at a one-sided significance level of 5%.

Subjects are considered as primary effectiveness endpoint failures if they have reported any of the following events:

- Residual or re-accumulation of their subdural hematoma (>10mm) at 6 months as assessed by the independent Imaging Core Lab;
- Any re-operations or surgical procedures on the cSDH within 6 months post-randomization.

The number and percentage of subjects with events will be summarized by treatment arm and cohort.

For subjects who didn't receive any re-operations or surgical procedures on the cSDH, but with missing values on the subdural hematoma thickness at 6 months, their missing hematoma thickness at 6 months will be imputed, further details refer to section 10.5.5.8.

Subjects whose hematoma thickness at 6 months is missing due to death prior to the 6-month CT scan and the death is due to an AE found by the CEC to be related to the study device or underlying disease state (i.e., lack of efficacy in study treatment), will be considered failures on this endpoint.

The endpoint will be considered successful if the p-value the continuity corrected CMH test is significant at the 0.05. The study will be considered successful if the primary effectiveness endpoint is claimed a success.

**2. Primary safety endpoint: Occurrence of all AEs through 6 months**

All AEs through 6 months will be summarized descriptively using the As Treated analysis set in treatment with eMMA (surgery + eMMA and NSMM + eMMA) vs. treatment with SOC (surgery alone and NSMM alone). The same analysis will be repeated using the ITT and PP analysis sets as supportive analyses.

### 10.5.5.2. Secondary Endpoints and Associated Hypotheses

Hypotheses on secondary endpoints will only be tested if the primary effectiveness endpoint is achieved.

These hypotheses will be analyzed in the ITT analysis set per the following order.

**1. <u>Good functional outcome at 3 months (mRS 0-2 or no worsening from baseline if baseline mRS ≥3)</u>**

The null and alternative hypotheses for the non-inferiority test on this endpoint are

$$H_0: P_{SOC+eMMA} - P_{SOC} \leq -12\%$$
$$H_A: P_{SOC+eMMA} - P_{SOC} > -12\%$$

where $P_{SOC+eMMA}$ and $P_{SOC}$ are the proportions of success in subjects who reported good functional outcome at 3 months in the treatment of SOC+ eMMA and SOC alone (across both cohorts), respectively. A subject is considered a success for this endpoint if mRS is 0-2 at 3 months, or there is no worsening from baseline if baseline mRS is ≥3.

Based on the precedent for the same endpoint in the EMBOLISE Study (NCT04402632) presented at the International Stroke Conference (Davies et al., 2024) and in agreement with the MEMBRANE study Co-Principal Investigators (PIs), the application of the 12% non-inferiority margin will not yield a clinically meaningful difference from the treatment of standard of care.

Subjects with missing data at 3 months will be imputed per section 10.5.5.8. The null hypothesis will be rejected if the one-sided 95% lower confidence bound is greater than -12%.

2. **Subjects requiring a surgical procedure on the cSDH within 12 months**

The null and alternative hypotheses for the superiority test on this endpoint are

$$H_0: \theta_{CMH \cdot sp} \geq 1$$

$$H_A: \theta_{CMH \cdot sp} < 1$$

where $\theta_{CMH \cdot sp}$ is the common odds ratio for surgical procedure endpoint failure. Cochran-Mantel-Haenzel test with continuity correction, and stratification by cohort (surgery or NSMM) at a one-sided significance level of 5% will be performed.

Subjects are considered as surgical procedure endpoint failures if they experienced any re-operations or surgical procedures on the cSDH within 12 months.

The endpoint will be considered successful if the p-value from the continuity corrected CMH test is less than at the 0.05.

**3. Mean change in hematoma volume at 6 months compared to baseline as assessed by an independent core laboratory**

The null and alternative hypotheses for this endpoint are

$$H_0: \Delta \geq 0$$

$$H_A: \Delta < 0$$

where $\Delta = \mu_{SOC+eMMA} - \mu_{SOC}$ is the difference in mean change in hematoma volume at 6 months compared to baseline between treatments of SOC+eMMA vs. SOC alone. $\mu_{SOC+eMMA}$ is the mean change hematoma volume with SOC and eMMA (6 months – baseline); while $\mu_{SOC}$ similarly is the mean change in hematoma volume in SOC alone. Baseline is defined as the pre-randomization image.

ANOVA (analysis of variance) will be performed to test this secondary endpoint. Change in hematoma volume at 6 months will be the outcome variable. Main effects for treatment (SOC alone or SOC with eMMA) and cohort (surgery or NSMM) will be included in the model. Subjects with missing values on hematoma volume at baseline or 6 months will be imputed according to the strategy described in section 10.5.5.8. The null hypothesis will be rejected if the one-sided 95% upper confidence bound on $\Delta$ is less than 0.

### 10.5.5.3. Other Secondary Endpoint Analyses – Effectiveness

Secondary effectiveness endpoints will be summarized by the planned treatment arm and cohort using the ITT and PP analysis sets. Missing values on the assessments will be excluded.

**1. Mean change in hematoma volume at 3 and 12 months compared to baseline as assessed by an independent core laboratory**

Mean change in hematoma volume and change from baseline will be summarized at 3and 12 months. Baseline is defined as the pre-randomization image.

**2. Reduction of > 50% hematoma volume at 3, 6 and 12 months as assessed by an independent core laboratory**

Logistic regression will be used to obtain the predicted probability and estimated odds ratios for the reduction of >50% in hematoma volume at 3, 6 and 12 months. Details of the logistic regression models will be provided in the SAP. The predicted probabilities of reduction >50% at 3, 6 and 12 months will be summarized. Baseline is defined as the pre-randomization image.

**3. Complete resolution of the cSDH at 3, 6 and 12 months assessed by an independent core laboratory**

Logistic regression will be used to obtain the predicted probabilities and the estimated odds ratios of complete resolution of cSDH at 3, 6 and 12 months. Details of the logistic regression model(s) will be provided in the SAP. The predicted probabilities of complete resolution at 3, 6 and 12 months will be summarized.

**4. Median time to achieve complete resolution of the cSDH**

Inverse prediction from logistic regression will be used to estimate the median time to achieve complete resolution of the cSDH, where the median time is the time corresponding to 50% predicted probability of achieving complete resolution of the cSDH. Details of the logistic regression model(s) will be provided in the SAP.

**5. Subjects that develop an acute component of their existing cSDH or a new cSDH at 3, 6 and 12 months as assessed by an independent core laboratory**

Stratified Kaplan-Meier analyses by cohort and treatment will be used to summarize the cumulative incidence of an acute component of the existing cSDH or a new cSDH at 3, 6 and 12 months.

**6. Subjects requiring surgical procedure on the cSDH within 3 and 6 months post randomization**

Stratified Kaplan-Meier analyses by cohort and treatment will be used to summarize the cumulative incidence of surgical procedures on the cSDH within 3 and 6 months.

**7. Subjects requiring more than one surgery on the cSDH within 3, 6 and 12 months post randomization**

The number and percentage of subjects who require more than one (i.e., two or more) surgical procedures or re-operations on the cSDH within 3, 6 and 12 months post randomization will be summarized by cohort and treatment.

### 10.5.5.4. Secondary Endpoint Analyses – Safety

Secondary safety endpoints will be summarized using ITT, PP and As Treated analysis sets.

**1. mRS distribution change at 3, 6 and 12 months**

mRS distribution at baseline and post-baseline mRS at 3, 6 and 12 months will be summarized across all subjects by treatment and cohort. Subjects with missing mRS scores post-baseline due to all-cause death will be considered to have a score of 6 in the analysis,

subjects with missing mRS scores due to reasons other than all-cause death will be excluded from the analysis.

**2. Death, stroke, myocardial infarction or thromboembolic complications within 3, 6 and 12 months as assessed by the Clinical Events Committee**

Death, stroke, myocardial infarction or thromboembolic complications are considered as a composite endpoint. Stratified Kaplan-Meier analyses by cohort and treatment will be used to summarize the cumulative incidence of the composite endpoint within 3, 6 and 12 months.

**3. Development of new onset of seizures within 3, 6 and 12 months as assessed by the Clinical Events Committee**

Stratified Kaplan-Meier analyses by cohort and treatment will be used to summarize of the cumulative incidence of new onset of seizures within 3, 6 and 12 months.

**4. Change in Markwalder Grading Scale at 3, 6 and 12 months compared to baseline**

Mean Markwalder Grading Scale score at each timepoint and change from baseline at 3, 6 and 12 months will be summarized.

**5. Change in MMSE score at 6 months compared to baseline**

Mean MMSE score and change from baseline at 6 months will be summarized.

#### 10.5.5.5. Secondary Endpoint Analyses – Health Economics

Health economic endpoints will be summarized in PP analysis set.

**1. Hospital days and ICU days**

Index procedure hospitalization for the eMMA treatment will be summarized by cohort.

All-cause hospitalizations during follow-up will be summarized separately by treatment arm and cohort. The number of hospitalizations, proportion of subjects who are hospitalized, length of stay in ICU, and total length of stay in days (including ICU days) will be summarized separately. Subjects who die before discharge will be summarized separately.

**2. Change in EQ-5D-5L score at 6 months compared to baseline**

Mean EQ-5D-5L score at baseline and follow-up visits and change from baseline at 6 months and 1 year; and change between 6 months to 1 year will be summarized as well.

#### 10.5.5.6. Safety Analyses

Safety analyses will be summarized by treatment arm and cohort in As Treated analysis set.

All AEs collected in the study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs, SAEs, device or procedure-related AEs, AEs by severity, UADEs and deaths will be summarized with frequencies and listed.

Study device malfunctions will be summarized and listed.

#### 10.5.5.7. Plans for Interim Analyses

There are no planned interim analyses in the study.

#### 10.5.5.8. Handling of Missing Data

- Missing data for primary effectiveness endpoint at 6 months

For the primary effectiveness endpoint, subjects who did not receive any post-randomization re-operations or surgical procedures on the cSDH, but with missing values on the subdural hematoma thickness at 6 months will be imputed with multiple imputation method that will make use of the subject's own baseline hematoma thickness values and other potential auxiliary variables from each cohort.

The multiple imputation method results in a large collection of imputed datasets. The imputed primary effectiveness endpoint value (success or failure) will then be analyzed through CMH test. Estimates of common odds ratio from continuity corrected CMH test and associated variance will then be computed in each imputed dataset and pooled together per Rubin's method (1996). Additional imputation details will be elaborated in the SAP.

Missing data will be imputed in the primary analysis with ITT analysis set. The supportive analysis using PP and AT analysis set will use the observed values, no missing data to be imputed.

- Secondary endpoint: Good functional outcome at 3 months (mRS 0-2 or no worsening from baseline if baseline mRS ≥3)

Subjects with missing mRS scores due to death prior to 3 months will be considered to have a score of 6 in the analysis. Subjects with missing data at 3 months due to reasons other than death will be imputed with multiple imputation that will make use of baseline mRS and other auxiliary variables. Estimates of risk difference of the treatments and associated variance will then be computed in each imputed dataset and pooled together per Rubin's method.

- Secondary Endpoint: Missing data for surgical procedures on the cSDH within 12 months

Subjects with unknown status on surgical procedures within 12 months due to early discontinuation from the study will be imputed with multiple imputation method that will make use of the subject's hematoma thickness values and other potential auxiliary variables in each cohort. The estimates of common odds ratio and associated variance from each imputed dataset will then be handled in the same way as the primary effectiveness endpoint.

- Secondary Endpoint: Missing data for mean change in hematoma

volume at 6 months

Subjects with missing values on hematoma volume at 6 months will be imputed with multiple imputation method that will make use of the subject's baseline hematoma volume and other potential auxiliary variables in each cohort. The imputed hematoma volume at 6 months will then be used to in the model. Estimates of mean hematoma volume at 6 months and associated variance from each imputed dataset will then be combined per Rubin's method.

- No missing data imputation is planned for the analyses of other secondary endpoints

#### 10.5.5.9. Sensitivity Analyses

The sensitivity analysis for the primary effectiveness endpoint will include a Gail-Simon test (1985) for a potential qualitative interaction between the two cohorts at an alpha level of 0.15. Additional sensitivity analyses will be detailed in the SAP.

#### 10.5.5.10. Subgroup Analyses

The primary effectiveness endpoint will be analyzed by subgroups with clinically meaningful risk factors using the ITT analysis set. Summary statistics will be presented at each subgroup level by cohort. Further details will be detailed in SAP.

#### 10.5.5.11. Sex Specific Analyses

To investigate the effects by sex on the primary effectiveness endpoint, a logistic regression using the ITT analysis set will be performed and a treatment by sex interaction term will be included. The binary outcome on the primary effectiveness endpoint will be used as the response variable. The interaction term will be tested at an alpha level of 0.15 using Wald chi-square test statistic. A non-significant p-value on the interaction term (p-value > 0.15) will support poolability of outcomes across females and males. Summary statistics by sex will be presented by cohort.

#### 10.5.5.12. Assessment of Site/Region Homogeneity

Homogeneity of odds ratio of the primary effectiveness endpoint across sites and regions (US vs. OUS) will be assessed at an alpha level of 0.15 using the ITT analysis set. Logistic regression will be performed and a region by treatment interaction test will be included. A separate logistic regression will be performed in a similar way testing for site by treatment interaction. Then the Holm-Bonferroni multiplicity adjustment method will be used to control the family-wise error rate at 15% for the site and region hypothesis tests of homogeneity of the primary effectiveness endpoint. Sites with insufficient number of subjects will be pooled by geographic region before the actual analyses. The OUS enrollment is small (50) and is expected to be distributed between the two treatments and two strata. If there are model convergence issues, descriptive statistics by region will be provided.

# 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, including assurance that the study is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, as well as the regulatory requirements of the Food and Drug Administration and local government. The Sponsor will also maintain compliance with Good Clinical Practice (International Conference on Harmonization (ICH) version 4 du 1 May 1996), the European standard EN ISO 14155:2020 (Clinical Investigation of Medical Devices for Human Subjects), Sponsor general responsibilities (21 CFR 812.40), selection of investigators (21 CFR 812.43), monitoring (21 CFR 812.46), supplemental applications (21 CFR 812.35 [a] and [b]), maintaining records (21 CFR 812.140 [b]), and submitting reports (21 CFR 812.150 [b)]), and to local regulations where required.

- General Responsibilities

Sponsor's general duties consist of submitting the IDE application to FDA, assuring that sites have received IRB/EC approvals prior to starting the study, 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 federal regulations and informing proper authorities of unanticipated adverse effects and deviations from the protocol.

- 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 the FDA and investigators to obtain IRB/EC re-approval. A justification for each amendment will be documented.

- Maintaining Records

Sponsor will maintain copies of correspondence, signed Investigator Agreements, data, adverse device effects, financial disclosure and other records related to the study.

- Submitting Reports

Sponsor will submit any required regulatory reports identified in this section of the regulation. This includes unanticipated adverse device effects, withdrawal of FDA approval, current investigators list, annual progress reports, recall information, final reports and device use without informed consent.

## 11.2. Institutional Review Board / Ethics Committee

The protocol, ICF, 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 the Sponsor 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. The Sponsor 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 Process

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

Patient's informed consent must be obtained and documented.

The IRB/EC must review and approve an ICF specific to this study. Cerenovus will provide each study center with an example ICF. The clinical center, to meet specific IRB/EC requirements, may modify this example ICF; however, the ICF must contain all of the informed consent elements required by 21 CFR 50.25 or according to applicable local requirements. Each investigational site will provide sponsor 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.

### 11.3.2. Consent 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 conducted with the patients and their families. The investigator, or designee, will explain the research study to the patient 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 written consent form and to ask questions prior to signing. The patients should be allowed additional time as desired to consider the study prior to agreeing to participate. Prior to participation in the study, the ICF will be signed and personally dated by the patient or his/her legal representative. 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 ICF 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 PHI, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) 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 with compliance with HIPAA and any local privacy regulation and ultimately that the subject's privacy is guaranteed.

It is not expected that the TRUFILL n-BCA System will be used emergently as eligibility confirmation includes a screening process, and subjects requiring emergent hematoma evacuation will not be eligible to participate in the study. Therefore, consent under emergency circumstances does not apply.

### 11.3.3. 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. Imaging Core Lab, Clinical Research Associate, Central Lab 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 in the analysis and reporting of this evaluation will be used ensuring security and privacy of protected health information in accordance with HIPAA.

## 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 is required by regulation to 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 (i.e. Quality Assurance (QA) by the Sponsor and its representatives, 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. Any worksheets shall be signed by the investigator at the given site and will serve as the source document for those data parameters. 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 AEs, 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, local government authorities, or the FDA, acting in their official capacities, will have access to these confidential files.

### 13.1.4. Health Economic Data

The frequency of health care utilization during hospitalization for the study index procedure and any additional hospitalizations during the study period will be collected. This data will not be provided to the FDA as part of the IDE reporting because it does not support the safety and efficacy of the investigational device.

The hospitalization health care data to be collected may include, but is not limited to, the subject's admission date, discharge date, procedure date, ICD-10 and procedure codes and DRG assignment (if applicable).

In addition, the Sponsor will collect health economic data associated with follow up care including any additional or necessary procedures/surgeries resulting from the index

procedure, ER visits, and/or outpatient visits to address issues related to the target cSDH. Data collected may include quality of life data, length of hospital stay, and readmissions.

### 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.

## 13.2. 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 in compliance with FDA regulations per 21 CFR 812.140(d). Documents must be retained 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, or as specified per country specific record retention requirements, after the study is completed and or terminated. 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 regulation and applicable 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 may proceed without prior approval of the sponsor and the IRB/EC. Such deviations shall be documented and reported to the sponsor and IRB/EC 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 like, but not limited to www.ClinicalTrials.gov.

## 16.2. Steering Committee

A Steering Committee comprised of physicians with experience in the areas of neurosurgery, neurology or interventional neuroradiology has been 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 investigator training
- 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.

Clinical investigators will complete financial disclosure forms prior to initiating the study and update them annually or when changes occur related to stock and stock options and income from salary, honorariums, and consulting fees.

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