# Official Study Title: The SQUID Trial for the Embolization of the Middle Meningeal Artery (STEM) for Treatment of Chronic Subdural Hematoma

## NCT Number: NCT04410146

## Protocol Date: 01-MAR-2023

# THE SQUID TRIAL FOR THE EMBOLIZATION OF THE MIDDLE MENINGEAL ARTERY (STEM) FOR TREATMENT OF CHRONIC SUBDURAL HEMATOMA

## CIP-201912-SQUID
## VERSION 5.0

## 1-Mar-2023

**PRINCIPAL INVESTIGATORS:**
**DAVID FIORELLA, M.D., PH.D.**
**STONY BROOK UNIVERSITY MEDICAL CENTER**
**DEPARTMENT OF NEUROLOGICAL SURGERY**
[redacted]
**EMAIL:** [redacted]

**ADAM ARTHUR, M.D., M.P.H**
**SEMMES-MURPHEY NEUROLOGIC AND SPINE INSTITUTE**
**UNIVERSITY OF TENNESSEE HEALTH SCIENCES CENTER**
**DEPARTMENT OF NEUROSURGERY**
[redacted]

**SPONSOR AND FUNDER:**
**BALT USA, LLC**
[redacted]

[redacted]

## Clinical Protocol: STEM
## SPONSOR APPROVALS

Table 1. Sponsor Approvals

# TABLE OF CONTENTS

## FIGURES & TABLES



## APPENDICES

Table 2. STEM Trial Contact information

| Representative | Role |
|---|---|
| **Sponsor** | |
| Balt USA, LLC<br>[redacted] | |
| [redacted] | Sr. Manager, Clinical Affairs |
| **Global Principal Investigators** | |
| David Fiorella, M.D., Ph.D.<br>Stony Brook University Medical Center<br>Dept. of Neurological Surgery<br>[redacted] | Principal Investigator |
| Adam Arthur, M.D., M.P.H.<br>Semmes-Murphey Neurologic and Spine Institute<br>University of Tennessee Health Sciences Center<br>Department of Neurosurgery<br>[redacted] | Principal Investigator |
| **Neuropsychology Investigator** | |
| Brandon C. Baughman, Ph.D., ABPPCN<br>Semmes-Murphey Clinic<br>[redacted] | Neuropsychology Investigator |
| **Core Lab** | |
| Mayo Foundation for Medical Education and Research<br>200 First St SW,<br>[redacted] | |

| Table 3. Protocol Synopsis | |
|---|---|
| **Study Title** | The **S**QUID **T**rial for the **E**mbolization of the **M**iddle Meningeal Artery (STEM) for Treatment of Chronic Subdural Hematoma |
| **Protocol ID - Version** | CIP-201912-SQUID, v5.0 |
| **Study Device** | SQUID Liquid Embolic Agent |
| **Study Objective** | To provide an assessment of the safety and effectiveness of adjunctive Middle Meningeal Artery embolization (MMAE) with SQUID for the management of Chronic Subdural Hematoma (cSDH) |
| **Study Design** | A pivotal, international, multi-center, prospective, stratified combination randomized controlled trial |
| **Study Population** | Up to 310 Subjects with cSDH who present for neurological assessment– allocated prospectively to either surgical or medical management based upon the opinion of the treating team and then randomized (1:1) to either SQUID embolization or standard management (286 evaluable Subjects[1]). |
| **Estimated # of Sites** | Up to 35 sites in the US and up to 10 sites OUS |
| **Enrollment and Subject Participation Duration** | The duration of the enrollment period is expected to be up to 36 Months. Due to the impact of COVID-19, the enrollment period may be extended if required.<br>The overall Study duration for each Subject includes a follow-up period of up to 1-year (+/- 8 weeks). |
| **Primary Effectiveness Endpoint**[2] | Treatment failure as defined by the occurrence of any of the following events:<br>1. Residual or re-accumulation of the SDH (≥10 mm) on 180-day scan from intervention;<br>2. Re-operation (after index procedure) or surgical rescue within 180-days of intervention[3];<br>3. Any new, major disabling stroke[4], myocardial infarction (MI)[5] or death from any (neurological) cause within 180-days of intervention. |
| **Primary Safety Endpoint** | • Major disabling stroke or any death within 30-days from intervention |
| **Secondary Endpoints** | • mRS (analyzed as shift) at 180-days from intervention<br>• Any investigational device/procedure-related AE/SAE |

[1] Evaluable subjects are those who have started with their assigned treatments and based on available data, a determination can be made regarding the presence or absence of treatment failure for primary effectiveness endpoint
[2] 180 days visit (180 days +/-6w)
[3] Re-operation or surgical rescue includes cSDH evacuation via any surgical procedure OR embolization of the MMA with any commercially available product
[4] An increase in the NIHSS of 4 points or more from baseline that persists for 24 or more hours from the time of the event (Major stroke), AND results in a mRS of 3 or greater at 90 days from the event (Disabling stroke).
[5] Detection of a rise and/or fall of cardiac troponin (cTn) values with at least 1 value above the 99th percentile upper reference limit (URL) and with at least one of the following: Symptoms of acute myocardial ischemia; New ischemic electrocardiogram (ECG) changes; Development of pathological Q waves; Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.

| | |
|---|---|
| **Additional Endpoints** | • mRS (analyzed as shift) at 30-day, and 1-year from intervention<br>• mRS ≤ 2 (binary) at 30-day, 180-day, and 1-year from intervention<br>• Cognitive improvement, as measured by blinded assessment, utilizing the comprehensive neuro- cognitive battery at: Baseline, 30-day, 180-day and 1-year from intervention<br>• Hospital Days<br>• Intensive Care Unit (ICU) Days<br>• EQ-5D-5L (including EQ-VAS): Baseline vs. 30-day, 180-day, and 1-year from intervention<br>• NIHSS Baseline vs Discharge and 90-day<br>• CT/MRI: Baseline vs 180 days[6] |
| **Inclusion Criteria** | Subjects must meet ALL of the following criteria:<br><br>1. Male or female Subject whose age is ≥ 30 at the time of consent<br>2. Pre-morbid mRS 0-1 (Within the previous 12 months)[7]<br>3. cSDH measures ≥ 10 mm in greatest thickness<br>4. cSDH exerts mass effect upon the subjacent brain, Indicated by local cortical flattening and/or midline shift<br>5. Imaging characteristics indicative of chronicity (≥ 50% of the volume of the collection should be isodense or hypodense to normal cortical gray matter on Computed Tomography (CT))<br>6. Subject presents with one or more of the following neurological symptoms:<br>• headache;<br>• cognitive decline;<br>• speech difficulty or Aphasia;<br>• gait impairment or imbalance;<br>• focal neurological deficit (weakness, paresthesia or sensory deficit involving of one or more extremities or facial droop);<br>• and/or seizure<br>7. Subject, or his/her legally authorized representative, understands the nature of the procedure, consents to participation in the study and provides a signed Informed Consent<br>8. Female Subjects of child-bearing potential must be able to provide a current negative urine pregnancy test and agree to an appropriate method of contraception throughout the trial<br>9. Subject is able and willing to return to the investigational site for all follow-up visits (e.g., 30- day, 90-day, 180-day and 1-year), as required per protocol |

[6] Measuring cSDH Thickness (actual measurement, ≥ 10 mm), reduction of the SDH by 50% to 75%, cSDH Density (homogeneous vs. heterogeneous), any new intracranial hemorrhage (Subarachnoid Hemorrhage, Intracerebral Hemorrhage, SDH), new large vessel territory stroke

[7] Subjects had No symptoms at all (equivalent to mRS=0), or No significant disability despite symptoms; able to carry out all usual duties and activities (equivalent to mRS=1) in the last 12 months and any current morbid state (i.e., the clinical decline) can be reasonably attributed to the presenting cSDH

| | |
|---|---|
| **Exclusion Criteria** | Subjects shall be excluded if ANY of the following conditions exist:<br><br>1. Subject with prior ipsilateral craniotomy or burr hole evacuation of cSDH<br>2. Subject with prior embolization of either MMA<br>3. Subject requires (in the opinion of the treating surgeon) a full or mini craniotomy<br>4. Subject with urgent or emergent (within 1 hour of assessment) subdural hematoma evacuation needed<br>5. Subject with a cSDH with a focal location (confined to the frontal or temporal base or the inter- hemispheric space without cerebral convexity involvement)<br>6. cSDH developed due to underlying condition such as a vascular lesion, brain tumor, arachnoid cyst, spontaneous intracranial hypotension or secondary to a previous craniotomy<br>7. Life expectancy of <1 year<br>8. Subject who presents with an intracranial mass other than subdural hematoma<br>9. Subject who presents with a meningioma with mass effect and/or ≥1 cm or currently undergoing radiation therapy for carcinoma or sarcoma of the head or neck region<br>10. Subject with serum creatinine level > 3.0 mg/dL at time of enrollment (this will restrict the use of contrast) and not on dialysis<br>11. Subject with significant liver function impairment at time of enrollment<br>12. Subject with a life-threatening allergy to radiographic contrast (unless treatment for allergy is tolerated or can be managed medically)<br>13. Subject who is currently enrolled in another investigational study protocol that could potentially confound the current study endpoints |
| **Study Procedures** | Pre-Screening will be completed by the study team and if suitable for STEM trial, the subject or LAR will sign the informed consent form. Screening / Baseline evaluations will include assessment of study eligibility (including imaging of cSDH), relevant medical history, vital signs, concomitant medications, neurocognitive assessment and neurological and quality of life assessments (pre-morbid mRS, NIHSS, EQ-5D-5L). Baseline imaging can be CT/MRI collected at baseline visit or imaging performed within 7 days prior to screening/baseline.<br><br>Based upon the opinion of the treating team and pre-screening evaluation, Subjects who meet eligibility are allocated prospectively to either surgical or medical management. Under each management strata, subjects will then be randomized to either SQUID embolization or standard management.<br>Study design is depicted in Figure 1.<br><br>Only subjects who sign informed consent, pass eligibility criteria, and are randomized, may move forward with the assigned intervention (medical or surgical). Interventions are discussed in section 8.4. |
| **Schedule of Events** | Tables 5 and 6 list all the follow-up visits and required assessments. Subject Follow-up and Disposition is depicted in Figure 2. |

| Table 4. ACRONYMS | |
|---|---|
| AE | Adverse Event |
| ADE | Adverse Device Effect |
| ASADE | Anticipated Serious Adverse Device Effect |
| AVMs | Arteriovenous Malformations |
| CAPA | Corrective and Preventative Actions |
| CCA | Common Carotid Artery |
| CE | European Conformity |
| CEC | Clinical Events Committee |
| CFR | Code of Federal Regulations |
| COWAT | Controlled Oral Word Association Test |
| CRF | Case Report Form |
| CRO | Clinical Research Organization |
| cSDH | Chronic Subdural Hematoma |
| CSF | Cerebral Spinal Fluid |
| CT | Computed Tomography |
| CTA | Clinical Trial Agreement |
| CV | Curriculum Vitae |
| dAVF | Dural Arteriovenous Fistula |
| DMSO | Dimethyl Sulfoxide |
| DoA | Delegation of Authority |
| DSMB | Data Safety Monitoring Board |
| EC | Ethics Committee |
| ECA | External Carotid Artery |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |

| Table 4. ACRONYMS | |
|---|---|
| EQ-5D-5L | EuroQol Group - 5 Dimensions-5 Levels (measure of health) |
| EQ-VAS | EuroQol Group Visual Analogue Scale (measure of health) |
| eTMF | Electronic Trial Master File |
| EU | European Union |
| EVOH | Ethylene Vinyl Alcohol |
| EVT | Endovascular Treatment |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| HVLT-R | Hopkins Verbal Learning Test - Revised |
| HVTs | Hyper Vascular Tumors |
| IA | Ischemic Attack |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization |
| ICH | Intracerebral Hemorrhage |
| ICU | Intensive Care Unit |
| IDE | Investigational Device Exemption |
| IFU | Instructions for Use |
| IRB | Institutional Review Board |
| ISO | International Organization for Standardization |
| ITT | Intent to Treat |
| LAR | Legally Authorized Representative |
| LD 50 | Lethal Dose 50% |
| LE | Liquid Embolic |
| LEA | Liquid Embolic Agent |

| Table 4. ACRONYMS | |
|---|---|
| LOCF | Last Observation Carried Forward |
| MI | Myocardial Infarction |
| mm | Millimeter(s) |
| MMA | Middle Meningeal Artery |
| MR | Magnetic Resonance |
| mRS | Modified Rankin Scale |
| NIHSS | National Institutes of Health Stroke Scale |
| OR | Operating Room |
| OUS | Outside United States |
| PA | Posterior Anterior |
| PHI | Protected Health Information |
| PMA | Premarket Approval |
| PVA | Polyvinyl Alcohol |
| QOL | Quality of Life |
| RCT | Randomized Controlled Trial |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAH | Subarachnoid Hemorrhage |
| SDH | Subdural Hematoma |
| SEPS | Subdural Evacuating Port System |
| STEM | The SQUID Trial for the Embolization of the Middle Meningeal Artery |
| TIA | Transient Ischemic Attack |
| TMT | Trail Making Test |
| UADE | Unanticipated Adverse Device Effect |
| USADE | Unanticipated Serious Adverse Device Effect |

| Table 4. ACRONYMS | |
|---|---|
| VA | Veterans Affairs |

# 1 INTRODUCTION

Chronic subdural hematoma (cSDH) is a common disease affecting primarily older adults. In a recent Veterans Affairs (VA) study, an analysis of administrative data reflected a rate of 79.4 SDHs per 100,000 persons. The authors predicted that incidence rates of chronic SDH in United States in VA and civilian aging populations will reach 121.4 and 17.4 cases per 100,000 persons, respectively, by 2030, at which time, approximately 60,000 cases of chronic SDH will occur each year in the United States[1].

In these patients, it is believed that the underlying pathology is related to an inflammatory process during which the dura releases angiogenic factors which leads to exuberant neovascularization with subsequent bleeding and re-bleeding from these friable new vessels. This leads to spontaneous bleeding into the subdural space and the accumulation of blood over the cerebral convexities, which can result in significant mass effect, neurological dysfunction and sometimes death[2,3,4]. This process is exacerbated by anti-platelet and anti-coagulant medications, which are also frequently required by patients in this demographic[5]. The surgical and medical management of these patients is frustrating and complex, marked by frequent hospitalization, numerous follow-up imaging studies, surgical evacuation, hemorrhage re-accumulation and numerous subsequent re-operations for hemorrhage removal[1]. Moreover, the discontinuation of anti-coagulant medications in these patients is also associated with its own morbidity and mortality.

A number of case reports and case series have demonstrated that embolization of the middle meningeal artery can be effective in reducing the neovascularity which can make surgical evacuation more successful and can lead to higher rates of spontaneous resorption of the cSDH in non- surgical patients[6,7,8,9]. Recently a prospective evaluation of the technique in a series of 72 patients demonstrated that Polyvinyl alcohol (PVA) embolization of the middle meningeal artery seemed beneficial with lower rates of re-operation and cSDH re-accumulation than in a retrospective series of patients managed conventionally (without embolization) at the same institution[10]. These authors concluded that the procedure holds great promise, but that a randomized controlled trial (RCT) is needed[10].

In almost all of the existing studies investigating embolization for cSDH, PVA particles have been used to achieve devascularization of the meninges. The objective of this study is to demonstrate the safety and effectiveness of MMA embolization with SQUID for the management of cSDH in both surgical and non-surgical subjects. SQUID is a non-adhesive, liquid embolic agent consisting of an ethylene vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO) and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. SQUID is injected into the vascular site to be treated under fluoroscopic control. DMSO dissipates in the blood and causes precipitation of EVOH in which the tantalum powder is trapped. It then forms a consistent spongy embolus. This embolus solidifies from the outside inwardly while moving distally in the vessel. The non-adhesive character of the embolus allows slow and controlled injections while leaving in place the microcatheter.

In the present study, we have proposed using SQUID™, a liquid embolic agent, for several reasons. First, unlike embolization particles, the SQUID embolic material is directly visualized, offering a superior safety profile with a reduced risk of embolization for unintended targets. This is an important consideration, as the meningeal artery can have small anastomoses to the ophthalmic artery and retina as well as arteries near the skull base that supply critical cranial nerves. This superior visualization also allows the operator to more easily visualize penetration of the embolic agent into the arteries, supplying the dura and subdural membranes. A conventional CT or in-room cone beam CT will show, in great detail, the distribution of the embolic agent both within the larger meningeal branches as well as within the microvasculature of the subdural membranes. PVA particles are not radio-opaque and as such, it is not possible to ascertain the exact distribution of this embolic agent after the procedure. Second, the meningeal branches tend to be small and are prone to vasospasm and occlusion following catheterization with a microcatheter – this is particularly the case in older patients. PVA particles require robust antegrade blood flow to carry them into the more distal meningeal vascular bed. In many cases, PVA embolization will be incomplete and ineffective, as the microcatheter will essentially occlude flow in the target arteries precluding the injection of any significant volume of particles and limiting their distribution into the distal vascular bed (which is the key to achieving a successful embolization). Liquid embolic agents, like SQUID, in contrast, function optimally in an occlusive catheter position. In this situation, SQUID can be pushed forward into the dural bed with a controlled injection. This allows a more controlled, more distal, more complete, and safer embolization. Third, PVA particles are temporary agents. The PVA is resorbed over the course of several weeks, leading to re-canalization and potentially incomplete resorption or delayed recurrence of the cSDH. The liquid embolics, like SQUID, are permanent, providing the desired stable devascularization of the diseased meningeal membrane.

Finally, particulate injections can take a protracted period of time, particularly if multiple branches of the dura are targeted. SQUID embolization of each branch can be accomplished in just a few minutes, limiting procedure and anesthesia time and reducing fluoroscopy time.

SQUID has been marketed outside the United States under CE mark approval since March 2012. Since commencement of marketing until the end of 2017, a total of 43,700 units of SQUID (SQUID12, 12LD, 18, 18LD & SQUIDPERI 12, 12LD, 18, 18LD) have been supplied.

A clinical literature review and analysis of post-market surveillance (PMS) and adverse event reports for EVOH-based liquid embolization agents (LEAs) including SQUID and ONYX™ were compiled to identify any new risks or trends associated with the use of EVOH presentations for the treatment of lesions of the central and peripheral vascular system, including Arteriovenous Malformations (AVMs), Dural Arteriovenous Fistulas (dAVF) and Hyper Vascular Tumors (HVTs). The objective of this effort was to determine the agents' respective clinical safety and effectiveness for embotherapy of these pathologies.

There were 36 publications of ONYX and 3 publications for SQUID reviewed[11]. The clinical evidence met the applicable Essential Requirements and Specifications, supporting the safety and effectiveness of the SQUID Liquid Embolic Agent when used as intended for the embolization of lesions affecting the central and peripheral vascular system, including AVMs, dAVFs and HVTs. It was further concluded that the risks associated with the use of SQUID were found to be acceptable when weighed against the benefits to the patient[11].

### 1.1 Ethical Considerations – Europe

SQUID is a CE-marked, approved device. SQUID will only be used at the physician's discretion and for its indicated use in-line with the Instructions for Use. The collection and analysis of the data requires ethical approval; however, the use of SQUID under this trial protocol in Europe does not introduce any new ethical concerns beyond those present when treating any cSDH patient with an approved liquid embolic agent.

### 1.2 Ethical Considerations – United States

SQUID is not FDA cleared in the U.S. SQUID is an investigational device that may be used in the U.S. within the confines of the STEM IDE Study. The purpose of this Study is to gather information on device performance to support an application for FDA clearance.

## 2 STUDY OBJECTIVE

The objective of this Study is to demonstrate the safety and effectiveness of adjunctive MMA embolization with SQUID™ for cSDH patients undergoing either surgical or medical management.

## 3 STUDY DESIGN

A pivotal, international, multi-center, prospective, stratified combination randomized controlled trial (1:1 randomization under each treatment management stratum). The Investigational Device Exemption (IDE) Trial for indication will follow the International Organization for Standardization (ISO) 14155:2020 - Good Clinical Practices (GCP), 21 CFR Parts 11, 50, 54, 56, 812 and applicable sections of ICH E6 Guidelines. Imaging will be Core-Lab adjudicated. Clinical data will be externally monitored.

The hypothesis is that embolization of the middle meningeal artery with SQUID as an adjunct to standard management (either medical management or surgical management) is safe and effective in reducing the incidence of residual or recurrent cSDH at 6 months, the need for surgical rescue or re-operation, and neurological death, stroke or MI.

Sample Size Justification: Assuming a 19% failure rate in the embolization group (embolization followed by surgery or embolization alone) and a 36% failure rate in the control group (standard surgical or medical management), a total sample size of 286 evaluable subjects (allocated 1:1 between groups) will allow for a 90%

power to see a difference between groups (0.05 alpha). In order to account for dropouts, a total sample size of up to 310 subjects will be randomized.

Based upon the best judgment of the treating team, non-emergency cSDH Subjects will be stratified (allocated prospectively) into two main groups (strata), either Surgical or Medical Management. Each stratum will have at least 110 subjects (with a maximum of approximately 190 subjects in each stratum). Within each of these strata, each subject will then be randomized (1:1) to either standard management, or MMAE with SQUID (See Figure 1).

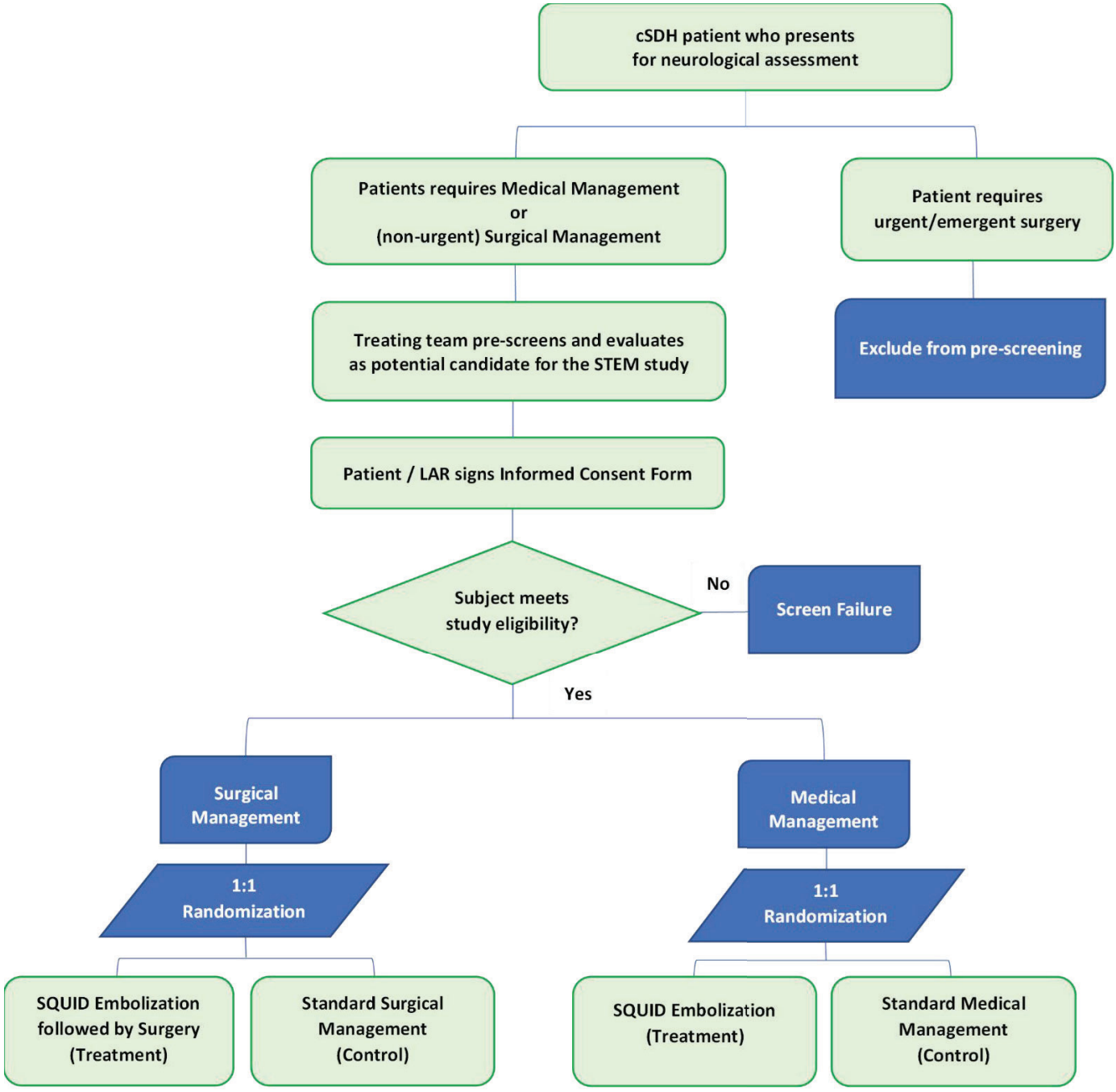


Figure 1. STEM Study Design

If assigned by the treating team to the Medical Management, subjects will then be randomized to either 'SQUID Embolization' (treatment arm) or 'Standard Medical Management' (control arm). If assigned by the treating team to the Surgical Management stratum, subjects will then be randomized to either 'SQUID Embolization followed by Surgery' (treatment arm) or to 'Surgery-only' (control arm). This study will compare subjects in the embolization group (under either management) to those in the control group (under either management).

Subject follow-up & disposition is depicted in the flowchart in Figure 2.

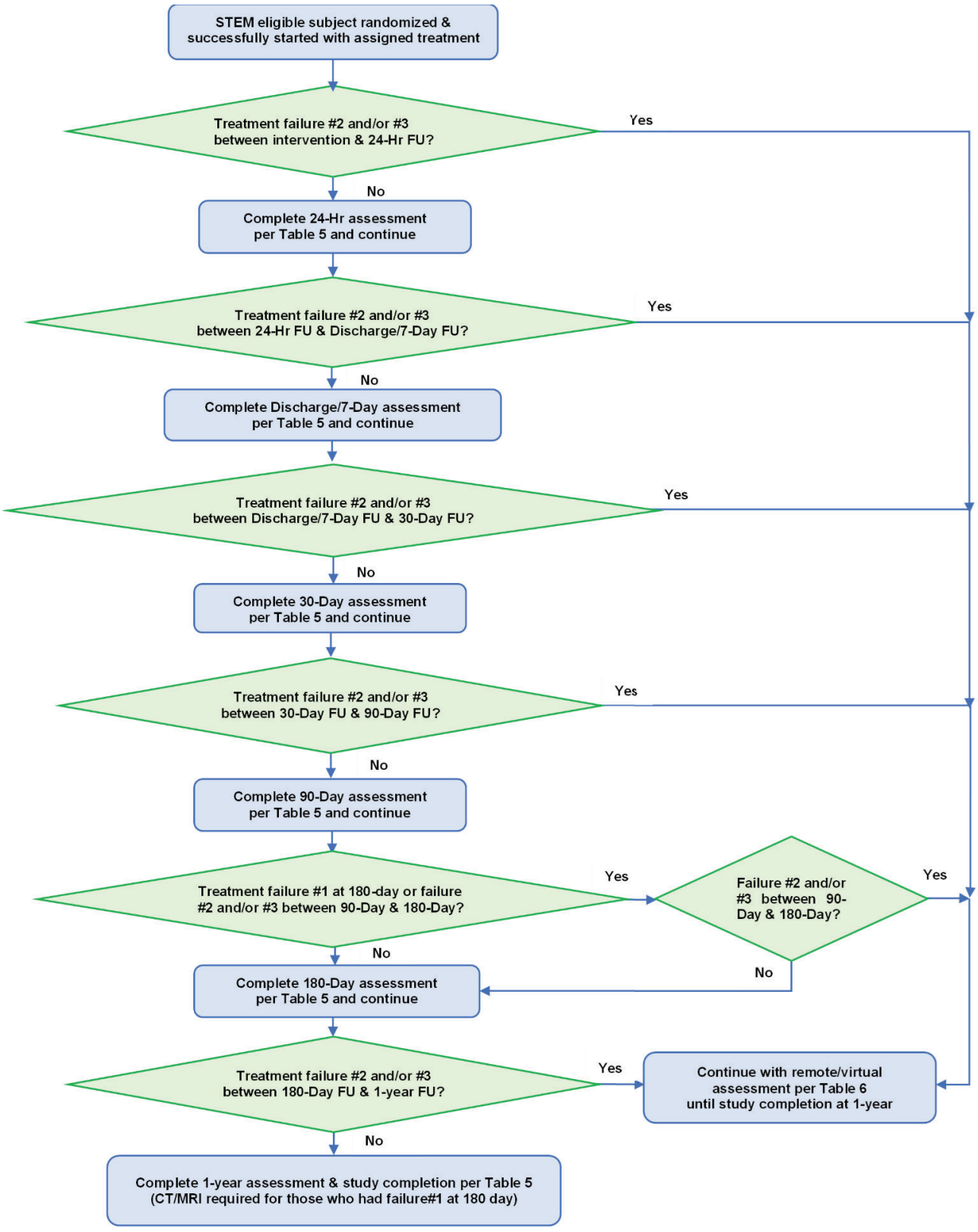


Figure 2. Subject Follow-up and Disposition

# 4 STUDY MATERIALS

## 4.1 STUDY DEVICE

### 4.1.1 Device Description

SQUID™ is a non-adhesive, liquid embolic agent consisting of an ethylene vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO) and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy.

### 4.1.2 OPERATING MODE

SQUID™ is injected into the vascular site to be treated under fluoroscopic control. DMSO dissipates in the blood and causes precipitation of EVOH in which the tantalum powder is trapped. It then forms a consistent spongy embolus.

This embolus solidifies from the outside inwardly while moving distally in the vessel. The non-adhesive character of the embolus allows slow and controlled injections while leaving the microcatheter in place.

### 4.1.3 FORMULATIONS

SQUID™ is available for single use in the following formulations and will be selected based on the discretion of the Investigator's evaluation of the Subject's condition undergoing embolization:

- SQUID12 (4% by weight of EVOH; 30% by weight of tantalum)
- SQUID12LD (4% by weight of EVOH; 20% by weight of tantalum)
- SQUID18 (5.3% by weight of EVOH; 30% by weight of tantalum)
- SQUID18LD (5.3% by weight of EVOH; 20% by weight of tantalum)
- SQUID34 (7% by weight of EVOH; 30% by weight of tantalum)
- SQUID34LD (7% by weight of EVOH; 20% by weight of tantalum)

Note:
SQUIDXX: SQUID in 1.5-mL vial size configuration
SQUIDXXLD: SQUID Low Density in 1.5-mL vial size configuration

### 4.1.4 MATERIAL COMPOSITION

Copolymer: EVOH (ethylene vinyl alcohol; 48 mol%) Solvent: DMSO (dimethyl sulfoxide)
Radiopaque agent: Micronized Tantalum Powder

### 4.1.5 PACKAGING

The SQUID™ Liquid Embolic Agent consists of:
Composition for SQUID 1.5-mL vial-size configuration:

- One (1) (1.5-mL) vial of SQUID EVOH
- One (1) (1.5-mL) vial of DMSO
- One (1) Tyvek® pouch containing:
  - Two (1-mL) SQUID delivery syringes
  - One (1-mL) DMSO delivery syringe
  - Two syringe adapters

The vials and the pouch are packaged in a cardboard box with the Instructions for Use (IFU).
See Figure 3, SQUID™ Liquid Embolic System and Figure 4, Packaging Pouch Sample (OUS).

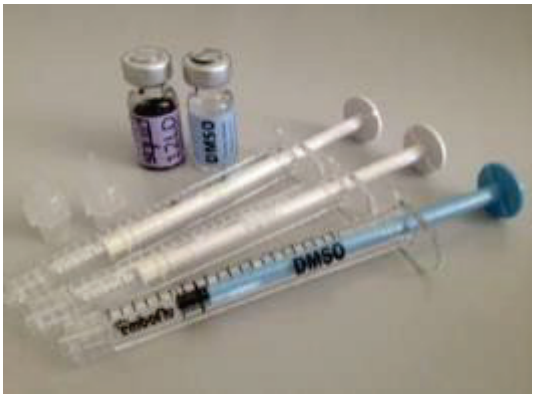


Figure 3. SQUID™ liquid embolic agent


Figure 4. Packaging Pouch Sample (OUS)

### 4.1.6 PROPOSED INDICATION AND INTENDED USE

The SQUID™ Liquid Embolic Agent is indicated for use in adult patients with unilateral or bilateral chronic subdural hematomas.

### 4.1.7 DEVICE LABELING AND STORAGE

Investigational devices will be clearly labeled with the name and place of business of the manufacturer, packer, or distributor / authorized representative, the quantity of contents and the following statement, “CAUTION – Investigational Device. Limited by Federal (or United States) law to investigational use.” The label, or other labeling, shall describe all relevant contraindications,

hazards, adverse effects, interfering substances or devices, warnings and precautions.

In countries where SQUID is already CE-marked, Investigational Device labels do not apply.

Investigational SQUID devices are to be used only in accordance with this protocol and under supervision of the PI or a duly designated person. It is the PI's responsibility to ensure that all study devices are kept in a locked, secure location with access limited to individuals authorized by the Investigator only and maintained in accordance with the Instructions for Use.

### 4.1.8 DEVICE ACCOUNTABILITY

Each vial of SQUID will be identified by a model number, lot number, and expiration date.

A device accountability log will be maintained to document the dates of receipt, use, expiry, return or disposal of the device, the device lot number and the Subject number in whom the device was used.

The device accountability log must be maintained by the site until the conclusion of the Study. Following accountability of the study devices by the Sponsor (or its designee), all unused study devices will be disposed of or returned to the Sponsor / Designee, as directed in writing, by the Sponsor or Designee for reconciliation. In the event of a suspected or confirmed device deficiency, the device must be returned to the Sponsor for analysis. Instructions for returning the device will be provided by the Sponsor or designee.

# 5 STUDY POPULATION

## 5.1 NUMBER OF SUBJECTS

Subjects with cSDH, who are potential candidates for STEM study, will be pre-screened and offered the opportunity to participate in STEM trial. The treating team will evaluate and allocate subjects to either surgical or medical management. Subjects will then be randomized (1:1) into 2 arms: SQUID embolization or standard management. Up to 310 Subjects will be randomized.

The maximum per-site randomization limit is 25 subjects. Any additional increase in per-site randomization limits must be approved in writing by the sponsor.

## 5.2 NUMBER OF SITES

Up to thirty-five (35) US sites and up to ten (10) sites OUS (globally) will be expected to be activated for enrollment in this Study.

## 5.3 STUDY POPULATION CHARACTERISTICS

Male or female adult subjects, of any race or ethnicity, at least 30 years of age at the time of consent, with unilateral or bilateral chronic subdural hematomas measuring ≥10 mm and with mass effect upon the subjacent brain will be considered for participation in the Study. The study will include subjects who require non-emergent surgery, as well as those who are to be treated conservatively with observation and serial imaging.

For the present Study, a subject with cSDH eligible for enrollment will be defined as those with a cSDH including a collection of blood products in the subdural space which:

- Measures ≥ 10 mm in greatest thickness (with a measurement taken perpendicular to the inner table of the skull, from the inner table to the cerebral cortical surface) on cross- sectional (CT or MR) imaging; and
- Exerts mass effect upon the subjacent brain as indicated by local cortical flattening or midline shift; and
- Has imaging characteristics indicative of chronicity.
    - ≥ 50% of the volume of the collection should be isodense or hypodense to normal cortical gray matter on CT/MRI
        - The collection may have some component of acute (hyperdense) blood, however, this must represent ≤ 50% of the volume of the collection

Symptomatic cSDH subjects, eligible for enrollment in the present Study, will be defined as those with a chronic subdural collection meeting the imaging criteria (described above) in a subject with one or more of the following neurological symptoms:

- Headache or head pressure
- Cognitive decline
- Speech difficulty or Aphasia
- Gait impairment or imbalance
- Focal neurological deficit (weakness, paresthesia or sensory deficit involving of one or more extremities or facial droop); and/or
- Seizure

Subjects with a uniformly hyperdense subdural collection identified within the context of recent significant trauma (i.e., an acute traumatic subdural hematoma) do not qualify for the Study. However, if such a subject demonstrates persistence or enlargement of the collection beyond 4 weeks with evolution of hypodense components, the subject may be included in the Study.

Once the consent form is signed, the subjects are considered enrolled in the study. For those subjects allocated to embolization (Embolization, or Embolization followed by Surgery), it is possible that during catheter angiography in preparation for embolization, it may become clear that a subject has dangerous anatomical variants or has vascular anatomy that is otherwise unsuitable for embolization. This includes subjects who

possess middle meningeal arteries that arise from the ophthalmic artery or those in whom the ophthalmic artery arises from the middle meningeal artery without the possibility of navigating a microcatheter safely distal to this origin.

These subjects, who are identified as "with dangerous anatomical variants" or with "MMA anatomy that is otherwise unsuitable for embolization", will not receive embolization. If such an anatomical variation is observed, the SQUID investigational device is NOT opened during the procedure. These subjects will be followed for AEs/SAEs from the time of consent through 30 days post randomization.

## 5.4 Inclusion and Exclusion Criteria

### 5.4.1 Inclusion Criteria

Subjects must meet ALL of the following criteria:

1. Male or female Subject whose age is ≥ 30 at the time of consent
2. Pre-morbid mRS 0-1 (within the previous 12 months)[8]
3. cSDH measures ≥ 10 mm in greatest thickness
4. cSDH exerts mass effect upon the subjacent brain as indicated by local cortical flattening or midline shift
5. Imaging characteristics indicative of chronicity (≥ 50% of the volume of the collection should be isodense or hypodense to normal cortical gray matter on Computed Tomography (CT))
6. Subject presents with one or more of the following neurological symptoms:
   - headache
   - cognitive decline
   - speech difficulty or Aphasia
   - gait impairment or imbalance
   - focal neurological deficit (weakness, paresthesia or sensory deficit involving of one or more extremities or facial droop), and/or
   - Seizure
7. Subject, or his/her legally authorized representative, understands the nature of the procedure, consents to participation in the study and provides a signed Informed Consent Form
8. Female Subjects of child-bearing potential must be able to provide a current negative urine pregnancy test and agree to an appropriate method of contraception throughout the trial
9. Subject is able and willing to return to the investigational site for all follow-up visits (e.g., 30-day, 90-day, 180-day and 1-year), as required per protocol

### 5.4.2 Exclusion Criteria

Subjects shall be excluded if ANY of the following conditions exist:

1. Subject with prior ipsilateral craniotomy or burr hole evacuation of cSDH
2. Subject with prior embolization of either MMA
3. Subject requires (in the opinion of the treating surgeon) a full or mini craniotomy
4. Subject with urgent or emergent (within 1 hour of assessment) subdural hematoma evacuation needed
5. Subject with a cSDH with a focal location (confined to the frontal or temporal base or the inter-hemispheric space without cerebral convexity involvement)
6. cSDH developed due to underlying condition such as a vascular lesion, brain tumor, arachnoid cyst, spontaneous intracranial hypotension or secondary to a previous craniotomy
7. Life expectancy of <1 year
8. Subject who presents with an intracranial mass other than subdural hematoma
9. Subject who presents with a meningioma with mass effect and/or ≥ 1 cm or currently

[8] Subjects had No symptoms at all (equivalent to mRS=0), or No significant disability despite symptoms; able to carry out all usual duties and activities (equivalent to mRS=1) in the last 12 months and any current morbid state (i.e., the clinical decline) can be reasonably attributed to the presenting cSDH

undergoing radiation therapy for carcinoma or sarcoma of the head or neck region
10. Subject with serum creatinine level > 3.0 mg/dL at time of enrollment (this will restrict the use of contrast) and not on dialysis
11. Subject with significant liver function impairment at time of enrollment
12. Subject with a life-threatening allergy to radiographic contrast (unless treatment for allergy is tolerated or can be managed medically)
13. Subject who is currently enrolled in another investigational study protocol that could potentially confound the current study endpoints

## 5.5 Study Completion

Each subject in the study will be considered completed when all applicable assessments through 1-year follow-up have been performed in accordance with the study protocol.

For subjects who only experience treatment failure #1 (so called radiological failure as assessed at the 180-day visit), should continue the study through 1-year follow-up according to schedule of events (Table 5). These subjects require an extra assessment at 1-year follow-up (CT/MRI scan).

Subjects who experience treatment failure #2 and/or #3 at any time after start of the assigned intervention, should be followed up to 1-year according to the modified schedule visit (Table 6) and their mRS, AE/SAE, and concomitant medication should be assessed virtually or remotely.

If subject experiences neurological death at any time after the start of the assigned intervention, a mRS of 6 will be entered into CRFs.

## 5.6 Subject (Early) Exit/Termination

It is important to record the reasons why subjects exit the trial in the case report forms (CRFs). Potential reasons for (early) exit include:

### 5.6.1 Screen Fail

Subjects presenting with cSDH who are consented, but do not meet I/E criteria, will be considered a Screen Failure and will be exited from the study. These subjects would NOT proceed with randomization.

### 5.6.2 Not meeting Eligibility Criteria after randomization

Subjects who have been randomized but subsequently are found to not meet inclusion/exclusion criteria (e.g., anatomical issues, pregnancy, etc.) will be early exited from the study.

### 5.6.3 Subject withdrawal

At any point during the study, a subject who wishes to withdraw their consent for any reason is entitled to do so without any obligation. Subjects who withdraw consent will be exited from the study and no further data should be collected.

If at any time during the Study, the Investigator concludes that it is necessary to remove the Subject from the study, the Subject may be withdrawn. Investigator's qualifying reason for withdrawal must be captured in the CRF.

Subject withdrawal may happen at any point (before or after randomization).

### 5.6.4 Not starting with the Expected treatment

Subjects who sign consent and are randomized and FOR ANY REASON (e.g., treating team change of plans, subject not accepting the assigned treatment) do not start with the expected treatment (either medical or surgical management with/without embolization), will be followed for AEs/SAEs from the time of consent through 30 days post randomization.

#### 5.6.5 DEATH

Death is a reason for early termination from the study. Within 24 hours of learning of a Subject death, the Investigator or Study Staff delegate shall notify the IRB / EC and Sponsor. An appropriate Serious Adverse Event report shall be completed.

# 6 ENROLLMENT AND SUBJECT PARTICIPATION DURATION

The duration of the enrollment period is expected to be 36 Months. Due to impact of COVID-19, the enrollment period may be extended if required.

The overall Study duration for each Subject includes a follow-up period of up to 1-year (+/- 8 weeks). All subjects who have started with their assigned medical or surgical management should continue follow-up evaluations per the schedule of events delineated in Table 5 (including those that experience treatment failure #1, re-accumulation of the SDH (≥10 mm) on 180-day scan from intervention[9]). However, Subjects experiencing treatment failure based upon criteria #2 (re-operation or surgical rescue) or #3 (new, major disabling stroke, myocardial infarction (MI) or neurological death) at any point after start of the assigned intervention will follow a modified schedule of events delineated in Table 6.

# 7 STUDY ENDPOINTS

## 7.1 PRIMARY EFFECTIVENESS ENDPOINT[10]

Treatment failure is defined by the occurrence of any of the following events:

- Residual or re-accumulation of the SDH (≥10 mm) on 180-day scan from intervention;
- Re-operation (after index procedure) or surgical rescue[11] within 180-days of intervention;
- Any new, major disabling stroke[12], myocardial infarction (MI)[13] or death from any (neurological) cause within 180-days of intervention.

## 7.2 PRIMARY SAFETY ENDPOINT

- Major disabling stroke or any death within 30-days, from intervention

## 7.3 SECONDARY ENDPOINTS

- mRS (analyzed as shift) at 180-day from intervention
- Any investigational device/procedure-related AE/SAE

## 7.4 ADDITIONAL ENDPOINTS

- mRS (analyzed as shift) at 30-day and 1-year from intervention

---

[9] These subjects require an extra assessment (CT/MRI scan at 1-year follow-up). If they also experience treatment failure #2 and/or #3, they have to follow a modified schedule of events

[10] 180 days visit (180 days +/-6w)

[11] Re-operation or surgical rescue includes cSDH evacuation via any surgical procedure OR embolization of the MMA with any commercially available product

[12] An increase in the NIHSS of 4 points or more from baseline that persists for 24 or more hours from the time of the event (Major stroke), AND results in a mRS of 3 or greater at 90 days from the event (Disabling stroke).

[13] Detection of a rise and/or fall of cardiac troponin (cTn) values with at least 1 value above the 99th percentile upper reference limit (URL) and with at least one of the following: Symptoms of acute myocardial ischemia; New ischemic electrocardiogram (ECG) changes; Development of pathological Q waves; Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.

- mRS ≤ 2 (binary) at 30-day, 180-days and 1-year, from intervention
- Cognitive improvement, as measured by blinded assessment, utilizing the comprehensive neuro-cognitive battery HVLT-R, COWAT, Animal Naming, Trail making tests at: Baseline, 30- day, 180-day and 1-year from intervention
- EQ-5D-5L (including EQ-VAS): Baseline vs. 30-day, 180-days and 1-year from intervention
- Hospital Days
- Intensive Care Unit (ICU) Days
- NIHSS Baseline vs Discharge and 90-day
- CT/MRI: Baseline vs 180 days[14]

[14] Measuring cSDH Thickness (actual measurement, ≥ 10 mm), reduction of the SDH by 50% to 75%, cSDH Density (homogeneous vs. heterogeneous), any new intracranial hemorrhage (Subarachnoid Hemorrhage, Intracerebral Hemorrhage, SDH), new large vessel territory stroke

# 8 STUDY PROCEDURES

## 8.1 RECRUITMENT AND SCREENING

The screening process evaluates potential participants for their eligibility to take part in the study. Any Subjects presenting with cSDH at the investigational center during the Study enrollment phase, who is likely to meet inclusion/exclusion criteria, is a candidate for screening. Subjects or their legally authorized representative (LAR) will be approached for the opportunity to participate in the Study. Before any Study- specific evaluations such as eligibility assessment/screening are performed, a trained investigative staff member, as indicated by the Investigator on the Delegation of Authority (DoA) Log, will identify and consent subjects and / or LARs using the approved IRB / EC informed consent form (ICF) and current protocol version.

### 8.1.1 INFORMED CONSENT PROCESS[15]

The following describes the process to be used for enrolling subjects in the Study:

- The subject / subject's legal representative will be provided the Informed Consent Form prior to signature, allowing ample time for review, consideration, and decision to participate.
- With local IRB approval, due to COVID-19 restrictions, the consent process may be conducted via eConsent.
- The subject / subject's legal representative will be asked if he / she would like to participate. If yes, the subject / subject's legal representative as well as the investigator obtaining consent, will be asked to sign and date the ICF.
- After signing the ICF, the Subject is assigned a sequential clinical study number from the investigational site's list of Study numbers for subject-protection confidentiality measures. These numbers are used for Subject identification.
- The ICF must be signed before a Subject has any study-specific evaluations completed. Once the consent form is signed, the subject is considered enrolled as a study subject.
- The original signed ICF must be kept in the subject binder at the study site. A copy of the signed consent should also be provided to the Subject / subject's legal representative.

Informed Consent may be given by subject's legal representative only if a subject is unable to provide informed consent for themselves (e.g., mental illness or disability). In such cases, the subject shall also be informed about the Study within his/her ability to understand.

If a subject or subject's legal representative is unable to read or write, Informed Consent shall be obtained through a supervised oral process. An independent witness shall be present throughout the process. The written ICF, and any other applicable information, shall be read aloud and explained to the subject and/or the subject's legal representative and, whenever possible, either shall sign and personally date the ICF. The independent witness also signs and personally dates the ICF attesting the information was accurately explained and informed consent was freely given.

For any subject / subject's legal representative who retracts participation after signing an ICF, the data collected up to the point of study withdrawal should be maintained and the reason for refusal of participation shall be documented. If required, due to impact of COVID-19 or other site-specific subject protection measures, the informed consent process may include mailing the consent form to the subject / subject's legal representative, having a trained and qualified site study team member telephone the subject / subject's legal representative and consent the subject / subject's legal representative over the telephone, and the subject / subject's legal representative returning the signed and dated consent form via mail. Alternative methods of consenting subjects must be approved by the Ethics Committee/Institutional Review Board prior to implementing that consent method. The consent process will be documented. Study visits may also be conducted remotely, at alternative locations, out of window, or with other measures implemented, if required, as per local health protection guidelines and in alignment with Ethics Committees/Institutional Review Board

[15] For Europe, subject / subject's legal representative / independent physician can be provided with ICF. Follow EC policy regarding independent physician based on ICH E6 (R2).

approval. Any changes to protocol-required visits or study conduct related to COVID-19 or other impact will be documented and reported as protocol deviations.

## 8.2 Screening / Baseline Evaluation

### 8.2.1 Pre-Intervention Data Collection

- Informed Consent
- Inclusion / Exclusion criteria verification
- Subject demographics (height, age, race (as applicable), etc.)
- Medical history / comorbidities
- Physical Exam
- Pregnancy Test (for Female Subjects of child-bearing potential)
- Pre-morbid mRS (should be 0-1 within the previous 12 months) (assessed by certified site study personnel)
- NIH Stroke Scale (NIHSS)
- Chronic Subdural Hematoma Imaging Assessment
- Quality of Life Questionnaire (EQ-5D-5L including EQ-VAS)
- Comprehensive Neuro-Cognitive Battery Testing
- Imaging CT/MRI performed at Baseline or imaging performed within 7 days prior to screening/baseline
- Adverse Events
- Concomitant medications (Anti-platelets / Anti-coagulants / Steroids)

If during eligibility evaluation, in the opinion of the treating team, it becomes clear that the Subject requires a full or mini craniotomy or emergency surgery, that subject is ineligible for participation in the study. Subjects who do not meet eligibility criteria are considered screen failures and will be terminated from the study.

Subjects may be enrolled as unilateral or bilateral cSDH. A subject can be enrolled as a “bilateral cSDH” only if both cSDH collections meet all inclusion criteria and no exclusion criteria.

During this visit, the treating team will review the eligible subject’s assessment and decide on the treatment strata (Medical or Surgical Management).

### 8.2.2 Pre-Intervention Medication

There are no protocol-required pre-intervention medications. Anti-platelet and anti-coagulation medications will be held, reversed, continued or re-started at the discretion of the managing physician team.

### 8.2.3 Concomitant Medications

For the purpose of this protocol, only anti-platelets and anti-coagulants will be collected and reported. Steroid usage will be reported and notated in a “yes” or “no” format.

The usage of anti-platelet or anticoagulation medications will be carefully recorded in the source documentation and CRF at each subject encounter. Because the indications for these medications are so variable (e.g., new versus old, bare metal versus drug-eluting and single versus multi-vessel coronary stents for anti-platelet medications, e.g., mechanical valve versus tissue valve or high versus low-risk atrial fibrillation for anti-coagulation medications), their peri-intervention reversal, and the time of resumption, must be made on an individualized basis. Intra-procedural medications (e.g, procedural heparin) will NOT be recorded as concomitant medications.

### 8.2.4 FEMALE SUBJECTS OF CHILDBEARING POTENTIAL

A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women whose male partners have been vasectomized or have received, or are utilizing, mechanical contraceptive devices.

The Investigator will follow standard medical practices to ensure that all female Subjects of childbearing potential are not pregnant at the time of the study procedure. Appropriate precautions should be taken to guard against inadvertent exposure of fetuses to potentially toxic agents and to inform female Subjects the potential risk and need for precautions. Therefore, any female Subject of childbearing potential with a positive pregnancy test should not be included in the Study.

## 8.3 RANDOMIZATION

Subjects' current mRS should be recorded in the randomization eCRF. The occurrence of any AEs/SAEs between informed consent and randomization should be recorded.

Within each stratum, each subject will be randomized (1:1) into one of two different categories: standard management, or SQUID embolization (See Figure 1). If assigned by the treating team to Medical Management stratum, subjects will be randomized to either 'SQUID Embolization' arm (treatment) or 'Standard Medical Management' arm (control). If assigned by the treating team to the Surgical Management stratum, subjects will be assigned to either 'SQUID Embolization followed by Surgery' arm (treatment) or to 'Surgery only' (control).

## 8.4 INTERVENTION: SUBJECT DEVICE / TREATMENT / INTRA-PROCEDURAL EVALUATION

Each subject should be assigned to/analyzed in only one of the 4 listed interventional arms (2 control arms and 2 treatment arms):

Standard Medical Management arm (control)
Subjects in Standard Medical Management will be followed by the clinical team and treated as per the Standard of Care established at the institution for the management of cSDH. Standard of care typically includes cSDH monitoring and medical intervention to control symptoms. Standard medical management should include administration of this treatment as per the institution's standard of care. For standard medical management, "intervention start time" is defined as time of randomization. For this arm only, randomization timepoint is also the point at which all follow up windows are to be calculated.

Subjects placed in the Medical Management stratum and then randomized to Standard Medical Management, are not required to have a CT or other imaging performed within 24 hours of randomization, if those subjects were not admitted at the hospital or released prior to 24 hours.

If Standard Medical Management subjects need subsequent intervention (e.g., operation or surgical rescue) at ANY TIME after randomization, they will be considered a Treatment Failure and should continue with the study by switching to the modified schedule of events (Table 6).

Surgery arm (control)
For subjects undergoing surgical evacuation only (i.e., surgical management but no embolization), the surgical evacuation should occur within 48 hours of randomization.

Subjects assigned to the "Surgical-only" arm will be followed by the clinical team and treated as per the Standard of Care established at the institution for the management of cSDH. Surgery will include the placement of one/two burr-holes, with irrigation of the hematoma and placement of a subgaleal or subdural drain. Twist-drill drainage, such as Subdural Evacuating Port System (SEPS™; Medtronic), will be allowed, provided the subject's overall health continues to be acceptable for a twist-drill drainage procedure as determined by the treating team. If the subject is enrolled as a "bilateral cSDH", bilateral cSDH surgical drainage will be

performed.

The source documentation and the eCRF will record type of surgical procedure, start and stop times of the surgical procedure, (e.g. “knife to skin” time start and stop) method for irrigation, placement of a drain, post-operative activity and timing of resumption of anti-coagulation or anti-platelet medications. Adverse events and concomitant medication have to be collected at intervention visit.

For subjects assigned to the “Surgery“ arm, within 24-hours of the procedure end time, a 24-Hour visit (i.e., 24 Hour ± 12 Hours) conventional CT/MRI should be performed (note: if an in-room cone-beam CT/MRI or immediate post-procedural image is performed, the images will be collected, but this is not considered to count as the 24-hour post procedure CT). Additional imaging will be performed within the context of Standard of Care during the subject’s hospitalization, as dictated by the subject’s condition, and as frequently as-is required. The follow-up visit window will be calculated beginning from the time of surgery stop time.

SQUID Embolization arm and SQUID Embolization followed by Surgery arm (treatment)
Subjects designated to “SQUID Embolization followed by Surgery” will be required to have the embolization occur within 24 hours of randomization and surgical evacuation occur within 48 hours of randomization. If the subject is enrolled as a “bilateral cSDH”, then both cSDH collections must meet all inclusion criteria and no exclusion criteria, and it is assumed that both sides will undergo the allocated treatment and complete bilateral cSDH surgical drainage will be performed. The intervention start time will be captured as “the wrist/groin puncture”. Follow-up window calculations for “embolization followed by surgery” assigned subjects begins at the end of the surgical procedure. Adverse events and concomitant medication have to be collected at intervention visit.

For subjects assigned to Embolization Only or Embolization followed by Surgery, within 24-hours of the procedure end time, a 24-Hour visit (i.e., 24 Hour ± 12 Hours) conventional CT/MRI should be performed (note: if an in-room cone-beam CT/MRI or immediate post-procedural image is performed, the images will be collected but this is not considered to count as the 24-hour post procedure CT). Additional imaging will be performed within the context of Standard of Care during the subject’s hospitalization, and as dictated by the subject’s condition, and as frequently as-is required.

Embolization procedures may be performed under general anesthesia or conscious sedation, as per the preference of the interventionist. In addition, arterial access may occur via femoral or radial approach, as per the preference of the interventionist. A conventional angiogram will be performed initially to include at a minimum standard PA and lateral views of the head, with injection from a catheter positioned within the common carotid artery (CCA). Only branches of the MMA distal to the foramen spinosum / skull base will be evaluated and targeted for embolization. Posterior meningeal and accessory meningeal arteries will not be targets for embolization. A guiding catheter of choice will be navigated into the external carotid artery (ECA) under fluoroscopic control. A DMSO-compatible microcatheter of choice will be navigated into the targeted branch of the MMA.

NOTE - DMSO-compatible catheters, approved in the United States, include: (Balt USA) Eclipse 2L, (Medtronic) Marathon™, Echelon™, Apollo™, Rebar™, (MicroVention) Scepter C® and XC®, Headway™ 17, Headway™ Duo, (Terumo) Progreat®, (Stryker) Excelsior® XT-17™ and (Boston Scientific) Renegade™ HI-FLO™. In the EU, SONIC (Balt Extrusion) would be the preferred DMSO-compatible catheter of choice for use within this protocol; however, any commercially available CE-marked DMSO- compatible catheter may be used. Check with the microcatheter manufacturer’s instructions for use for DMSO compatibility prior to utilizing with SQUID.

The microcatheter will be placed as distally as possible in these targeted MMA branches and embolization will be performed, to the extent possible, prior to removal of the microcatheter. The MMA branches may be embolized as proximally as 1 cm above the foramen spinosum. Super selective angiography will be performed through the microcatheter. Following the IFU, the SQUID™ infusion (injected immediately after mixing) will then be performed under fluoroscopic visualization with the goal of achieving distal penetration into the meningeal branches. The treating physician will select the SQUID™ formulation that is consistent with typical embolization techniques and consistent with the instructions for use. SQUID12 will travel more distally and penetrate deeper into the vascular bed due to its lower viscosity compared to SQUID18 or SQUID34. Eight (8) stickers have been designed to be applied on the SQUID™ vials before placing them in the mixer. By numbering

the vials in advance of placing in the mixer, it is easier to identify the proper order for use after being sufficiently mixed. Shake SQUID at least 20 minutes in a mixer (Scientific Industries Genie 2, Model No(s). 120V SI-0236, 240V SI-0246, Vial Attachment No. SI-0570) at a setting of 8. Continue mixing until ready to inject SQUID according to the instructions of the corresponding step below. Failure to continuously mix SQUID for the required time (20 minutes) may result in inadequate fluoroscopic visualization during delivery and / or microcatheter occlusion. Inject SQUID with not more than one minute delay following mixing. If SQUID injection is delayed, Tantalum settling can occur within the syringe, resulting in poor visualization of SQUID during injection and /or microcatheter occlusion. Inject SQUID and DMSO at a slow, steady rate, not to exceed 0.3 ml/minute. DO NOT interrupt SQUID injection for longer than two minutes prior to re-injection as solidification of SQUID may occur at the catheter tip, resulting in catheter occlusion and use of excessive pressure to clear the catheter may result in catheter rupture. The LD50 of 100% DMSO has been previously published at 10.9g/kg. The anticipated maximum dose of SQUID / DMSO for the treatment of cSDH is 4 vials SQUID/1 vial DMSO in unilateral cases and 8 vials SQUID/2 vials DMSO in bilateral cases (note: the worst-case amount of DMSO that is anticipated to be delivered to the Subject with cSDH in the proposed clinical study is .87g/kg.). The microcatheter will be removed after completing the injection. Control angiography will be repeated by use of the guiding catheter. Additional branches of the MMA will be catheterized, studied angiographically and embolized at the discretion of the interventionist with the goal of achieving a complete occlusion of all major branches of the MMA arising distal to the foramen spinosum.

Following embolization of all accessible MMA branches, completion angiography will be obtained from catheter positions in the external carotid (oblique PA and lateral projections) and common or internal carotid artery (standard PA and lateral projections). The embolization procedure will be performed unilaterally in all cases. If angiography demonstrates the potential for bilateral MMA supply to the meningeal membranes, or if bilateral cSDH collections are present, then bilateral embolization may be performed at the discretion of the interventionist. The total volume of SQUID injected will be recorded for each procedure (and each side, in the case where bilateral embolization is performed).

## 8.5 FOLLOW-UP

### 8.5.1 24-HOUR FOLLOW-UP (± 12 HOURS):

List of potential assessments during this visit:

- Physical Exam
- Adverse Events
- Imaging CT / MRI (head) required for subjects randomized to surgery, embolization-only, embolization followed by surgery. CT/imaging is not required for Standard Medical Management arm if not admitted and/or already discharged prior to 24 hours
- Concomitant Medications (Anti-platelets / Anti-coagulants / Steroids)

This visit is ***not*** required for subjects in Standard Medical Management arm who have not been admitted and/or already discharged prior to 24 hours post randomization. However, if the Standard Medical Management arm assigned subject has been admitted, the above listed assessment should be performed within 24 hours of randomization.

For subjects assigned to “Surgery”, “SQUID Embolization followed by Surgery” and “SQUID Embolization”, if Discharge occurs ***prior to 24 hours from the end of the intervention***, the post-procedure imaging and assessment, and Discharge visit must be performed prior to the actual physical discharge. In that case, the 24-hour visit (including 24-hour imaging) is **not** required.

For Subjects in the Surgery arm, the SQUID Embolization arm, and the SQUID Embolization followed by Surgery arm, the follow-up window is calculated based on the time embolization procedure or surgical procedure was completed (whichever occurred later).

***If after start of the assigned intervention and prior to 24-hour follow-up, subjects experience treatment failure # 2 and/or 3, they are not required to complete this visit as per schedule of events (Table 5) and instead should follow a modified scheduled visit (Table 6), starting with 180-day remote/virtual assessment, as outlined in section 8.5.8.***

### 8.5.2 DISCHARGE / 7-DAY FOLLOW-UP (WHICHEVER OCCURS FIRST):

List of potential assessments during this visit:

- Physical Exam
- NIHSS
- Discharge Details
- Adverse Events
- Concomitant Medications (Anti-platelets / Anti-coagulants / Steroids)

Note: These visits are ***not*** required for subjects in Standard Medical Management arm, if they were not admitted or hospitalized.

If Discharge occurs ***prior to 7 days post-intervention***, Discharge visit should be performed, and no additional 7 Day visit is required to be performed.

***If after 24-Hr follow-up and prior to Discharge/7-day follow-up visit subjects experience treatment failure #2 and/or #3, they are not required to complete this visit as per schedule of events (Table 5) and instead should follow a modified scheduled visit (Table 6), starting with 180-day remote/virtual assessment, as outlined in section 8.5.8.***

### 8.5.3 30-DAY FOLLOW-UP (± 2 WEEKS):

List of potential assessments during this visit:

- Physical Exam
- mRS (assessed by certified site study personnel)
- EQ-5D-5L (including EQ-VAS)
- Comprehensive Neuro-Cognitive Battery
- CT/MRI Imaging (head); Imaging is ***only*** captured if this is standard of care at the institution
- Adverse Events
- Concomitant Medications (Anti-platelets / Anti-coagulants / Steroids)

***If after Discharge/7-day and prior to 30-day follow-up visit subject experienced treatment failure #2 and/or #3, they are not required to complete this visit as per schedule of events (Table 5) and instead should follow a modified scheduled visit (Table 6), starting with 180-day remote/virtual assessment, as outlined in section 8.5.8.***

### 8.5.4 90-DAY FOLLOW-UP (± 4 WEEKS):

List of potential assessments during this visit:

- Physical Exam
- mRS (assessed by certified site study personnel)
- NIHSS
- Imaging CT / MRI (head); Imaging is ***only*** captured if this is standard of care at the institution
- Adverse Events
- Concomitant Medications (Anti-platelets / Anti-coagulants / Steroids)

***If after 30-day and prior to 90-day follow-up visit subjects experienced treatment failure #2 and/or #3, they are not required to complete this visit as per schedule of events (Table 5) and instead should follow a modified scheduled visit (Table 6), starting with 180-day remote/virtual assessment, as outlined in section 8.5.8.***

### 8.5.5 180-DAY FOLLOW-UP / (± 6 WEEKS):

List of potential assessments during this visit:

- Physical Exam
- mRS (assessed by certified site study personnel)
- EQ-5D-5L (including EQ-VAS)
- Comprehensive Neuro-Cognitive Battery
- Imaging CT / MRI (head); Imaging is required for ***all*** applicable subjects. If treatment failure #2 and/or #3 after start of the assigned treatment and prior to 180-day visit, this imaging in not required.
- Adverse Events
- Concomitant Medications (Anti-platelets / Anti-coagulants / Steroids)

***For subjects who have experienced treatment failure #1 (residual or re-accumulation of the SDH (≥10 mm) on 180-day scan from intervention) and not treatment failures #2 and/or #3, they should continue to follow schedule of events (Table 5). If after the 90-day and prior to the 180-day visit subjects experience treatment failure #2 and/or #3 (with/without treatment failure #1), they are not required to complete this visit as per the schedule of events (Table 5) and instead should follow a modified scheduled visit for 180-day follow-up (Table 6) as outlined in section 8.5.8.***

### 8.5.6 1-YEAR FOLLOW-UP (± 8 WEEKS):

List of potential assessments during this visit:

- Physical Exam
- mRS (assessed by certified site study personnel)
- EQ-5D-5L (including EQ-VAS)
- Comprehensive Neuro-Cognitive Battery
- Adverse Events
- Concomitant Medications (Anti-platelets / Anti-coagulants / Steroids)
- Imaging CT / MRI (head): Imaging is only required for subjects that experienced treatment failure #1 or if this is standard of care at the institution

***If after the 180-Day follow-up and prior to the 1-year visit, subjects experience treatment failure #2 and/or #3, they are not required to complete this visit as per the schedule of events (Table 5) and instead should follow a modified scheduled visit for 1-year follow-up (Table 6) as outlined in section 8.5.8.***
***If subjects only experience treatment failure #1 at 180-Day visit and not treatment failures #2 and/or #3, they are required to have an extra assessment (CT/MRI scan) at 1-year follow-up.***

### 8.5.7 UNSCHEDULED VISIT

List of potential assessments during this visit:

- Physical Exam
- mRS (only necessary if Subject presents with new neurological symptoms)
- NIHSS (only necessary if Subject presents with new neurological symptoms)
- Subdural Hematoma Assessment (only necessary if Subject presents with new neurological symptoms)
- Imaging CT / MRI (head); Imaging is ***only*** captured if this is standard of care at the institution
- Adverse Events
- Concomitant Medications (Anti-platelets / Anti-coagulants / Steroids)

***At any time after start of the assigned intervention, if subjects experience treatment failure #2 and/or #3 and return for an Unscheduled Visit, they should follow a modified schedule of events. They are not required to complete unscheduled visit assessment as per Table 5 and***

***instead should follow the unscheduled visit assessment per Table 6 as outlined in section 8.5.8.***

### 8.5.8 Follow Up for Subjects Meeting treatment failure #2 and/or #3

At any point after start of the assigned intervention (medical or surgical), if subjects experience treatment failure #2 and/or #3, instead of the schedule of events and the assessments (Table 5), they should switch to a modified scheduled visit and assessments as listed below (Table 6).

- **180-DAY FOLLOW-UP (± 6 WEEKS):**
  - mRS (assessed by certified site study personnel)
  - AE/SAE
  - Concomitant Medication
- **1-YEAR FOLLOW-UP (± 8 WEEKS):**
  - mRS (assessed by certified site study personnel)
  - AE/SAE
  - Concomitant Medication
- **UNSCHEDULED:**
  - mRS (assessed by certified site study personnel)
  - AE/SAE
  - Concomitant Medication

### 8.5.9 Lost to Follow-up

In case a Subject fails to attend a protocol-required visit, the Investigator or Study Staff delegate will make repeated attempts to contact the Subject. After three documented attempts by the Investigator or Study Staff delegate to reach the Subject with no response, a certified letter will be sent to the Subject. The Subject shall be considered Lost-to-Follow-up in case of two consecutive missed visits. Subject status should not change to lost-to-follow-up prior to reaching the primary endpoint assessment at 180 days.

## 8.6 MEASURED OUTCOMES

### 8.6.1 Modified Rankin Score (mRS)

The modified Rankin Scale will be used to assess disability in patients, and particularly those who have suffered a stroke and is compared over time to check for recovery and degree of continued disability.

The ‘shift’ analysis evaluates the entire range of the mRS at a visit (all 7 levels: 0 = no symptoms at all, 1 = no significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = death), unlike the binary mRS analysis which classifies the 7 levels into two groups (<2 and ≥2).

### 8.6.2 NIH Stroke Scale (NIHSS)

The NIH Stroke Scale is a widely used tool that was built to assess the cognitive effects of a stroke. The scale is made up of 11 different elements that evaluate specific ability. The score for each element is a number between 0 and 4, 0 being normal functioning and 4 being completely impaired. The patient’s NIHSS score is calculated by adding the number for each element of the scale; 42 is the highest score possible. In the NIHSS, the higher the score, the greater the degree of impairment.

### 8.6.3 EQ-5D-5L

The EQ-5D questionnaire is made up of two components: health state description and evaluation.

In the description part, health status is measured in terms of five dimensions (5D); mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Mobility dimension asks about the person's walking ability. Self-care dimension asks about the ability to wash or dress by oneself, and usual-activities dimension measures performance in work, study, housework, family or leisure activities. In pain / discomfort dimension, it asks how much pain or discomfort they have, and in anxiety / depression dimension, it asks how anxious or depressed they are. The respondent's self-rate their level of severity for each dimension using a five-level (EQ-5D-5L) scale.

In the evaluation part, the respondents evaluate their overall health status using the visual analogue scale (EQ-VAS).

### 8.6.4 NEUROCOGNITIVE BATTERY

Despite the prevalence of cSDH in the population, relatively little has been done to examine the long-term neuropsychological consequences of the injury, including neuropsychological response to intervention. Extant literature has primarily focused on and identified impairments in memory (Kawasaki, et al., 2012; Schesbesch et al., 2008; Schoedel et al., 2016). Select studies have also shown improvement in cognition following neurosurgical intervention for cSDH (Gill et al., 2018); however, these are often limited to brief, non-specific mental status screening outcome measure (i.e., Mini Mental Status Exam). Considering these data, there is a need for more systematic assessment and monitoring of cognition in the cSDH sample.

The salience of assessing neuropsychological status is gleaned from lessons learned from other large-scale studies in neurovascular subjects. For example, as described in the neuropsychological sub-study of the International Subarachnoid Aneurysm Trial (N-ISAT: Scott et al., 2010), there are a number of aneurysmal subarachnoid hemorrhage survivors with normal disability ratings (i.e., modified Rankin Scale), who demonstrate significant cognitive impairment. Without the inclusion of neuropsychological assessment, these impairments would otherwise be undiscovered, which is problematic given that cognitive impairment contributed to important health-related quality of life.

Towards this end, cognition will be measured by a brief battery of reliable and valid tests previously tested for feasibility within previous clinical trials. The battery will consist of measures of verbal memory (Hopkins Verbal Learning Test-Revised; HVLT-R), phonemic verbal fluency (Controlled Oral Word Association Test; COWAT), semantic verbal fluency (Animal Naming) and processing speed and executive function (Trail Making Test, Trails A and Trails B).

As there is no consensus "gold standard" neurocognitive battery established with the target subject population (i.e., chronic subdural hematoma), we selected measures known to be reliable and valid, as well as sensitive to cognitive domains commonly seen as sequelae in subjects with neurovascular disease. Additionally, several of the measures selected have been utilized effectively in a wide range of clinical trial batteries, including Huntington's Disease (HD-CAB: Stout et al., 2014) and schizophrenia (NIMH-MATRICS: Green et al., 2004). The HVLT-R, COWAT and TMT comprise of a battery that has been shown to be feasible and reliable for use in radiation-oncology trials (Regine et al., 2004).

**Hopkins Verbal Learning Test, Revised (HVLT-R: Brandt & Benedict, 2001)**

The HVLT-R is a word-list learning and memory test that is designed to be brief, easy to administer and well tolerated by even moderately demented subjects. The test consists of a 12-item word list presented over three consecutive learning trials, followed by a 20-25-minute delay recall and recognition trial. The test renders indices of learning and recall, delayed recall and memory recognition. Test-retest reliability and construct, concurrent and discriminant validity have been established. The test provides six alternate forms, allowing for serial assessment. The HVLT-R

normative data sample consists of individuals aged 16-92 (n=1179). However, additional normative data is available for elderly samples 65-96 (Duff, 2016).

**Trail Making Test (TMT: Lezak, 2004)**

The TMT is a measure of attention, speed and mental flexibility. The test was originally developed in the Reitan lab but is now in the public domain and can be reproduced without permission (Lezak, 2004). The estimated administration time is 5 to 10 minutes. The test is divided into two parts (i.e., A and B). Part A requires the subject to draw lines connecting 25 encircled numbers randomly arranged on a page. Part B is similar but requires the respondent to draw lines connecting encircled numbers and letters in an alternating order (i.e., 1-A-2-B…). Normative data is available from multiple data sets ranging, with age ranges of 15 to 89. Correction for additional demographic factors (i.e., education, race, gender) is also available.

**Controlled Oral Word Association Test (COWAT: Benton & Hamsher, 1989)**

The COWAT measures phonemic verbal fluency. The task requires approximately five minutes and requires the subject to produce orally as many words as possible, beginning with a specified letter during a fixed period of time (i.e., one minute). The COWAT uses a set of three-letters (dependent upon translation). Several normative data sets are available for COWAT, covering a subject age range from 6-97 years. Meta-norms are also available, combining data from 32 studies with a sample of n=17,625. Internal consistency, test-retest reliability and construct validity have been established.

**Semantic Verbal Fluency (Animal Naming)**

Semantic fluency tasks require the respondent to generate words in specific categories over a specified interval, typically one minute. “Animals” is the most common semantic category employed in clinical testing and in research contexts. Multiple data sets are available, allowing for correction of various demographic factors (i.e., age, education, gender, race). The most comprehensive, demographically corrected normative set (Heaton, et al., 2004) covers an age range of 20-85 (n=1145). Internal consistency, test-retest reliability and construct validity have been established.

Measures in the battery benefit from the availability of multiple parallel forms, allowing for serial assessment and control of practice effects; suitable for clinical trials employment of multiple assessment points. As noted above, multiple, large normative data sets are available, controlling for the effects of age, education, gender, and/or race. Multiple language translations are available for the paper and pencil version.

All neurocognitive measures and procedures will be coordinated by the neuropsychology Investigator, including measure selection, implementation, review and analysis. The neuropsychology Investigator will develop study-specific training material and will implement a training program to certify study site examiners. Consistent with consensus criteria for neuropsychological assessment, study site personnel, including site coordinators, psychometrists, or research nurses, will be trained to administer all tasks according to standardized test instructions. The neuropsychology PI will provide quality control review for all study assessments, via centralized scoring, and shall enter cognitive and QOL data into a secure study database.

Table 5. SCHEDULE OF EVENTS

| Assessments | Screening/ Baseline | Randomization | Intervention | 24Hr FU (±12 Hr.) | Discharge/ 7Day FU whichever occurs first | 30D FU (±2W) | 90D FU (± 4W) | 180D FU (±6W) | 1Y FU (± 8W) | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|
| **Informed Consent** | X | | | | | | | | | |
| **Inclusion; Exclusion** | X | | | | | | | | | |
| **Demographics; Medical History** | X | | | | | | | | | |
| **Physical Exam** | X | | | X | X | X | X | X | X | X |
| **Pregnancy Test** | X[1] | | | | | | | | | |
| **Screening mRS** | X[2] | | | | | | | | | |
| **mRS** | | X[2] | | | | X | X | X | X | X[3] |
| **NIHSS** | X | | | | X | | X | | | X[3] |
| **Subdural Hematoma Assessment** | X | | | | | | | | | X[3] |
| **Randomization** | | X | | | | | | | | |
| **EQ-5D-5L (including EQ-VAS)** | X | | | | | X | | X | X | |
| **Neuro Cog Battery Testing** | X | | | | | X | | X | X | |
| **Intervention** | | | X[4] | | | | | | | |
| **Discharge** | | | | | X | | | | | |
| **Imaging CT/MRI** | X[5] | | X[6,7] | X[7, 8] | | X[8] | X[8] | X | X[9] | X[8] |
| **Adverse Events[10]** | X | X | X | X | X | X | X | X | X | X |
| **Concomitant Medications[11]** | X | | X | X | X | X | X | X | X | X |

1. Female subject of childbearing potential

2. Pre-morbid mRS (0-1 Within the previous 12 months) should be documented in Screening eCRF at screening/Baseline timepoint. Subjects current mRS should be recorded in randomization eCRF.

3. Only required if subject presents with new neurological symptoms

4. Intervention includes: Standard medical management, surgery, embolization, embolization followed by surgery. Follow-up visits start time is defined differently for the different arms. Start times are as follows: Standard medical management: time of “randomization”, Embolization-only or embolization-followed-by-surgery: time of “wrist/groin puncture”, Surgery-only: time of “knife to skin”. For Embolization, intervention should happen within 24hrs of randomization. For Surgery, intervention should happen within 48hrs of randomization. For Embolization followed by surgery, embolization should happen within 24hrs of randomization and should be followed by Surgery within 48hrs of randomization.

5. Baseline imaging can be CT/MRI collected at baseline visit or imaging performed within 7 days prior to screening/baseline.

6. Intervention CT/MRI scan only required for Surgery, Embolization, or Embolization followed by Surgery (not for standard medical management)

7. 24 hr CT/MRI required for Surgery, Embolization, or Embolization followed by Surgery, and standard medical management who have been admitted to hospital for at least 24 hr.

8. If CT/MRI Imaging was not required but collected per standard of care (e.g., for the standard medical management that was not admitted), it will be submitted to the core lab.

9. Subjects experiencing treatment failure #1 (assessed at 180 days) and no failure #2 or #3, should continue with scheduled study assessments through 1-yr follow-up but will require an additional 1-year CT/MRI scan

10. Adverse Events should be collected from consent to study exit

11. Concomitant Medications (Anti-platelets/ Anti-coagulants/ Steroids) should be collected from consent to study exit (except at randomization visits)

**Other Notes:**

**All imaging and image submissions shall be performed in accordance with the Core Lab recommended image acquisition guidelines provided to the sites.**

**At any time after start of the assigned intervention, if subject experiences treatment failure #2 and/or #3, please stop following this table and instead switch to the modified schedule of events (Table 6).**

-Randomization should happen within 7 days from Screening/Baseline visit

-180-day FU CT/MRI is required for all applicable subjects (as long as they are following the schedule of events Table 5). If, after start of the assigned treatment and prior to 180-day visit, subjects experience treatment failure #2 and/or #3, this imaging is not required.

-For subjects assigned to “Surgery”, “SQUID Embolization followed by Surgery” and “SQUID Embolization”, if Discharge occurs prior to 24 hours from the end of the intervention, the post-procedure imaging and assessment, and Discharge visit must be performed. In that case, the 24-hour visit is not required. Discharge/7-day FU is not required from standard medical management.

Table 6. MODIFIED SCHEDULE OF EVENTS

| Assessments | 180D FU (±6W) | 1Y FU (± 8W) | Unscheduled Visit |
|---|---|---|---|
| **mRS[3]** | X | X | X |
| **Imaging CT/MRI** | X[1] | | X[2] |
| **Adverse Events[3]** | X | X | X |
| **Concomitant Medications[3]** | X | X | X |

1. CT/MRI scan not required for subjects who experience treatment failure #2 and/or #3 after start of the assigned treatment and prior to 180-days follow-up

2. CT/MRI should be shared with core lab if collected per standard of care

3. mRS, AE, and concomitant medication should be assessed virtually or remotely.

Intervention includes standard medical management, surgery, embolization, embolization followed by surgery. At any point after start of the assigned intervention, if subjects experience treatment failure #2 and/or #3, they have to switch to modified Schedule of events. Therefore, even if treatment failure #2 and/or #3 happens prior to 180-day visit, their earliest assessment is 180-day remote/virtual assessment.

# 9 SAFETY ASSESSMENT

## 9.1 DEFINITIONS

### 9.1.1 ADVERSE EVENT (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in Subjects, users or other persons, whether or not related to the investigational medical device.

Note – medical conditions that exist at Study enrollment are not considered AEs, unless the condition worsens after enrollment.

### 9.1.2 ADVERSE DEVICE EFFECT (ADE)

An AE related to the use of an investigational medical device. This also includes any event resulting from insufficiencies or inadequacies in the Instruction for Use or deployment of the device and includes any event that is a result of a user error.

### 9.1.3 ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (ASADE)

An effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

### 9.1.4 SERIOUS ADVERSE EVENT (SAE)

A serious adverse event is any AE that:

- Led to death.
- Led to serious deterioration in the health of the Subject that either resulted in:
  - A life-threatening illness or injury; or
  - A permanent impairment of a body structure or a body function; 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 body function; or
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note – Planned hospitalization for a pre-existing condition or a procedure required by the study protocol without serious deterioration in health is not considered an SAE.

All adverse events that do not meet any of the above criteria for serious should be regarded as non-serious adverse events.

### 9.1.5 SERIOUS ADVERSE DEVICE EFFECT (SADE)

An AE effect that has resulted in any consequences characteristic of a SAE.

### 9.1.6 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

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 investigation plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of Subjects.

### 9.1.7 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

### 9.1.8 DEVICE DEFICIENCY

A device deficiency is the inadequacy of a medical device with respect to its identity, quality,

durability, reliability, safety or performance. This includes malfunctions, user error and inadequate labelling. For a list of Anticipated Adverse Events Related to Endovascular Treatment of cSDH, refer to Appendix 1. For a list of Anticipated Side Effects of EVOH and DMSO, refer to Appendix 2.

## 9.2 Procedure for Reporting Events

In order to ensure prompt reporting of AEs, it is required that all reportable AEs (as well as all related study data) be entered into the Electronic Case Report Forms (eCRFs) in the web-based database in a timely manner. All UADEs and USADEs should be reported to the sponsor, preferably in the EDC within 24 hours of the site staff first being made aware of the occurrence.

## 9.3 Adverse Event Reporting Period

For the purpose of this Study, all Adverse Events (AEs) and Serious Adverse Events (SAEs) will be reported. All Adverse Events should be reported from enrollment through Study Exit. The Investigator at each site is ultimately responsible for reporting AEs to the appropriate parties. SAEs should be reported within 24 hours of site awareness.

AEs will be reported in the source documentation and in the eCRFs. Whenever possible, the event should be reported as a diagnosis. If unable to provide a diagnosis, report the symptoms as separate events. Adverse Events with an outcome status of “ongoing” or “continuing” should be assessed at each follow-up visit to determine if the event has resolved. Relationship to study device or procedure should be reported.

## 9.4 Pre-existing Condition

A pre-existing condition is one that is present at baseline is considered part of medical history of the subject. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens after baseline.

## 9.5 Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- Clinically significant abnormal labs at enrollment/screening are considered medical history. Clinically significant labs occurring after screening/enrollment should be reported as AEs
- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management, further diagnostic investigation, etc

## 9.6 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition requiring surgery should be documented as an adverse event if the condition meets the criteria for an adverse event. Standard of care planned surgical procedures are not considered adverse events.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition (e.g., polytrauma from original accident).
- Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

If, due to the temporal proximity of the AE to study procedure or study product administration, there is a

reasonable possibility that the device or procedure may have caused the AE or may have contributed to the severity or duration of an event caused by other means, the event will be evaluated for inclusion as an Adverse Device Effect. Causality is defined as not-related, unlikely, possibly-related, probably-related and causal-relationship, as defined further in Table 7.

.

Table 7. Incident Severity and Causality Ratings

| Incident Severity | Description |
|---|---|
| **Mild** | Awareness of sign or symptom that does not interfere with the Subject's usual activity or is transient, resolved without treatment and with no sequelae. |
| **Moderate** | Interferes, but does not hinder, the Subject's usual activity and / or may require treatment. |
| **Severe** | Symptom(s) causing severe discomfort and significant impact on the Subject's usual activity and requires treatment or intervention. |
| **AE Relationship** | **Description** |
| **Not-Related** | A temporal relationship to study product administration or procedure, which makes a causal relationship clearly and incontrovertibly due to extraneous causes, such as other drugs, products, chemicals, underlying diseases, environment, etc. Not-related to the study product or procedure administration. |
| **Unlikely** | The relationship with the use of the study product or procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. |
| **Possibly-Related** | Occurring within a reasonable period of time relative to study product or procedure administration which makes a causal relationship possible, but plausible explanation may also be provided by other causes, such as other drugs, products, chemicals, underlying disease, environment, etc. Possibly- related to treatment with study product or procedure. |
| **Probably-Related** | Occurring within a reasonable period of time relative to study product or procedure administration, which makes a causal relationship probable where the relationship cannot be attributed to other causes, such as other drugs, products, chemicals, underlying disease, environment, etc. Probably-related to study product or procedure. |
| **Causal-Relationship** | The AE is associated with the study product or with procedures beyond reasonable doubt when: the event is a known side effect of the device category the device belongs to or of similar devices and procedures; the event has a temporal relationship with study product / application or procedures; the event involves a body-site or organ that the study product or procedures are applied to or have an effect on; the event follows a known response pattern to the study product or procedure (if the response pattern is previously known);, impact on the event (when clinically feasible; other possible causes have been adequately ruled out; harm to the Subject is due to error in use; in order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device / procedures and the event. |

### 9.7 Assessing and Recording Adverse Events

As discussed above, all signs and symptoms not previously noted at Screening/Baseline, or which become worse during follow-up will be reported regardless of their severity or whether they require treatment. All AEs must be assessed and recorded in the Subject's source documents and then transcribed onto the appropriate eCRF from enrollment (consent) through Study Exit.

The need to capture AEs is not dependent upon whether the clinical event is associated with the use of the study product or study procedures (e.g., SQUID embolization or evacuation). Subjects should also be instructed to call the Investigator or designee to report any problems between visits.

Each AE recorded must be documented as follows:

- Describe the event by stating the underlying cause (the diagnosis), coexisting disease, or other. In order to avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the Subject's own words when possible.
- Note duration by entering the date of onset and date of resolution. If the event is present at the final study visit, the continuing box must be marked.
- Note the worst **intensity** of the event as mild, moderate or severe.
- Note the **frequency** of the event as a single episode, intermittent or continuous.
- Note the action taken as none, medication, procedure, medication and procedure, or other. Any prescribed anti-platelet(s), anti-coagulation(s) and/or steroid(s) must be noted in the Subject's medical records and then transcribed onto the appropriate CRF.
- Note the **relationship to study product or procedure** as not-related, unlikely, possibly- related, probably-related or causal-relationship.

All AEs will be followed through subject study exit. Any unresolved AE at a Subject's final study visit must be marked as "continuing" on the appropriate eCRF.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) will be reported and followed until the end of the Subject's participation in the Study.

## 10 RISK / BENEFIT ASSESSMENT

### 10.1 Potential Risks

The risks related to MMA embolization are similar to those encountered during any conventional catheter angiography or extra-cranial angiographic embolization procedure. These are related to arterial access (bleeding, infection, damage to the arteries or surrounding structures), cranio-cervical vessel catheterization (arterial dissection or embolic stroke) and embolization of a non- target organ (eye, brain or cranial nerve(s)) with subsequent infarction and dysfunction (blindness, stroke or cranial neuropathy). In comparison to most neuro-interventional procedures, MMA embolization potentially includes less risk, as it does not require selective catheterization of intracranial pial vessels and the guide catheter and microcatheters are manipulated exclusively within the external carotid artery and branches. In comparison to other available particulate embolic agents (e.g., PVA particles), the proposed liquid embolic agent (SQUID™) is theoretically safer as it is more visible during the procedural application and involves a controlled delivery method (see Introduction section).

### 10.2 Potential Benefits

Preliminary studies have demonstrated that embolization of the MMA in subjects with cSDH results in resolution of the subdural hematoma and, in subjects who undergo both embolization and surgery, a lower rate of re-hemorrhage and return to the hospital. We hypothesize that the prompt and reliable resolution of the cSDH will result in better quality of life and neurocognitive function as well as an overall lower rate of neurological impairment, disability, and death.

### 10.3 POSSIBLE RISKS OF THIS STUDY EVALUATION

This is a treatment study where the standard techniques are used for conventional, standard of care catheter angiography and MMA embolization. A potential risk of participating in this study is a breach in the confidentiality of subject privacy due to study-related activities that fall beyond the scope of routine clinical care. There may be risks to a study subject, a fetus or an embryo which are unknown at this time.

## 11 SITE SELECTION

### 11.1 QUALIFICATION

The Sponsor, or a representative of the Sponsor, will evaluate each potential investigational site to ensure the PI has the adequate facilities and resources required to conduct the Study.

PIs and sites will be selected based upon the following criteria, including, but not limited to:

- Previous experience with embolization procedures using liquid embolic agents
- Previous experience with clinical research and conducting clinical trials
- Ability to enroll an adequate number of subjects in the Study
- Ability to perform protocol-required examinations
- Ability to prove adequate equipment, storage, and resources to appropriately conduct the Study

### 11.2 TRAINING

In order to provide the safe use of SQUID™, the primary consideration in operator selection is adequate experience, commitment to safety and consistency in adherence to the clinical protocol.

All study personnel will be trained and qualified to perform their study activities prior to participation in the study, and training will be documented. In order to accommodate site-specific requirements related to COVID-19, training may be performed via in person visits, remote visits (teleconference or web-based training) or a combination of the two.

### 11.3 SITE INITIATION

Prior to initiation of Subject enrollment at each site, the following must be obtained and provided to the Sponsor:

- Signed Confidentiality Agreement for Institution (prior to disclosure of any Study-related information
- IRB / EC Approval
- Copy of approved IRB / EC Informed Consent Form (ICF)
- A fully executed Clinical Trial Agreement (CTA)
- Signed and dated protocol signature page (Principal Investigator, at minimum), and Investigator Agreement (by Principal Investigator and all Sub-Investigators)
- Signed and dated current Curriculum Vitae (CV) for each participating site investigator.
- Current medical license for participating Investigators (as applicable and available, per geographic region)
- Signed Financial Disclosure Statement, for all investigators
- Completed Delegation of Authority (DoA) form
- Training records for study site personnel, as appropriate to role
- GCP Training Certificate (or completion of Site Initiation Visit training, which includes training on GCP)
- Certification copies for administrator of the tests (mRS, NIHSS, Neurocognitive)

While enrollment can begin before an *individual* study site team member has been trained, that *individual* team member may not personally enroll or perform any Study-specific activity with subjects prior to completing training and being delegated by the Principal Investigator.

Additional study site team members may be added to the Study at any time, pending approval by the IRB / EC (as applicable), documentation of Principal Investigator delegation on the Delegation of Authority form, and documented completion of training.

# 12 DATA CONSIDERATIONS

## 12.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITY

Data collection, entry and appropriate reporting is the responsibility of the site clinical study staff under the supervision of the Investigator. The Investigator or their designee are 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, or their designee, will be responsible for ensuring the overall integrity of the database.

## 12.2 ELECTRONIC CASE REPORT FORMS (eCRFs)

eCRFs have been developed to capture the information outlined in this study protocol. Data on these eCRFs will be entered into the EDC, monitored, queried by the monitors or data managers, then corrected by sites, if necessary, to ensure accurate and complete data entry into a validated study 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 identification of the person who changed the data. The Investigator will electronically sign all Subject eCRFs as verification the data have been reviewed and correctly reflect the source documentation. Data from these eCRFs will be used in analyses of study results.

## 12.3 SOURCE DOCUMENTS

CRF information should be verifiable upon review of source documents. Information and questionnaires completed by the Subject or evaluator or collected by the study site and related to study conduct, will be considered source documents and supportive study documentation.

Other records that may be considered source documents are hospital records, progress notes, lab results, clinic charts, imaging and test results, autopsy reports (if available), any notes related to adverse events and/or deaths.

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, or the person creating the entry at the given site and may serve as the source document for those data parameters. 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 must be printed, dated and signed and added to the Subject's paper file. A print-out of an eCRF cannot be used as source documentation.

## 12.4 STUDY RECORD RETENTION AND ARCHIVING

The Investigator and site will maintain all essential study documents and source documentation which support the data collected on the study Subjects according to local regulations after the end of the Study. 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 the records are no longer required, for purposes of supporting a Premarket Approval application (PMA). The Investigator will take measures to ensure 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 and is approved by authorizing parties (e.g., IRB / EC, Sponsor). Sponsor must receive written notification of this change and study-documented information recorded appropriately.

### 12.5 PROTOCOL DEVIATIONS

A protocol deviation occurs when the clinical Investigator or site personnel did not (intentionally or unintentionally) conduct the study according to the protocol and/or the Investigator Agreement. Examples include late visits, missed visits, required follow-up testing not completed, non- adherence to Inclusion/Exclusion criteria, etc. Such events shall be reported to the Sponsor and will be reviewed and assessed by the Sponsor.

The Investigator is not allowed to deviate from the protocol, except under emergency circumstances where necessary, to protect the life or physical well-being of a Subject. These emergency deviations should be reported to the IRB and Sponsor in writing as soon as possible, but no later than five (5) working days after the emergency occurred.

There will be unforeseen circumstances that are beyond the Investigator's control (e.g., Subject did not attend a scheduled visit). Prior approval will not be expected in these situations, but the Investigator should report these events upon determining that a deviation has occurred.

The Investigator is responsible to comply and adhere to IRB / EC procedures for reporting deviations. All study deviations should be listed on the appropriate Protocol Deviation CRF and submitted electronically to the Sponsor or designated representative.

The Sponsor or designee shall verify the conduct of the Study is in compliance with the approved protocol, as well as applicable regulations, and shall identify deviations and any issues of non- compliance. Corrective and preventative actions (CAPA) will be implemented promptly, as necessary. Significant protocol deviations that raise Subject safety concerns, or indicate repeated non-compliance, may be grounds for Investigator and/or site suspension or termination.

Protocol deviations related to COVID-19 will be reported in the source documentation, the eCRF and included in study reports. The Principal Investigator remains responsible for overall study oversight from study site activation through study site closeout.

For analysis, Subjects who have major protocol deviations will not be included in the statistical analysis of the "per-protocol" Subjects, as defined in the Statistical Considerations section of the protocol.

## 13 STATISTICAL CONSIDERATIONS

### 13.1 GENERAL CONSIDERATIONS

Continuous data will be summarized using standard descriptive statistics including the mean, standard deviation, median and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages. For events that can occur more than once in a single subject, such as Adverse Events, the percentage will be based on subjects experiencing the event; both subject and event counts will be reported.

P-values will be two-sided, with values less than 0.05 indicating statistical significance. All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.4 or higher, SAS Institute Inc., Cary, NC) or R (version 3.2 or higher, R Foundation for Statistical Computing, Vienna, Austria).

### 13.2 ANALYSIS POPULATIONS

A total of 5 analysis populations will be utilized in the study.

1. Enrolled population: This includes all subjects who sign informed consent.

2. Safety population: This includes all subjects who sign informed consent and are randomized. Subjects included in the safety population will be analyzed according to the treatment actually received regardless of randomization assignment. This population will be used for all safety analyses.

3. Modified ITT (MITT) population: This population includes subjects who sign informed consent, are

randomized, and the assigned intervention has started. This is the primary analysis population. Further details for the MITT group are provided below:

- For Standard Medical Management subjects, the MITT status will be considered to have been started at randomization.
- For Embolization-Only and Embolization-followed-by-Surgery subjects, the MITT status will be considered to have been started at the time of wrist/groin puncture (with the intent of embolization).
- For Surgery-Only subjects, the MITT status starts at “knife to skin” time.

4. Intent-To-Treat (ITT) population: This includes all subjects who sign informed consent and are randomized. Subjects included in the ITT population will be analyzed as randomized. The ITT population will be used for analyses of demographics, baseline characteristics, and effectiveness.

5. Per Protocol population: This includes all subjects who complete the study without a major protocol deviation. Major protocol deviations are deviations that affect the scientific integrity of the study and will be identified prior to database lock for final analysis.

## 13.3 Missing Data

The analysis for the primary and secondary effectiveness endpoints will use multiple imputation for missing data. Details of the multiple imputation methodology will be in the Statistical Analysis Plan.

## 13.4 Baseline Analysis

Subject demographic characteristics, medical history, and other pre-intervention metrics observed on the date of evaluation, will be summarized, and tabulated overall and by randomized treatment group.

## 13.5 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the occurrence of treatment failure, defined as the occurrence of one or more of the following events:

1. Residual or re-accumulation of the SDH (≥10 mm) on scan at the 180-day visit; or
2. Re-operation (after index procedure) or surgical rescue within 180-days of intervention; or
3. Any new major disabling stroke, myocardial infarction (MI) or death from any neurological cause within 180 days of intervention

The primary endpoint will be tested for superiority of the treatment (embolization) to control (no embolization). Since randomization was stratified by assignment to Surgical Management or Medical Management, the statistical analysis will also be stratified by the same factor. As additional analyses, results will also be reported separately for each stratum; however, in a two-stratum design, statistical significance is neither necessarily expected nor required to be demonstrated at the individual stratum level for study success.

As the primary endpoint is a binary (yes/no) random variable, testing will be conducted using the Cochran-Mantel-Haenszel (CMH) test, where Surgical vs Medical Management assignment serves as the stratification factor. Formal hypotheses for a test of superiority are as follows:

$H_0$: R = 1
$H_A$: R ≠ 1

where R is the odds ratio of experiencing treatment failure at 180 days for the treatment (embolization) to control (no embolization) groups, respectively. Rejection of the null hypothesis at the 5% level, with a lower observed incidence for embolization than control (i.e., estimated R < 1) constitutes a finding of superiority of treatment (embolization) to control (no embolization).

Sensitivity and supportive analyses will be performed for the primary effectiveness endpoint. This includes

performing the analysis for the ITT and PP populations, performing subgroup analyses, performing a Breslow-Day test for the homogeneity of odds ratio across strata, performing an unstratified Pearson's chi-square test, a complete case analysis, and a tipping point analysis for data that are missing for non-random reasons. Full details will be provided in the Statistical Analysis Plan (SAP).

## 13.6 Primary Safety Endpoint

- Major disabling stroke or any death within 30-days from intervention

There is no hypothesis test associated with this endpoint. The incidence of major disabling stroke or any death within 30 days from intervention will be presented by treatment group (aggregated across and also within each of the surgical management and medical management strata). 95% confidence intervals will be presented for the incidence in each cohort and for the difference between treatment groups (aggregated across and within strata).

## 13.7 Secondary Endpoints

The following endpoint is a secondary effectiveness endpoint, for which statistical assessment of outcomes between randomized treatment groups will be performed and labeling claims made in the event of successful hypothesis testing:

- mRS (analyzed as shift) at 180-day from intervention

In order to maintain family-wise Type I error at an overall level of 0.05, statistical testing of this effectiveness endpoint will only be performed if the primary endpoint hypothesis has been met, in which case the secondary effectiveness endpoint will be tested at the 0.05 level. Treatments will be compared using a van Elteren test.

The following endpoint is a secondary safety endpoint:

- Any investigational device/procedure-related AE/SAE

There is no hypothesis test associated with this endpoint. Investigational device/procedure-related AE/SAE will be summarized descriptively and reported according to section 13.10.

## 13.8 Additional Endpoints

The following are considered additional effectiveness endpoints. All additional effectiveness analyses will be performed on the MITT and ITT populations without any imputation for missing data.

- mRS (analyzed as shift) at 30-day, and 1-year from intervention
- mRS ≤ 2 (binary) at 30-day, 180-day, and 1-year from intervention
- Cognitive improvement, as measured by blinded assessment, utilizing the comprehensive neuro-cognitive battery to be performed at: Baseline, 30-day, 180-day, and 1-year, from intervention
    - Hopkins Verbal Learning Test, Revised (HVLT-R)
    - Controlled Oral Word Association Test (COWAT)
    - Animal Naming Test
    - Trail Making Test, Trails A and Trails B
- Hospital Days
- Intensive Care Unit (ICU) Days
- EQ-5D-5L (including EQ-VAS): Baseline vs. 30-day, 180-day, 1-year, from intervention
- NIH Stroke Scale (NIHSS)
- Computed Tomography (CT) imaging
    - cSDH Thickness
        - Actual measurement
        - ≥ 10 mm (Y/N)
    - cSDH Density

        - Homogeneous vs. heterogeneous
        - Densest component (hyperdense compared to cortex, isodense compared to cortex, hypodense compared to cortex, isodense to CSF)
    - Reduction of the SDH thickness by > 50% (Y/ N)
    - Reduction of the SDH thickness by > 75% (Y/ N)
    - New intracranial hemorrhage of any kind (Subarachnoid Hemorrhage (SAH), Intracerebral Hemorrhage (ICH), SDH)
    - New large vessel territory stroke

### 13.9 Interim Analysis

No formal interim analyses will be conducted unless requested by the Data Safety Monitoring Board.

### 13.10 Safety Variables

Adverse Events will be reported according to the principles in Section 13.1; the percentage reported will be based on Subjects experiencing the event; both Subject and event counts will be reported.

AE summaries (number of events and incidence) conducted on the Safety population will be presented for:

- AEs
- SAEs
- ADE's
- SADEs
- UADEs
- USADEs
- Deaths
- Device and Procedure Related AEs
- Device deficiencies

### 13.11 Poolability Across Sites and Regions

An assessment for poolability of the primary effectiveness results across clinical sites and by region (defined as US versus outside US) will be conducted. Details of the analytical methods will be presented in the Statistical Analysis Plan.

### 13.12 Justification of Sample Size

Sample size was computed based on the primary endpoint in PASS 2013 for two independent proportions in a stratified design, assuming the following:

- 19% failure rate in each of the embolization arms (embolization followed by surgery, embolization alone)
- 36% failure rate in each of the non-embolization (control) arms (surgical or medical management)
- This is equivalent to an odds ratio of 0.4170
- 1:1 allocation between groups
- 90% desired power
- Two-sided superiority test at alpha of 0.05

Under these assumptions, a sample of size 286 (143 evaluable in each arm) is required for the Cochran-Mantel-Haenszel test to achieve 90% power. In order to account for dropouts a total sample size of 310 subjects will be randomized.

## 14 MONITORING COMPLIANCE

### 14.1 Site Monitoring

A clinical monitoring plan, under separate cover, will be developed to ensure adequate monitoring of the study. All monitors will train to the monitoring plan and have this training documented prior to performing monitoring

activity. The Investigator and study team shall cooperate with the Study Monitors designated by the Sponsor. This includes, but is not limited to, allowing the assessment of facilities utilized for this clinical investigation, providing access to Subject medical records and study teams, and access to the Investigative Site File. Sites must allow auditing and inspections, as applicable. Sites must provide, for review by the monitors, any Subject report forms reasonably requested by the Sponsor or Study Monitor. The site shall also permit, at reasonable times, an authorized officer or employee of applicable regulatory agencies to inspect the facilities utilized for the clinical investigation and allow copying and verification of records required, as part of, or relevant to the investigation.

## 15 CLINICAL EVENTS COMMITTEE (CEC)

The Clinical Events Committee (CEC) is comprised of independent physicians with relevant therapeutic expertise. The CEC will review individual adverse events that are reported by the trial investigators or determined by the Sponsor/designee to be potential clinical endpoints and confirm whether the event met the study-specific criteria. The composition, guiding policies, and operating procedures governing the CEC are described in a separate CEC charter.

## 16 DATA SAFETY MONITORING BOARD (DSMB)

The Data Safety Monitoring Board (DSMB) is comprised of independent physicians with relevant therapeutic expertise and a statistician. The DSMB will review interim cumulative data from the Study at prescribed intervals for the purpose of providing oversight in safety of the participants and ensuring study data integrity. The composition, guiding policies, and operating procedures governing the DSMB are described in a separate DSMB charter. Based on the data review at each meeting, the chairman will recommend continuing the study as is, make modification to the protocol, or halt the clinical trial. All final decisions, however, rest with the Sponsor. If the DSMB's recommendation is to pause or terminate the study, Balt will comply with the recommendation and pause enrollment to ensure the adequate protection of human subjects. FDA will be consulted prior to early termination of the study.

## 17 IMAGING CORE LAB

All imaging and image submissions shall be performed in accordance with the core laboratory recommended image acquisition guidelines provided to the sites.

An independent core laboratory will provide an unbiased and standardized assessment of all imaging collected during this Study. While reviewing images, it may be apparent to the core lab which subjects have undergone surgical interventions, but to minimize bias, the core lab image assessors will be blinded to the Subjects' previous medical history and treatment assignment. The core lab will evaluate imaging and CT scans from the following timepoints:

- Screening/Baseline (i.e., prior to randomization)
- 24-hours (+/- 12 hours) post-intervention; (note: Standard Medical Management who have not been admitted to hospital/released prior to 24-hour are not required to have this imaging performed, and this is not a deviation)
- 30-day (+/- 2 weeks) follow-up; as per standard of care
- 90-day (+/- 4 weeks) follow-up; as per standard of care
- 180-day (+/- 6 weeks) follow-up
- 1-year (+/- 8 weeks) follow-up; only required for subjects that experienced treatment failure #1 ***or*** if this is standard of care at the institution
- Unscheduled visits; as per standard of care

The CT scans will be read for the following:

1. cSDH Thickness
    a. Actual measurement
    b. ≥ 10 mm (Y/N)

2. cSDH Density
    a. Homogeneous vs. heterogeneous
    b. Densest component (hyperdense compared to cortex, isodense compared to cortex, hypodense compared to cortex, isodense to CSF)
3. Reduction of the SDH
    a. Reduction of the SDH thickness by >50% (Y/ N)
    b. Reduction of the SDH thickness by > 75% (Y/ N)
4. New intracranial hemorrhage of any kind (Subarachnoid Hemorrhage (SAH), Intracerebral Hemorrhage (ICH), SDH)
5. New large vessel territory stroke

With regards to quantifying CT calculations, a measurement of the subdural hematoma at its largest thickness on an axial or coronal CT or MR image (whichever depicts the thickness, to the best in the opinion of the core lab) and then drawing a perpendicular line from the inner table of the skull to the pial surface of the brain.

# 18 ETHICAL CONSIDERATIONS

## 18.1 CODE OF CONDUCT

The Investigator will ensure that the clinical Study is conducted in accordance with applicable sections of ICH GCP, ISO 14155, 21 CFR Parts 50, 54, 56, and 812 and all regulatory and institutional requirements, including those for Subject privacy, informed consent, IRB or EC approval and record retention, and the appropriate local regulatory body's guidelines for the conduct of clinical trials. The rights, safety and well-being of clinical study Subjects shall be protected by the ethical principles laid down in the Declaration of Helsinki. These practices shall be understood, observed and applied at every step in this clinical study.

## 18.2 INSTITUTIONAL REVIEW BOARD (IRB) / ETHICS COMMITTEE (EC)

The Investigator must obtain appropriate IRB / EC approval before the Study can be initiated. A copy of the written approval from the IRB / EC and a copy of the approved ICF must be sent to the Sponsor. It is also necessary to submit a list of the IRB / EC members (including their Institution affiliations and occupations); or supply a statement from the IRB / EC specifying that the membership complies with applicable regulations.

If the Investigator advertises for Subject study recruitment, whether in a professional or consumer publication, radio, television or community notices, all advertising must receive documented prior approval by Sponsor and the IRB / EC.

Any changes to the protocol must be discussed and approved by the Sponsor in writing unless the change is made to assure the safety of the Subject. In the non-emergent setting, after agreement on the changes has been reached, an amendment to the protocol will be provided by Sponsor for submission to the IRB / EC for review and approval prior to initiation of the change. Any change made emergently must be documented in the Subject's medical record.

The Investigator must immediately forward to the IRB / EC any written safety reports or updates from the Sponsor. The Investigator must keep the IRB / EC informed of the progress of the Study at least annually and according to local regulatory requirements.

## 18.3 INFORMED CONSENT

It is the responsibility of the Investigator and/or approved and delegated staff, to obtain written informed consent from each subject or his/her LAR participating in this Study, after adequate explanation of the aims, methods, potential benefits and potential hazards of the Study have been reviewed. The informed consent procedure must be documented at each study site for each subject. No non-standard of care study-related procedures or evaluations may be performed prior to obtaining written informed consent.

The Investigator must clearly and understandably explain that taking part in the Study is entirely voluntary and

the subjects are free from obligation to enter the Study, and may withdraw from the Study, at any time and for any reason, without penalty. Similarly, the Investigator has the option to withdraw the subject from the Study at any time for safety reasons. Any other requirements necessary for the protection of the human rights of the subject will also be explained, in accordance with current ICH GCP Guidelines and FDA requirements.

The Sponsor will adapt the Master ICF to any appropriate country-specific regulation and local- language requirements. All modifications of the ICF will be approved by the Sponsor and submitted/ approved by the IRB / EC prior to being used by the Investigator and/or approved and delegated staff to consent a Subject.

### 18.4 SUBJECT CONFIDENTIALITY

The sites, CRO, core lab, Sponsor and designees will maintain the confidentiality of the identity of Subjects enrolled in the Study and the information contained in their study records. The Sponsor will also instruct the study Investigators in the importance of maintaining the confidentiality of study records. All subjects who provide written informed consent will be assigned an anonymized subject number to ensure subject de-identification. Subsequently, subjects will be identified in the eCRF only by their subject number (as allowed by local country regulations). Any publication of the data collected as part of this Study will only use de-identified data in order to prevent identification of any individual Subject. The information from this Study will be available within the Sponsor's organization and may be shared with appropriate regulatory authorities. This Study, and the data collected, may also be subject to an audit by the IRB/EC, the site compliance group, the sponsor/designee, or to an inspection by a regulatory agency, such as the Food and Drug Administration (FDA) or other Notified Body. The Subject's identity will remain protected, except as required for legal or regulatory inquiries. The records will be made available, as required, for review by the applicable regulatory agency and a reviewing IRB / EC, however to the extent possible, the Subject's identity will not be disclosed.

### 18.5 STUDY INSURANCE

When required by applicable local regulations, the Study will be covered by an insurance policy, subscribed by the Sponsor, and covering all aspects of the research.

## 19 STUDY SUSPENSION OR TERMINATION

Sponsor reserves the right to suspend or terminate enrollment or other study activities at an investigational site at any time, upon giving written notice. This may be based on any of the following reasons (but is not limited to):

- The site has not complied with the protocol, study agreement, requirements of the EC/IRB or regulations
- Repeated failure to complete CRFs
- Failure to report SAE, SADE, UADE, USADE, death, device deficiency/malfunction within two business days of awareness
- Repeated protocol violations
- Site Principal Investigator leaves the Institution, and no adequate replacement is available

The Sponsor will notify the relevant Site and/or Site's IRB / EC, if applicable, within five (5) business days in the instance of Site suspension / termination.

A suspended Site may not be allowed to enroll or treat subjects without giving reasonable proof to the Sponsor that sufficient preventative and corrective actions have been implemented to resolve root-causes of the problem identified. The sponsor must approve the enrolment or study suspension lift in writing. Approval of the reviewing IRB / EC may be required, where applicable.

The Sponsor, the Study Steering Committee, CEC and DSMB members will monitor the Study progression. If warranted, the Study may have enrollment or other study activity suspended or terminated at a site or across the study, or be discontinued or put on-hold for any of the following reasons (not inclusive):

- New findings invalidate the earlier positive benefit-risk assessment
- Time schedule cannot be met (recruitment phase; more than doubling of recruitment time)

In such an instance, FDA, Principal Investigators / Study Sites and the EC/IRB and other applicable entities will be informed in writing with the reason(s) for change in study status at the site or in the study overall.

Written notification of suspension or termination will occur no later than five (5) business days after Sponsor makes the determination. In the event of Study suspension or termination, the Sponsor will send a report outlining the circumstances to the appropriate regulatory authorities and entities (e.g., FDA, EC/IRB, and other entities) and all required Principal Investigators / Study Sites. A suspended or terminated Study may not be re-initiated without approval from the reviewing regulatory authority (e.g., IRB / EC, where applicable). The site should continue to follow any Subjects as per standard of care and follow instructions as provided by the sponsor/designee for ongoing data collection and/or resumption of suspended study activity, and/or site/study closure.

In the instance of a Study termination, any reportable AE(s) would continue to be reported and recorded through the end of the Subject's participation in the Study.

At the end of the Study, or at study Site closure, routine closeout activities will be conducted to ensure site records are complete, Study data are complete and accurate, remaining Study materials are returned to the Sponsor, all required records are collected, device accountability is accurate and complete, all investigational devices have been retrieved and/or disposed of as per written Sponsor instructions, arrangements are made for record retention and appropriate ECs/IRBs, FDA, and other required entities are notified in writing of site or study closure. Appropriate reports will be provided to required entities as per local EC/IRB, FDA or other requirements.

## 20 PUBLICATION POLICY

The multi-center Study results will be submitted for publication in an appropriate peer-reviewed journal, which will be discussed by the Scientific Committee or designee, prior to individual investigator publications.

Any participating Investigators wishing to publish data from this Study (poster, abstract, article, etc.), must first seek approval from the Sponsor. Where applicable, Study draft publications should be submitted to the Sponsor prior to submission for publication.

Table 8. References

**Literature and Articles**


| | |
|---|---|
| 1 | Balser D, Farooq S, Mehmood T, Reyes M, Samadani U. Actual and projected incidence rates for chronic subdural hematomas in united states veteran's administration and civilian populations. *Journal of neurosurgery*. 2015;123:1209-1215 |
| 2 | Kalamatianos T, Stavrinou LC, Koutsarnakis C, Psachoulia C, Sakas DE, Stranjalis G. Plgf and svegfr-1 in chronic subdural hematoma: Implications for hematoma development. *Journal of neurosurgery*. 2013;118:353-357 |
| 3 | Stanisic M, Aasen AO, Pripp AH, Lindegaard KF, Ramm-Pettersen J, Lyngstadaas SP, et al. Local and systemic pro-inflammatory and anti-inflammatory cytokine patterns in patients with chronic subdural hematoma: A prospective study. *Inflamm Res*. 2012;61:845-852 |
| 4 | Santarius T, Kirkpatrick PJ, Kolias AG, Hutchinson PJ. Working toward rational and evidence-based treatment of chronic subdural hematoma. *Clin Neurosurg*. 2010;57:112- 122 |
| 5 | Baechli H, Nordmann A, Bucher HC, Gratzl O. Demographics and prevalent risk factors of chronic subdural haematoma: Results of a large single-center cohort study. *Neurosurg Rev*. 2004;27:263-266 |
| 6 | Kang J, Whang K, Hong SK, Pyen JS, Cho SM, Kim JY, et al. Middle meningeal artery embolization in recurrent chronic subdural hematoma combined with arachnoid cyst. *Korean J Neurotrauma*. 2015;11:187-190 |
| 7 | Hirai S, Ono J, Odaki M, Serizawa T, Nagano O. Embolization of the middle meningeal artery for refractory chronic subdural haematoma. Usefulness for patients under anticoagulant therapy. *Interv Neuroradiol*. 2004;10 Suppl 2:101-104 |
| 8 | Hashimoto T, Ohashi T, Watanabe D, Koyama S, Namatame H, Izawa H, et al. Usefulness of embolization of the middle meningeal artery for refractory chronic subdural hematomas. *Surg Neurol Int*. 2013;4:104 |
| 9 | Ishihara H, Ishihara S, Kohyama S, Yamane F, Ogawa M, Sato A, et al. Experience in endovascular treatment of recurrent chronic subdural hematoma. *Interv Neuroradiol*. 2007;13 Suppl 1:141-144 |
| 10 | Ban SP, Hwang G, Byoun HS, Kim T, Lee SU, Bang JS, et al. Middle meningeal artery embolization for chronic subdural hematoma. *Radiology*. 2018;286:992-999 |
| 11 | SQUID CER REV-06 April 2018 |
| 12 | Benedict RHB., Schretlen D., Groninger L., and Brandt J. (1998). Hopkins Verbal Learning Test – Revised: normative data and analysis of inter-form and test-retest reliability. *The Clinical Neuropsychologist, 12*, 43-55 |
| 13 | Benton AL., and Hamsher KdeS. (1989). *Multilingual Aphasia Examination*. Iowa City, IA: AJA Associates |
| 14 | Gill M., Maheshwari V., Narang A., and Lingaraju TS (2018). Impact of Cognitive Improvement following burr hole evacuation of chronic subdural hematoma: a prospective observational study. *Journal of Neurosciences in Rural Practice, 9,* 457-460 |

Table 8. References


| | |
|---|---|
| 15 | Green MF., Nuechterlein KH., Gold JM., Barch DM., Cohen J., Essock S., et al. (2004). Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. *Biological Psychiatry, 56 (5)*, 1-7 |
| 16 | Lezak MD (2004). *Neuropsychological Assessment. 3rd Ed.* New York: Oxford University Press |
| 17 | Kawasaki, Y., Fujiki, M., Ooba, H., Sugita K., Hikawa T., Abe T., Ishii K., and Kobayashi H. (2012) Short latency afferent inhibition associated with cortical compression and memory impairment in patients with chronic subdural hematoma. *Clinical neurology and neurosurgery, 114,* 976-980 |
| 18 | Regine WF, Schmitt FA, Scott CB, et al. (2004). Feasibility of neurocognitive outcome evaluations in patients with brain metastases in a multi-institutional cooperative group setting: Results of Radiation Therapy Oncology Group trial BR-0018. *Int J Radiat Oncol Biol Phys. 58*:1346-1352 |
| 19 | Schebesch KM, Woertgen C., Rothoerl RD, Ullrich OW, and Brawanski AT. (2008). Cognitive decline as an important sign for an operable cause of dementia: chronic subdural haematoma. *Zentralblatte fur Neurochirurgie, 69,* 61-64 |
| 20 | Schoedel P., Bruendl E., Hochreiter A., Scheitzach J., Bele S., Brawanski A., Schebesch KM. (2016). Restoration of Functional Integrity After Evacuation of Chronic Subdural Hematoma-An Age-Adjusted Analysis of 697 Patients. *World Neurosurgery, 94,* 465-470 |
| 21 | Scott, R.B., Eccles, F., Molyneux, A.J., Kerr, R.S., Rothwell, P.M., and Carpenter, K. (2010). Improved cognitive outcomes with endovascular coiling of ruptured intracranial aneurysms: neuropsychological outcomes from the International Subarachnoid Aneurysm Trial (ISAT). *Stroke, 41 (8),* 1743-1747. |
| 22 | Stout JC., Queller S., Baker KN., Cowlishaw S., Sampaio C., Fitzer-Atlas C., Borowsky B., and HD-CAB Investigators (2014). HD-CAB: a cognitive assessment battery for clinical trials in Huntington's disease 1,2,3. *Movement Disorders, 29 (10)*, 1281-1288 |

# APPENDIX

| Appendix 1. Anticipated Adverse Events Related to Endovascular Treatment of cSDH | |
|---|---|
| • Allergic Reaction | • Loss of motor skills |
| • Anesthesia Reaction | • Medical co-morbidities |
| • Anxiety | • Multi-organ system failure |
| • Bleeding complications, resulting from hemodynamic changes induced by the embolization procedure or attempts to remove entrapped catheter | • (Intentionally left blank) |
| • Catheter entrapment, embolization of unintended areas, difficulty removing catheter or catheter rupture | • (Intentionally left blank) |
| • Confusion, coma or other change in mental status | • Myocardial Infarction (MI) |
| • Contrast reaction* | • Neurological deficits |
| • Cranial nerve damage | • Pain (e.g., neck, back, groin) |
| • Damage to access vessels | • Paralysis |
| • Death | • Parenchymal hemorrhage |
| • Delivery system failure with premature or inaccurate deployment* | • Paresis (numbness, tingling) |
| • Depression | • Perforation or rupture of parent artery* |
| • Development of clinical symptoms associated with “mass effect” | • Peripheral thromboembolism* |
| • Device migration* and/or device migration and cast movement | • Peripheral Vascular Disease (PVD) |
| • Device misplacement* | • Pneumonia |
| • Dissection of the parent artery or other access vessels* | • Progressive neurologic symptoms related to Ischemic Attack* |
| • Dizziness / Nausea / Vomiting | • Reaction to radiation exposure |
| • Dysrhythmias | • Renal failure / insufficiency |
| • Electrical arcing with tantalum metal in the SQUID material | • (Intentionally left blank) |

| Appendix 1. Anticipated Adverse Events Related to Endovascular Treatment of cSDH | |
|---|---|
| • Embolism or blood clot | • Respiratory failure |
| • Fever | • Retroperitoneal hematoma |
| • Groin injury, including bleeding, pain, vessel or nerve damage | • Seizure |
| • Headache | • Stenosis of the parent artery* |
| • Hematoma | • Subarachnoid hemorrhage* |
| • Hematuria | • Syncope |
| • Hemorrhagic Stroke* | • Thromboembolism* |
| • Hydrocephalus | • Thrombosis of branch vessel* |
| • Hypertension / Hypotension | • Thrombosis of parent artery* |
| • Hyperglycemia/Hypoglycemia | • Transient Ischemic Attack (TIA) |
| • Incomplete occlusion of the cSDH | • Trauma |
| • Infection / Inflammation* | • Unintended vascular occlusion |
| • Injury to normal vessels | • Vasospasm* and/or angio-necrosis |
| • Interaction of SQUID with other embolic agents | • (Intentionally left blank) |
| • Intracerebral bleeding* | • Vessel perforation |
| • Ischemic stroke* | • Vision impairment |
| • Laboratory abnormalities (e.g., elevated serum creatinine, bilirubin, hemoglobin, etc.) | • Weakness (left or right-sided) |
| • Loss of consciousness | • Wound infection (groin puncture) |

**Events listed with an asterisk could result in stroke, TIA or neurological syndromes, including motor or sensory loss, loss of higher cortical function, loss of speech, visual loss, seizure, or other syndromes or death.*

| Appendix 2. Anticipated Side Effects of EVOH and DMSO | |
|---|---|
| • Vasospasm | • Arterial Wall Rupture |
| • Angionecrosis | • Hemorrhage |
| • Cerebral Infarct | • Intimal Hyperplasia |
| • Hydrocephalus | • Granulomas |
| • Inflammation | |

There may be other risks that are unknown at this time, including unknown risks to an embryo, fetus, or study subject.

Table 9. Revision History

| Author | Revision | Description |
|---|---|---|
| Sherri Chamblee | 1.0 | ✦ Update 1<br>✓ Initial Release, Version 1 |
| Sherri Chamblee | 1.1 | ✦ Update 1<br>✓ Updated Inclusion Criteria #2 to 'Pre-morbid' mRS 0-1<br>✦ Update 2<br>✓ Corrected typo in Table 7, 30 Day FU to (+/- 14 days)<br>✦ Update 3<br>✓ Corrected Effectiveness Endpoints typo in Table 5 and section 13.5 to ≤ 2 (binary)<br>✦ Update 4<br>✓ Section 8.3.1, added Eclipse 2L due to 510(k) approval |

Table 9, Revision History

| Author | Revision | Description |
|---|---|---|
| Sarah Moeller | 1.1.1 | ✦ Update 1<br>✓ Title Page (1) : Added Version 1.1.1<br>✦ Update 2<br>✓ Section 5.3 (Pages 26-27): Change; Add definition of diagnostic imaging modality for patients allocated to embolization, (catheter angiography) at the time of the index procedure<br>✓ Section 5.3 (Pages 26-27): Change; Add definition of analysis for patients found to have MMA anatomy unsuitable for embolization, the procedure will be stopped after diagnostic angiography (i.e., no embolization will be performed). These patients will be included in the embolization arm in all subsequent ITT analyses<br>✦ Update 3<br>✓ Section 8.3.1 (Page 33): Corrected Effectiveness Endpoints typo in Table 5 and section 13.5 to ≤ 2 (binary)<br>✓ Section 8.3.1 (Page 33): Change; Patients designated to embolization plus evacuation will be required to have surgical evacuation occur within 48 hours of randomization<br>✦ Update 4<br>✓ Updated protocol version date to version 1.1.1 dated 11MAY2020 throughout document<br>✓ Added clarification text to section 5.3 to include possibility of subjects being declined for the embolization procedure due to dangerous anatomical variants or with MMA anatomy that is otherwise unsuitable for embolization, yet not be excluded from the study as they would have already been consented (enrolled) and randomized and therefore be included in the Intent To Treat cohort. |

Table 9, Revision History

| Author | Revision | Description |
|---|---|---|
| Philippa Hill | 2.0 | ✦ Update 1<br>✓ Administrative changes throughout document: Update Version and date, table identifiers, standardize formatting, change study product name from “liquid embolic system” to “liquid embolic agent” and added model number and expiry date for product identification, updated page numbers, Investigator Agreement and Protocol Signature Page: Removed and maintained under separate cover, update table 2:Summary of changes, updated staff changes, contact details and clarify Balt USA, LLC is sponsor. Update and clarify language for readability throughout document. Added language to support impact of COVID-19<br>✦ Update 2<br>✓ Table 4 Protocol Synopsis, Protocol Sections, 5.4.1, 5.4.2 (Pages 14,29-30) Removed Inclusion Criteria 3 and Exclusion Criteria 14 to align with protocol section 5.3<br>✓ Table 4 Protocol Synopsis, Protocol Sections 7.1, 7.2 (Pages 14. 33) Changed Primary endpoint to “Any new major disabling stroke, myocardial infarction(MI) or death from any (neurological) cause within 180 days of intervention”. Updated Safety endpoint to “Major disabling stroke or any death (within 30 days) from intervention”<br>✓ Table 4, Protocol Sections 5.1, 5.2 (Pages 14, 29) Updated number of US sites in alignment with FDA approval letter. Added clarification of up to 10 OUS sites. Updated language to reflect number of subjects randomized per site. This number can only be increased on written approval by sponsor.<br>✦ Update 3<br>✓ Figure 1 (Page 24) Updated figure to align with protocol text in sections 5.3, 5.6.1, 7.1, 7.2, 7.3, 8.3, 8.3.1 and updated names of randomization arms. Clarified timepoints for enrollment, screen failure, randomization and ITT starting point<br>✦ Update 4<br>✓ Sections 8.2, 8.4-8.4.6 (Pages 31-36) ,added pre-morbid mRS to align with inclusion criteria and that mRS is performed by a certified assessor, added clarification language for medication collection, positive pregnancy tests, source document requirements, and all visits. Clarified timing of ITT cohort start and which visits, and procedures were required per cohort to support endpoint analyses and align with standard of care<br>✦ Update 5<br>✓ Table 6 Schedule of Events (Page 44), Section 9 (Pages 45-47) Updated table and Section 9.0 to state that all adverse events will be collected from time of enrollment through study exit. Clarified image collection requirements and clarified AE definitions |

Table 9, Revision History

| Author | Revision | Description |
|---|---|---|
| Philippa Hill | 3.0 | ✦ Update 1<br>✓ Administrative changes update version date, table identifiers, figure identifiers, updated current ISO regulations, standardize formatting, updated page numbers, typos, clarified terms for readability. Also included staff changes, contact information and name of Core Lab.<br>✦ Update 2<br>✓ Table 3 Protocol Synopsis, Protocol Sections, 5.1,5.3, 5.4.1, 5.4.2,6, 7.2.2, 7.3 (Pages 8-11,) Increased study population from 228 to 310, increased US sites from 25 to 35 and updated enrollment timeline and clarified enrollment period to accommodate for COVID 19 enrollment challenges, modified the effectiveness endpoint to mRS analyzed at shift refined additional endpoints and added all endpoints which will be included in analysis. Inclusion criteria: clarified time limes for collecting pre-morbid mRS, Exclusion Criteria: added Ipsilateral craniotomy and subject with prior embolization of wither MMA, clarification to liver function timelines, and refined language for exclusion of a patient in another study.<br>✓ Table 5 Schedule of Events (Page 37) Updated for clarity by sites as it was proving hard to interpret and eliminated 2 time points (pregnancy test at intervention and inclusion/exclusion criteria at randomization as test/activities already completed at screening/baseline window) added mRS at 90 days as omitted unintentionally.<br>✦ Update 3<br>✓ Section 3 Study Design (Page 18) Added sample size justification statement to align with the increase in study population from 228 to 310. Clarification language of the strata groups.<br>✦ Update 4<br>✓ Figure 1 (Page 19) Created a new Figure 1 that aligns with the protocol text (Pages 29-31) Clarified baseline CT image timeline to be considered for inclusion in the study Clarified timepoints for initial clinical assessment, enrollment, and randomization,<br>✦ Update 5<br>✓ Section 5.3 (Page 22) deleted the language that stated Patients with prior surgical intervention for cSDH with subsequent re-accumulation of a qualifying cSDH are candidates for the Study. If the patient has had a craniotomy ipsilateral to the cSDH, the Investigator should verify that the MMA has not been surgically interrupted or ligated prior to enrollment and randomization as this is direct contraindication to the exclusion criteria. |

| | | |
|---|---|---|
| | | ➢ Update 6<br>✓ Section 7.1 (Page 26) defined for clarity what is considered re-operation or surgical rescue.<br>➢ Update 7<br>✓ Section 8.1.1 (Pages 27-28) added per country specifications the ability to have an independent physician consent where LAR consent is not allowed, Section 8.3.1 (Page 30) ,added pre-morbid mRS to align with inclusion criteria and that mRS is performed by a certified assessor,<br>➢ Update 8<br>✓ Sections 13.1,13.2,13.3,13.5,13.6,13.7,13.11 (Pages 48-50) updated clarification of general considerations, description of the analysis population, how missing data will be analyzed. Changed from Fisher exact to Pearson Chi-Square test and clarified the supporting analyses. Further clarified the reduction in cSDH thickness to be more accurate/specific. Explanation for the justification of increasing the evaluable sample size. Section 18 (Page 55) mirrored language from Stats section |
| **Justin Frazier** | **4.0** | ➢ Update 1<br>The synopsis was expanded to provide more clarity on subject disposition. Study flowcharts were added, as well as a description of study procedures.<br>➢ Update 2<br>A definition of study completion was added as section 5.5<br>➢ Update 3<br>A CT evaluation was added for subjects that only experienced Failure #1 at the 12-month follow-up. This imaging is standard of care (to track the progression of the SDH) and does not represent an additional burden to the patient. Section 8.5.6 has been updated accordingly.<br>➢ Update 4<br>All other changes made were administrative in nature (grammar, consistency between sections, rewording for readability), and do not change the study design, intent, or data collection process. Most notably, the following edits were made:<br>• study management personnel have been updated;<br>• exclusion criteria 6, 7, and 8 were deleted, as they are exactly the same as inclusion criteria 3, 4, and 5 (inverse wording);<br>• nomenclature harmonization – reference to ‘patients’ was changed to ‘subject’ in most instances;<br>• clarifications in section 8.4 about when CT imaging should be conducted during the study (no changes to prior imaging requirements); and<br>• follow-up windows were adjusted to reflect current clinical practice |

DocuSign

## Certificate Of Completion

Envelope Id: 87A37F155DF846F9891ABD1143BDA41E
Status: Completed
Subject: Complete with DocuSign: STEM_Protocol_v5.0_1MAR2023_CL.docx
Source Envelope:
Document Pages: 65
Signatures: 5
Envelope Originator:
Certificate Pages: 5
Initials: 0
[redacted]
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-08:00) Pacific Time (US & Canada)

## Record Tracking

Status: Original
3/2/2023 11:52:27 AM
[redacted]
Location: DocuSign

| Signer Events | Signature | Timestamp |
|---|---|---|
| Adam Arthur<br>[redacted]<br>Security Level: Email, Account Authentication (None) | DocuSigned by:<br>[redacted]<br>Signature Adoption: Pre-selected Style<br>Using IP Address: 76.107.133.98 | Sent: 3/2/2023 12:04:57 PM<br>Viewed: 3/5/2023 12:51:41 PM<br>Signed: 3/5/2023 12:51:53 PM |
| **Electronic Record and Signature Disclosure:**<br>Accepted: 3/5/2023 12:51:41 PM<br>ID: 1b954965-9039-40c3-9522-7fa4b89e0558 | | |
| [redacted]<br>Security Level: Email, Account Authentication (None) | [redacted]<br>e | Sent: 3/2/2023 12:04:55 PM<br>Viewed: 3/3/2023 8:58:49 AM<br>Signed: 3/3/2023 8:58:57 AM |
| **Electronic Record and Signature Disclosure:**<br>Accepted: 3/3/2023 8:58:49 AM<br>ID: 53efbf4d-3e39-4849-a4ea-1f32e9b255e0 | | |
| Dr. David Fiorella, M.D., Ph.D.<br>[redacted]<br>Level: Email, Account Authentication (None) | [redacted]<br>Signature Adoption: Pre-selected Style<br>Using IP Address: [redacted] | Sent: 3/2/2023 12:04:57 PM<br>Viewed: 3/2/2023 12:05:52 PM<br>Signed: 3/2/2023 12:06:05 PM |
| **Electronic Record and Signature Disclosure:**<br>Accepted: 3/2/2023 12:05:52 PM<br>ID: 228a6410-d397-4b5e-a619-11fd7ce66a01 | | |
| John ALLISON<br>[redacted]<br>Security Level: Email, Account Authentication (None) | [redacted]<br>Signature Adoption: Pre-selected Style<br>[redacted] | Sent: 3/2/2023 12:04:56 PM<br>Viewed: 3/2/2023 1:37:18 PM<br>Signed: 3/2/2023 1:37:23 PM |
| **Electronic Record and Signature Disclosure:**<br>Accepted: 3/2/2023 1:37:17 PM<br>ID: 108ca64d-b061-457b-8e42-f3fcfdffead7 | | |

| Signer Events | [redacted] | [redacted] |
|---|---|---|
| [redacted]<br>[redacted]<br>[redacted] Email, Account Authentication (None) | [redacted]<br>Signature Adoption: Pre-selected Style<br>[redacted] | Sent: 3/2/2023 12:04:53 PM<br>Viewed: 3/2/2023 12:05:47 PM<br>Signed: 3/2/2023 12:06:02 PM |

**Electronic Record and Signature Disclosure:**
Not Offered via DocuSign

| In Person Signer Events | Signature | Timestamp |
|---|---|---|

| Editor Delivery Events | Status | Timestamp |
|---|---|---|

| Agent Delivery Events | Status | Timestamp |
|---|---|---|

| Intermediary Delivery Events | Status | Timestamp |
|---|---|---|

| Certified Delivery Events | Status | Timestamp |
|---|---|---|

| Carbon Copy Events | Status | Timestamp |
|---|---|---|

| Witness Events | Signature | Timestamp |
|---|---|---|

| Notary Events | Signature | Timestamp |
|---|---|---|

| Envelope Summary Events | Status | Timestamps |
|---|---|---|
| Envelope Sent | Hashed/Encrypted | 3/2/2023 12:04:58 PM |
| Certified Delivered | Security Checked | 3/2/2023 12:05:47 PM |
| Signing Complete | Security Checked | 3/2/2023 12:06:02 PM |
| Completed | Security Checked | 3/5/2023 12:51:53 PM |

| Payment Events | Status | Timestamps |
|---|---|---|

| Electronic Record and Signature Disclosure |
|---|

## ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, [redacted] (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

### Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

### Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

### Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

### All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

**How to contact [redacted]**

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: [redacted]

**To advise [redacted] of your new email address**

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at [redacted]om and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

**To request paper copies from [redacted]**

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to [redacted]m and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

**To withdraw your consent with [redacted]**

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to [redacted].com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

**Required hardware and software**

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

**Acknowledging your access and consent to receive and sign documents electronically**

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify [redacted] as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by [redacted] during the course of your relationship with [redacted]