INVEST-REGISTRY: Minimally Invasive Endoscopic Surgical Treatment With Apollo/Artemis in Patients With Brain Hemorrhage: A Prospective Multicenter Registry
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INVEST-REGISTRY: Minimally Invasive Endoscopic Surgical Treatment with Apollo / Artemis in patients with Brain Hemorrhage: A Prospective Multicenter Registry

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Study Title: INVEST REGISTRY: Minimally Invasive Endoscopic Surgical Treatment with Apollo / Artemis in patients with Brain Hemorrhage: A Prospective Multicenter Registry

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Study Center: _____

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant parts of the appropriate regulatory requirements and the pertinent individual country laws/regulations.

_____ _____

Investigator Date

Print name:

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Study Synopsis:

Title: INVEST REGISTRY: Minimally Invasive Endoscopic Surgical Treatment with Apollo / Artemis in patients with Brain Hemorrhage: A Prospective Multicenter Registry

Objective: The primary objective of this multicenter prospective registry is to provide additional safety, technical outcomes and clinical outcomes data for minimally invasive endoscopic surgery (MIES) with Apollo / Artemis for the evacuation of supratentorial brain hemorrhage in adult patients who do not qualify for the concurrent INVEST Feasibility study at active United States (US) INVEST centers.

Study Design: This study will be a prospective, non-randomized, multi-center, single arm registry that will enroll up to 50 patients at up to 30 US centers.

Patient Population: Adult patients with supratentorial brain hemorrhages (ICH and/or IVH) who do not meet all INCLUSION criteria or who meet one or more EXCLUSION criteria for the INVEST feasibility study, but who will ultimately undergo MIES with Apollo or Artemis at active INVEST centers.

Indication: The Artemis Neuro Evacuation Device is used for the controlled aspiration of tissue and/or fluid during surgery of the Ventricular System or Cerebrum in conjunction with a Penumbra Aspiration Pump. The Penumbra Aspiration Pump is indicated as a vacuum source for the Penumbra Aspiration Systems. The Apollo system has been cleared for the controlled aspiration of soft tissue and/or fluid during endoscopically guided neurosurgery of the ventricular system. In the present study, we propose to investigate the safety and efficacy of this system for the minimally invasive evacuation of brain hemorrhage – both IVH, IVH with ICH and ICH alone – in patients who do not qualify for the INVEST trial.

Inclusion Criteria:

1. Age 22 years or older
2. Supratentorial brain hemorrhage, which may be:
    a. Intracerebral (ICH)
    b. Primarily Intracerebral (ICH) with a component of intraventricular hemorrhage (IVH)
    c. Primarily intraventricular hemorrhage (IVH) with a component of ICH
    d. Intraventricular hemorrhage (IVH)
3. Patient does not qualify for the concurrent INVEST Feasibility study

Exclusion Criteria:

1 Imaging
    a. Expanding hemorrhage on stability CT/MR scan
    b. "Spot sign" identified on CTA
        (i) May perform a second CTA at 12 hours to demonstrate resolution
    c. Hemorrhagic lesion which cannot be completely secured prior to the Artemis MIES, such as a vascular malformation (cavernous malformation, AVM etc), untreated or incompletely treated aneurysm, neoplasm
    d. Hemorrhagic conversion of an underlying ischemic stroke
    e. Infratentorial hemorrhage
    f. Midbrain extension/involvement

2 Coagulation Issues
   a. Absolute and imminent (within 7 days of treatment) requirement for long-term, full-dose, anti-coagulation (e.g., Mechanical valve replacement (bio-prostatic valve is permitted), high risk atrial fibrillation)
   b. Known, uncorrectable hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency
   c. Uncorrectable platelet count < 100 x 103 cells/mm3 or known platelet dysfunction
   d. INR > 1.5, elevated prothrombin time or activated partial thromboplastin time (aPTT), which cannot be corrected or otherwise accounted for (i.e., lupus anti-coagulant)

3 Patient Factors
   a. High risk condition for ischemic stroke (high risk Afib (e.g., mitral stenosis with Afib), symptomatic carotid stenosis);
   b. Requirement for emergent surgical decompression or uncontrolled ICP after EVD
   c. Unable to obtain consent from patient or appropriate surrogate (for patients without competence);
   d. Pregnancy, breast-feeding, or positive pregnancy test (either serum or urine). Woman of child-bearing potential must have a negative pregnancy test prior to the study procedure;
   e. Evidence of active infection indicated by fever at or over 100.7 °F, and/or open draining wound at the time of randomization;
   f. Any comorbid disease or condition expected to compromise survival or ability to complete follow- up assessments through 180 days;
   g. Based on investigator's judgment, patient does not have the necessary mental capacity to participate or is unwilling or unable to comply with protocol follow up appointment schedule;
   h. Active drug or alcohol use or dependence that, in the opinion of the site investigator would interfere with adherence to study requirements;
   i. Currently participating in another interventional (drug, device, etc) research project.

Primary Endpoint:

The primary objective of this multicenter prospective registry is to provide an additional safety, technical and clinical outcomes data for minimally invasive endoscopic surgery (MIES) with Apollo / Artemis for the evacuation of brain hemorrhage in patients who do not qualify for the concurrent INVEST feasibility study at active INVEST centers:

- Clinical Efficacy Endpoint: 180-day global disability assessed via the modified Rankin score (mRS), categorized as either mRS $\leq$ 3 or mRS > 3
- Technical Efficacy Endpoint: Rate of surgical success
  - Predominantly or Only ICH: Reduction to < 15 cc total volume AND >60% reduction in hemorrhage volume on immediate post-treatment CT scan
  - Predominantly or Only IVH: mGraeb score of $\leq$ 5 on day 7 CT scan
- Safety Endpoint: Rate of mortality at 30 days

Secondary Endpoints:

- mRS at 30 and 90 days
- Length of hospital stay
- Requirement for ventriculoperitoneal shunt (VPS) placement

Table of Contents

1. Introduction:

As discussed in detail in the companion INVEST submission, intracranial hemorrhage is a devastating disease associated with poor clinical outcomes. To date, no surgical or medical therapy (with the exception of blood pressure management) has been demonstrated to definitively improve outcomes in these patients. Of all the interventional therapeutic strategies tested, the most encouraging data exist for minimally invasive surgery[1]. The primary aim of minimally invasive surgery (MIS) for brain hemorrhage is to achieve an atraumatic evacuation of blood products from the brain to prevent the secondary injury that occurs after the initial bleed. To date, several pilot studies and a small Phase II feasibility trial have suggested that MIS with catheter mediated thrombolytic irrigation may be associated with an improvement in clinical outcomes in ICH. Similarly, pilot studies have indicated that catheter mediated lysis and drainage of hemorrhage from the ventricular system may be clinically beneficial[2]. While, initial data derived from these preliminary studies of thrombolytic-assisted catheter drainage have been encouraging, but there are significant potential shortcomings of this technique compared to the purely mechanical approach with the Apollo system or Artemis Device.

2. Purpose and Hypothesis

The Artemis Device or its predecessor the Apollo System have been commercially available in the US for the surgery in the ventricular system or cerebrum for over three years and early experience with the system in regards to its application to remove parenchymal and intraventricular hemorrhages has evolved[1, 3, 4]. As such, now that the technical approach has matured, it is necessary to proceed with a feasibility study to assess the potential clinical impact of the Artemis system in patients with supratentorial ICH. Currently no prospective study of any kind has evaluated the efficacy minimally invasive endoscopic surgery (MIES) with the Apollo or Artemis system for brain hemorrhages. The purpose of this prospective registry is to capture data from patients who do not qualify for INVEST feasibility study, but who undergo Apollo or Artemis treatment at participating US INVEST centers. We anticipate that these registry data will be useful to more fully understand the Apollo and/or Artemis procedure. Since this is a single-arm study of Apollo / Artemis MIES treatment, a formal hypothesis test is not planned.

Rationale for the INVEST Registry Design

The INVEST Feasibility study was specifically designed to provide an assessment of enrollment and follow up for this patient population after being treated with Apollo / Artemis MIES. There are other patients who will come to the INVEST centers who, in the experienced physicians' opinion, may benefit from the Apollo / Artemis MIES procedure, but are excluded from the feasibility study protocol for various reasons (e.g, large IVH with a small ICH, low admitting GCS score, large hemorrhage (>80cc), baseline mRS >1). In some cases, physicians at INVEST centers may decide to offer Apollo / Artemis MIES to these patients outside of the INVEST Feasibility study. The INVEST registry will allow experienced operators at these INVEST centers to enroll such patients into a prospective observational registry. This mechanism serves several important purposes. First, the INVEST REGISTRY data may be informative to a subsequent pivotal Phase III trial in conjunction with the concurrent INVEST feasibility study. Second, these data will provide a valuable surveillance of the application of MIES surgery and the Apollo system / Artemis Device in clinical practice at major academic institutions within the controlled, monitored setting provided by an observational registry. A core lab will assess technical outcomes in these patients independently. The study's Medical Monitor and Data Safety Monitoring Board (DSMB) will actively monitor clinical outcomes. Finally, the registry allows centers to enroll most all patients who are considered candidates for Apollo / Artemis MIES into a prospective study. It is our opinion that such a mechanism will facilitate the Feasibility enrollment at INVEST centers and will enhance the efficiency of the study. Avid enrollment in the INVEST studies increases protocol awareness, familiarity with mechanisms for screening and enrollment, familiarity with both protocols and protocol adherence.

The INVEST REGISTRY will allow the inclusion of patients with low presenting GCS (≤ 4). Patients with very low presenting GCS (3-4) represent a heterogeneous group. Many will have severe unrecoverable injuries potentially involving the brain stem. We did not want to potentially dilute our ability to detect a signal for a treatment effect by

including these patients in the Feasibility study. However, if operators feel that some patients in this group could potentially benefit from the Apollo / Artemis procedure and intend to treat the patients outside of the INVEST Feasibility, the INVEST REGISTRY will allow the prospective collection of data within the context of a controlled, monitored clinical study. These data may be informative to the subsequent Phase III pivotal trial in that they may indicate a potential for these patients to respond to treatment (i.e., if these registry patients have outcomes similar to GCS 5-8 patients in the feasibility study) or confirm that they do not respond.

The INVEST REGISTRY will include patients with isolated intraventricular hemorrhage (IVH) or IVH with a small ICH. The Apollo system and Artemis Device are cleared for the minimally invasive removal of tissue and fluid from the ventricular system. The INVEST Feasibility is specifically designed for the assessment of this technology to improve outcomes in ICH. The INVEST REGISTRY represents the first prospective study, which will monitor technical and clinical outcomes in patients with IVH.

2.1 Risk Analysis

The primary risks to subjects in this study are associated with the minimally invasive surgical procedure and the associated general anesthetic. Imaging performed throughout the course of the study, while specified in the protocol, falls well within the standard of care for the initial evaluation and follow-up of patients with intracranial hemorrhage. The Apollo / Artemis MIES procedure is performed in a manner, which is similar to that of other neuroendoscopic procedures, and the associated risks are likewise similar. In brief (see Section 5 for a detailed description of the procedure), the Apollo / Artemis MIES procedure itself involves the creation of a burr hole or mini- craniectomy and dural incision. An endoscopic sheath (19-22F) is then placed through this access site into the hematoma or ventricular system under imaging control using neuronavigation. Then, under endoscopic guidance, the hemorrhage is evacuated with the Apollo system / Artemis Device. Following the evacuation, the endoscope and Apollo system / Artemis Device are removed. Control operative CT imaging is performed to assess the remaining hemorrhage volume and to assess for immediate procedural complications. Based on the operative control CT imaging, either an additional pass(es) are made, or the procedure is terminated. Following the procedure, all equipment is removed and the cranial access is closed in a standard manner.

Risks related to the procedure include bleeding, infection or damage to surrounding structures during the creation of the cranial access or placement of the sheath. These risks are all unlikely and are estimated to occur in less than 5% of cases. During evacuation of hemorrhagic products with the Apollo system / Artemis Device, there is the possibility of inducing or encountering additional hemorrhage in the operative bed. In a retrospective multicenter study of the Apollo / Artemis procedure for the treatment of ICH, re-bleeding was encountered in 2 of 29 patients (6.9%). The risk related to the general anesthetic in this patient population is estimated to be approximately 1-5% for major morbidity and mortality (e.g. airway management issues, aspiration, hypotension or drug reaction), given that their ASA score would typically be 4 or 4e in this category of patients.

All information concerning subjects will be kept confidential. Subjects will be assigned study ID #. No personal identifying information will be used in presentation or publication of data from this study.

A list of all anticipated adverse events is listed in Appendix 1.

3. Objectives

3.1 *Primary Endpoint*

The primary objective of this multicenter prospective registry is to provide an additional safety, technical outcomes and clinical outcomes data for minimally invasive endoscopic surgery (MIES) with Artemis for the evacuation of brain hemorrhage in patients who do not qualify for the concurrent INVEST Feasibility study at active INVEST

centers:

- Clinical Efficacy Endpoint: 180-day global disability assessed via the modified Rankin score (mRS), categorized as either mRS ≤ 3 or mRS > 3
- Technical Efficacy Endpoint: Rate of surgical success
    - Predominantly or Only ICH: Reduction to < 15 cc total volume AND >60% reduction in hemorrhage volume on immediate post-treatment CT scan[4]
    - Predominantly or Only IVH: mGraeb score of ≤ 5 on day 7 CT scan[7]
- Safety Endpoint: Rate of mortality at 30 days

3.2 *Secondary Endpoints*

Secondary Endpoints:

- mRS at 30 and 90 days
- Length of hospital stay
- Requirement for VPS

4. Trial design

This is a prospective, multicenter, single-arm, registry of Apollo / Artemis MIES in patients with brain hemorrhage who do not qualify for the concurrent INVEST multi-center Feasibility study. Patients will be enrolled who meet the inclusion and exclusion criteria. Data on each patient will be collected at the time of enrollment and treatment, and at subsequent follow-up visits.

4.1 *Inclusion criteria*

1. Age 22 years or older
2. Brain hemorrhage which may be:
    a. Intracerebral (ICH).
    b. Primarily Intracerebral (ICH) with a component of intraventricular hemorrhage (IVH).
    c. Primarily intraventricular hemorrhage (IVH) with a component of ICH.
    d. Intraventricular hemorrhage (IVH).
3. Patient does not qualify for the concurrent INVEST feasibility study

4.2 *Exclusion criteria*

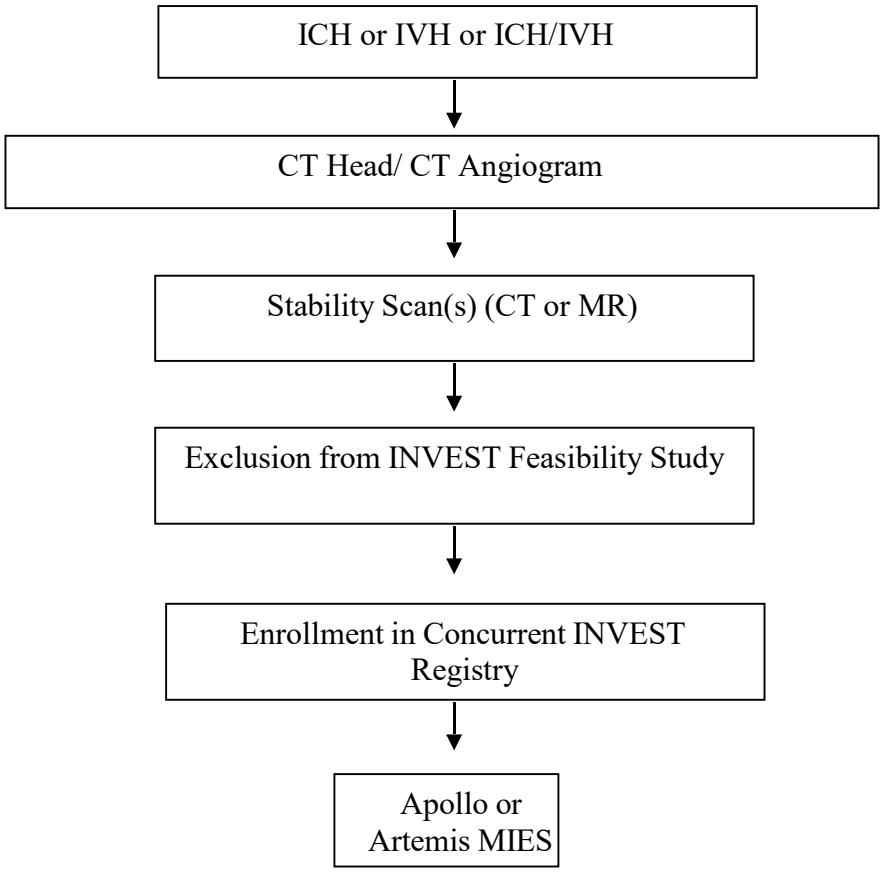
1. Imaging
    a. Expanding hemorrhage on stability CT/MR scan
    b. "Spot sign" identified on CTA
        i. May perform a second CTA at 12 hours to demonstrate resolution
    c. Hemorrhagic lesion with cannot be completely secured prior to the Apollo / Artemis MIES, such as a vascular malformation (cavernous malformation, AVM etc), untreated or incompletely treated aneurysm, neoplasm
    d. Hemorrhagic conversion of an underlying ischemic stroke
    e. Infratentorial hemorrhage
    f. Midbrain extension/involvement

2 Coagulation Issues
    a. Absolute and imminent (within 7 days of treatment) requirement for long-term, full-dose, anti-coagulation (e.g., Mechanical valve replacement (bio-prostatic valve is permitted), high risk atrial

fibrillation)
b. Known, uncorrectable hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency
c. Uncorrectable platelet count < 100 x 103 cells/mm3 or known platelet dysfunction
d. INR > 1.5, elevated prothrombin time or activated partial thromboplastin time (aPTT), which cannot be corrected or otherwise accounted for (i.e., lupus anti-coagulant)

3 Patient Factors
a. High risk condition for ischemic stroke (high risk Afib (e.g., mitral stenosis with Afib), symptomatic carotid stenosis);
b. Requirement for emergent surgical decompression or uncontrolled ICP after EVD
c. Unable to obtain consent from patient or appropriate surrogate (for patients without competence);
d. Pregnancy, breast-feeding, or positive pregnancy test (either serum or urine). Woman of child-bearing potential must have a negative pregnancy test prior to the study procedure;
e. Evidence of active infection indicated by fever at or over 100.7 °F, and/or open draining wound at the time of randomization;
f. Any comorbid disease or condition expected to compromise survival or ability to complete follow- up assessments through 180 days;
g. Based on investigator's judgment, patient does not have the necessary mental capacity to participate or is unwilling or unable to comply with protocol follow up appointment schedule;
h. Active drug or alcohol use or dependence that, in the opinion of the site investigator would interfere with adherence to study requirements;
i. Currently participating in another interventional (drug, device, etc) research project.

4.3 ***Overview of Study Flow***



All sites will keep a screen failure log of all brain hemorrhage patients presenting within 24 hours of symptom onset but who are not enrolled into either the INVEST Feasibility or the INVEST Registry. Reason(s) for exclusion will be recorded. Logs from the clinical sites will be reviewed on a monthly basis. Recruitment rates will be tracked over time for each hospital. The actual recruitment rates as well as potential recruitment rates will be useful for planning further clinical trials and determining the widespread utilization of the therapy.

4.4 *Study Visits*

Subjects enrolled to this study will follow the below visits schedule according to standard of care for stroke patient follow-up.

- Pre-Treatment
- Procedure
- Post procedure (24 hours, Apollo / Artemis MIES patients)
- 7 days post-enrollment or Discharge (whichever comes first)
- 1 month follow-up (+/- 14 days)
- 3 month follow-up (+/- 21 days)
- 6 month follow-up (+/- 28 days)

4.5 *Recruitment*

The target population for the INVEST registry are adult patients who have a diagnosis of supratentorial intracranial hemorrhage who do not require emergent open surgical decompression related to uncontrolled intracranial pressure or mass effect, who do not qualify for the INVEST multi-center Feasibility and who are to be treated with Apollo or Artemis MIES at an INVEST center.

Potential study participants and/or their legal authorized representative will be identified by the study team at each site to obtain consent and determine eligibility. Up to 30 United States sites will be included in this study and enroll up to 50 patients.

4.6 *Screening and Baseline Evaluation*

Consent is obtained, medical history screened, and available clinical/neurological exams obtained, and lab work and imaging information per institutional standard of care is evaluated to determine patient eligibility. The baseline neurologic examination will be performed by a health care provider or study team member, certified to administer the exams and able to give an unbiased neurological and functional assessments (NIHSS, Glasgow Coma Score (GCS), and mRS). CT imaging must be performed to provide an initial diagnosis of ICH. Hemorrhage volume will be determined using the A x B x C/2 method for ICH and a modified Graeb score (Appendix 2) for IVH. Subsequent stability imaging (CT (preferred) or MR) must be obtained at least 6 hours after the presenting scan to confirm stability in the hemorrhage volume. A CTA (preferred) or MRA must also be performed, as standard of care; either at presentation with the diagnostic CT or with the stability scan to exclude a vascular lesion or "spot sign". Enrollment will occur in consented patients with a stable hemorrhage volume on follow up CT or MR (< 5 cc increase in volume). In the case that the stability scan demonstrates hemorrhage volume increase (> 5 cc) or an increase in intraventricular hemorrhage (mGraeb score increase of $\geq$3), a second stability scan can be obtained q12 hours until stability is demonstrated. In the case of a "spot sign", follow up CTA (preferred) or MRA can be obtained q12 hours to show resolution of the "spot sign" prior to enrollment. A pregnancy test will be conducted for applicable subjects (<50 years old and of child bearing potential). Once the patient meets all eligibility criteria, and the patient or LAR has provided written informed consent, and a burr hole has been performed to initiate the Apollo / Artemis procedure, the patient will be considered enrolled into the study. Operators should attempt to perform

Apollo / Artemis MIES within 72 hours of the ictus.

4.7 *Informed Consent*

A member of the research team will explain the study's objectives to potential candidate patients, including describing standard treatment with the study device, the requirements of the clinical investigation, and risks and benefits of participating. All informed consent documents used under this study protocol will be consistent with applicable elements of ISO14155, Good Clinical Practice Guidelines and 21 CFR Part 50, and will be approved by the site's reviewing IRB/EC prior to study initiation. The study informed consent is included in Appendix 3.

5. Study Screening and Treatment Procedure

The treatment procedure is described briefly below.

5.1 *Imaging Assessment for Eligibility for Trial Participation*

The subject should be clinically evaluated in the same manner as any patient with non-traumatic spontaneous intra-parenchymal hemorrhage. Clinical assessment documenting NIHSS, GCS, baseline mRS and significant past medical history should be obtained. Imaging with CT and CTA (MRA is acceptable in CTA ineligible patients) is required to confirm the diagnosis of ICH and exclude a vascular etiology. Cerebral hemorrhage volume will be measured using an A x B x C/2 algorithm. IVH will be quantified using a mGraeb score. Additional anatomic, vascular and physiologic imaging with MRI, MRA or conventional angiography per the institutional standard of care should then be performed on patients as part of a standard evaluation for non-spontaneous hemorrhage etiology. In patients with a CTA "spot sign" on presentation imaging, a follow up CTA must be performed at 12 hours to verify resolution of this finding prior to enrollment. Increase in cerebral hematoma size of $\leq$5 cc will be considered "stable" on the stability scan. In the case that the stability scan demonstrates hemorrhage volume increase > 5 cc, a second stability scan can be obtained q12 hours until either stability is demonstrated or the patient is outside of the window for treatment (72 hours from the time of ictus). Ventricular hemorrhage will be considered stable if the mGraeb score increases by $\leq$3 points on the stability scan. Similarly, if the mGraeb score increases more than 3, a follow up scan can be performed in 12 hours to establish stability. Patients meeting all inclusion and no exclusion criteria will be eligible for enrollment after an acceptable stability scan.

5.2 Preparation for Treatment

Patients will receive best MM for intracerebral and/or intraventricular hemorrhage as determined by the attending physician as specified in the companion INVEST Feasibility study. All attending physicians will follow current AHA guidelines for the treatment of ICH[5]. Reversible coagulopathies at presentation will be corrected as determined by the attending physician managing the patient. Ventricular drains will be placed as deemed necessary by the clinical care team to manage ICPs. Apollo / Artemis MIES will be performed under general anesthesia. The subject should be prepared for the planned intervention according to standard hospital procedures. Apollo / Artemis MIES will be performed as described below (5.5)

5.3 Medication during Intervention

Medications may be administered during the procedure as determined by the attending anesthesiologist and/or interventionist in accord with established standard procedural management.

5.4 Devices and Equipment

In addition to the Apollo System and Artemis Device, other devices required for the procedure are listed in Table 5.

Table 5: Devices that are used during the Apollo / Artemis MIES procedure

Standard Cranial Access Devices and Endoscopy Sheath	All FDA cleared cranial access systems and suitably sized endoscopy sheaths (19-22F) will be allowed in the study
Neuronavigation System	All FDA cleared neuronavigation systems will be allowed in the study
Neuroendoscopy System	All FDA cleared neuroendoscopy systems (e.g. Storz Lotta) which incorporate a working channel that will accommodate either the 1.5, 2.1, or 2.8 mm Artemis Device will be allowed in the study
Penumbra Aspiration Systems	The Aspiration Pump and canister for all FDA cleared or CE marked (as applicable) Penumbra Aspiration Systems will be allowed in the study
Intra-Operative or Extra-Operative CT Monitoring	All FDA cleared computed tomography or cone beam computed tomography systems will be allowed in the study.

The specific types of devices used in each Apollo / Artemis MIES procedure will be recorded in the patient CRF.

5.5 Procedural Protocol

Appropriately protocoled (depending on the institution and neuronavigation units) MR or CT imaging studies will be uploaded into the neuronavigation software (e.g., iPlan Net, Brainlab, Feldkerchin Germany) for procedural planning and guidance. A trajectory will be selected by the operator that is both technically feasible and allows access to the longest possible axis of the cerebral hematoma (for ICH) or optimal position within the ventricular system (for IVH).

Patients will be placed supine upon the procedural table, and a sterile field prepared. An external localization array or other neuronavigation localization mechanism (e.g. Skull Reference Base with Skull Reference Array with Reflective Marker Spheres, Brianlab) will be placed for registration. Following registration, a second sterile field will be prepared over the region of the cranial access. A burr hole or minicraniotomy will then be created in a standard manner of a size large enough to accommodate the selected endoscopy sheath. A localization array (e.g., Instrument Adapter Clamp with Instrument Adapter Array, Brainlab) will be attached to the selected neuroendoscopic sheath (e.g., Aesculap Inc, Center Valley, PA) and registered to the navigation system. The sheath will then be advanced using neuronavigation into the targeted landing zone within the distal aspect of the hematoma and the inner obturator removed. The sheath will then be stabilized (e.g., manually stabilized, mechanically stabilized, or peeled away and stapled down) into position. The

neuroendoscope (e.g., Lotta, Karl Storz, Tuttlington, Germany) will then be inserted into the sheath and under direct visualization the Apollo Wand or Artemis Device will be placed through the working channel of the trocar. The sheath will be irrigated at the discretion of the operator using the irrigation port of the endoscope and the irrigant will be intermittently aspirated with the Apollo system or Artemis Device until a clear working view is created within the sheath that allows visualization of the surgical field at the sheath tip. When organized hematoma is visualized at the tip of the sheath, the Apollo Wand or Artemis Device will be advanced under direct visualization to, or just beyond the tip of the sheath and actuated to evacuate the blood products. If the working view becomes obscured by blood products within the sheath, additional irrigation and aspiration will be performed intermittently to clear the field. When all blood products are cleared from the working field, the sheath will be retracted serially and the procedure repeated. The position of the sheath will be continually monitored directly using the neuronavigation system. After the evacuation is completed, the neuroendoscopic trocar and Apollo Wand or Artemis Device will be removed. An intraoperative CT (e.g. dynaCT, Siemens, Medical Imaging, Erlangen, Germany) will then be performed using cone-beam CT, an intraoperative or portable conventional CT unit, or the OR room will be held open for re-operations and the patient may be scanned on a conventional departmental CT unit with the option to immediately return to the OR room if necessary. The control CT will function to confirm adequate hematoma evacuation and to assess for any complications (e.g., re-bleeding, hydrocephalus, increased mass effect).
Additional evacuation will be performed as specified above at the discretion of the operator, based upon the data from the CT. After the hemorrhage evacuation is completed, the sheath will be removed and the cranial access site will be closed in a standard manner.

5.6 Post-Procedure Care

All patients will receive best MM for ICH as determined by the attending physicians of the clinical team:

- General medical management according to AHA guidelines[5]
- Admission to monitored or intensive care unit for at least 24 hours
- Close monitoring of BP and glucose with treatment according to AHA guidelines[5]
- Follow-up imaging study required in any patient with neurologic deterioration

An immediate post-procedural CT scan will be obtained in all patients after Apollo / Artemis MIES. Neurological and functional exams will be conducted within 24 hours (+/- 12 hours) of the procedure. A CT (preferred) or MR scan will also be obtained 7 days after randomization in both groups. Additional imaging will be obtained at the discretion of the managing service based upon clinical data and established institutional standard of care.

5.6 Recovery

The subject will be recovered from the procedure and discharged from the hospital as per standard practices.

5.6.1 Discharge

At discharge, the following will be completed by a qualified member of the research or clinical care team: a focused physical exam, a neurological exam (including GCS, NIHSS and mRS) and a review of any adverse events. If discharge occurs before 7 days after randomization, the discharge clinical examinations will substitute for the 7-day clinical evaluation and a standard of care CT (preferred) or MR will be obtained at that time.

5.7 Hospital Costs

For each subject, overall costs will be collected for the initial hospitalization during which study enrollment took place. These costs will include device costs (the market price for each device), materials used to treat the hemorrhage, and number of days spent in the hospital (ICU and non-ICU length of stay). In summary, the total amount billed and the total amount reimbursed will be assessed.

5.8 Follow-Up Examination

5.8.1 Clinical

Several clinical outcome measures were selected for this study. These were chosen on the basis of their reliability, familiarity to the neurologic community, adaptability for use in patients who have had a stroke, and comparability to end points used in other trials of intracranial hemorrhage. All scores will be recorded in source documentation and entered into the electronic case report forms.

1. modified Rankin Scale (mRS, Appendix 4): mRS is an overall assessment of global handicap. In the original Rankin Scale, a score of zero indicates the absence of symptoms and a score of 5, severe disability. The modified Rankin Scale adds a score of 6 for fatal outcomes. A historical mRS will be obtained to assess the patient's level of function prior to the ICH. The score will be repeated as specified in Table 1.
2. The National Institutes of Health Stroke Scale (NIHSS, Appendix 5) is a 42-point scale that quantifies neurologic deficits in 11 categories. Normal function without neurologic deficit is given a score of zero. NIHSS should be done by a certified examiner as close to the specified times as possible.
3. EQ-5D-5L (Appendix 6) is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, the questionnaire provides a simple descriptive profile and a single index value for health status.

All day 7, discharge, day 30, day 90 and day 180 clinical outcome measures will be assessed by a qualified member of the research or clinical team either in person at a clinic visit, by phone or by mailed questionnaire. The schedule of neurological assessments is listed in Table 1. At each visit, the patient's medical record will be surveyed for any new or interim neurological adverse or serious adverse events. In addition, the patient or LAR will be asked about any interim neurological adverse or serious adverse events. The subject or LAR will also be specifically asked about any interim neurosurgical procedures.

5.8.2 Cross-Sectional Imaging

All scheduled CT and MR studies will be assessed by a central core lab neuroradiologist. The volume of hemorrhage will be calculated using a standard A x B x C/2 calculation. On the CT slice with the largest area of ICH, the largest diameter (A) is measured in cm. The dimension of the hemorrhage perpendicular

to the largest diameter (B), represents the second diameter. The third diameter (C) will be calculated either by multiplying the number of CT slices which depict the hematoma by the slide thickness or determined on coronal or sagittal reconstructions. The volume of hemorrhage plus peri-hematomal edema (PHE) will also be similarly calculated. Hemorrhage and hemorrhage + PHE volume as a percentage of presenting volumes will be calculated. Mass effect will be graded with each subsequent scan compared to the presentation scan (decreased, increased, no change). Intraventricular hemorrhage will be assessed on each scan and graded according to a modified Graeb score (Appendix 2). A detailed description of the imaging assessments are specified in the Imaging Interpretation Guidelines.

Scheduled imaging studies include the diagnostic/admission scan, the stability scan(s) (at least 6 hours after the diagnostic scan), CT or MR angiogram (with either the diagnostic or stability scan), Post-operative (Apollo / Artemis MIES), and the 7 day post presentation CT scan.

Table 1. Schedule of Events

ACTIVITY	**SCREENING /BASELINE**	**STABTILITY SCAN (at least 6 hours post initial CT)**	**TREATMENT**	**Post MIES (+/-12 hours)**	**DISCHARGE AND /OR 7 DAYS**	**1 MONTH (+/-14 days)**	**3 MONTHS (+/- 21 days)**	**6 MONTHS or END of study (+/- 28 days)**
Informed Consent	X							
Inclusion/ Exclusion Criteria	X							
Medical History	X							
Focused Exam	X	X		X	X	X	X	X
Standard of Care Labs	X	X		X	X			
Standard of Care CT/MR	X	X	X (immediately post treatment)	X	X			
CTA or MRA	X (or at stability)	X (if not done with Baseline)						
NIHSS	X	X		X	X	X	X	X
GCS	X	X		X	X	X	X	X
mRS	Historic				X	X	X	X
EQ---5D---5L								X
Pregnancy Test if childbearing potential	X	Or X						
Usual Medical Management per AHA Guidelines	X	X	X	X	X	X	X	X
Apollo /Artemis MIES under general anesthesia within 24 hours of sx onset			X					
Adverse Events			X	X	X	X	X	X
All brain imaging sent to central core lab	within 48 hours of test	within 48 hours of test		within 48 hours of test	within 48 hours of test			

5.8.3 Serious Adverse Events

All serious adverse events occurring during the 180-days of study participation will be recorded. Adverse events and serious adverse events are critical endpoints and will be assessed as they occur and at the scheduled clinic visits. A serious adverse event is one that is fatal or life-threatening, is permanently or substantially disabling, requires or prolongs hospitalization, or any event that the treating clinician judges to be a significant hazard, contraindication, side effect, or precaution. For each recorded serious adverse event, the patient's attending physician will be asked to classify the causal relationship of the event to the study treatment as probable, possible, unlikely, and unrelated. Detailed form and narrative reports of the following specific adverse events will be obtained:

- Death (all cause) within 30 days of enrollment
- Death within 7 days of enrollment: Immediate peri-procedural death
- Symptomatic Re-Hemorrhage or New Hemorrhagic Event: any new intracranial hemorrhage or increase in size of pre-existing hemorrhage (IPH, IVH or extra-axial bleed) within 30 days associated with an increase of 4 or more points on the NIHSS or GCS increase ≥ 2 persisting for at least 24 hours and/or requiring emergency surgical decompression or resulting in death[5, 6].
- Symptomatic Evolution of Peri-hematomal Edema: Edema with increased mass effect or uncontrolled ICPs within 30 days requiring emergency surgical decompression NOT related to new or increased hemorrhage (i.e. edema related) associated with an increase of 4 or more points on the NIHSS or GCS increase ≥ 2 persisting for at least 24 hours, requiring emergency surgical decompression or resulting in death.
- Symptomatic Ischemic Stroke: A new ischemic stroke (ipsilateral, contralateral; contiguous with bleed/operative site or remote; cortical, subcortical or perforator distribution) within 30 days associated with an increase of 4 or more points on the NIHSS or GCS increase ≥ 2 persisting for at least 24 hours, requiring emergency surgical decompression or resulting in death.
- Surgical complications related to Apollo /Artemis MIES: Surgical site infection, brain abscess or confirmed meningitis, or documented complication(s) deemed specifically related to the procedural anesthetic (medication, access or intubation related) within 30 days.

A medical monitor will review these specific categories of events. The DSMB will also function as the CEC and will review all events at regularly scheduled DSMB meetings, which will occur at approximately 6-month intervals during the study. The medical monitor has the authority to alert the DSMB at any time if a potential safety issue arises. If at any point, these reviews raise any safety concerns, the DSMB will be empowered to suggest that the trial be placed on hold and request additional analyses of the trial dataset. The DSMB will issue reports for each meeting. The DSMB will be composed of three cerebrovascular specialists and a statistician. Safety stopping rules for the primary safety endpoint will be developed and used to help the DSMB make its safety assessments. These stopping rules will be explicitly stated within the DSMB charter.

6. Study Primary Endpoints

Primary Endpoint:

The primary objective of this multicenter prospective registry is to provide an additional safety, technical and clinical outcomes data for minimally invasive endoscopic surgery (MIES) with Apollo /Artemis for the evacuation of brain hemorrhage in patients who do not qualify for the concurrent INVEST Feasibility study at active INVEST centers:

- Clinical Efficacy Endpoint: 180-day global disability assessed via the modified Rankin score (mRS), categorized as either mRS $\leq$ 3 or mRS > 3
- Technical Efficacy Endpoint: Rate of surgical success
    - Predominantly or Only ICH: Reduction to < 15 cc total volume AND >60% reduction in hemorrhage volume on immediate post-treatment CT scan. [4]
    - Predominantly or Only IVH: mGraeb score of $\leq$ 5 on day 7 CT scan[7]
- Safety Endpoint: Rate of mortality at 30 days

6.1 Analysis of Primary Endpoints

All primary and secondary endpoints efficacy and safety endpoints will be evaluated in the intent to treat and per protocol samples. Additionally, the primary safety and specified adverse events will be evaluated in the as treated sample.

6.1.1 Definition of Analysis Samples

1. Target Population

   The target population for the INVEST registry are adult patients who have a diagnosis of supratentorial intracranial hemorrhage who do not require emergent open surgical decompression related to uncontrolled intracranial pressure or mass effect, who do not qualify for the INVEST multi-center Feasibility study and who are to be treated with Apollo / Artemis MIES at an INVEST center.

2. Intent to Treat Sample

   As the primary analysis, all efficacy and safety outcome measures will be analyzed under the intent-to-treat (ITT) principle. Under this principle, the evaluable sample includes all subjects who are enrolled.

3. Per Protocol Sample

   In addition to the defined ITT analysis sample, a per-protocol sample is defined as a subset of the ITT sample. This sample will be used for secondary sensitivity analyses of the primary and secondary outcomes.

   The per-protocol sample will include all subjects that do not have the following protocol violations or deviations:
   a. Eligibility violation
   b. Treatment failure (no Apollo / Artemis MIES performed)
   c. Missing 180-day primary efficacy outcome (not including missing due to death prior to the 180 days)

4. As Treated Sample

   This sample will be used for analyses of the safety outcomes. The as treated sample will include all subjects that are enrolled and have Apollo / Artemis MIES performed.

7. General Statistical Considerations

General Design Issues

The primary objective of this multicenter prospective registry is to provide additional safety, technical outcomes and

clinical outcomes data for minimally invasive endoscopic surgery (MIES) with Apollo / Artemis for the evacuation of brain hemorrhage in patients who do not qualify for the concurrent INVEST feasibility study at active INVEST centers. This structure will allow INVEST centers to consider all patients presenting with intracranial hemorrhage who are potentially candidates for the Apollo / Artemis MIES procedure for a clinical research trial, which will facilitate enrollment as well as protocol familiarity and adherence. This structure will also yield the highest possible amount of data about this new procedure.

General Statistical Methods

As a single arm registry, all statistics reported for the entire cohort as well as subgroups will be purely descriptive. All confidence intervals presented will be two-sided. Statistical tests between subgroups will be two-tailed with a significance level of 0.05. Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables, effectiveness variables, and safety variables, as appropriate. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, range, and median). Frequency counts and percentage of subjects within each category will be provided for categorical data. The specific details of the statistical analyses will be described completely in the statistical analysis plan. The statistical analysis plan will be finalized prior to database lock.

Results collected at multiple visits will be summarized at each visit for which they are collected as described in **Table 1 Schedule of Events**. Summaries for all measures will include all observed data for each visit.

7.1 Sample Size Justification

Sample Size Calculation

The proposed study is a single-arm registry which will run concurrently with the INVEST feasibility study. A sample size of 200 provides 180 subjects at 180 days, with an estimated 10% attrition rate. Since this is a single- arm study of Apollo / Artemis MIES treatment, a formal hypothesis test is not planned. Assuming an effectiveness primary endpoint response rate for mRS 0 to 3 of 34% (61/180), the expected normal approximation to the binomial two-sided 95% confidence interval around the primary endpoint rate is (27%, 41%). Hence, the proposed sample size provides a precision estimate of ± 7% which is sufficient to assess the Apollo / Artemis MIES treatment. The precision for the estimated single proportion was calculated using SAS v 9.4 (SAS Institute, Cary, NC).

7.2 Statistical Evaluation of Primary Endpoint

Statistical Analysis of Primary Clinical Efficacy Outcome

The primary clinical efficacy endpoint will be calculated as the proportion of subjects with a 180 day mRS of 0 to 3. Subjects who die prior to the 180 day mRS assessment will be included in the analysis with an mRS score of 6. The proportion of patients with favorable clinical outcomes based on this criterian will be calculated, and a 95% confidence interval will be presented. The number and percentage of subjects in each mRS category (0 to 6) will also be presented.

Statistical Analysis of Primary Technical Efficacy Outcome

The proportion of subjects experiencing surgical success based on the following criteria will be calculated, and a 95% confidence interval will be presented.

- Predominantly or Only ICH: Reduction to < 15 cc total volume AND >60% reduction in hemorrhage volume on immediate post-treatment CT scan
- Predominantly or Only IVH: mGraeb score of < 5 on day 7 CT scan

7.3 Missing Data and Imputation Methods

Under the ITT principle, all patients who are enrolled are included in the analysis. Therefore, missing data, especially in the outcome measures, can be problematic. Every effort is to be made to keep all missing data, particularly the Day 180 outcomes, to a minimum. Despite the clinical sites' best efforts, some missing data may be inevitable mainly due to lost-to-follow-up (LTFU). The number and proportion of subjects eligible for and compliant with each follow-up examination will be presented. Subjects who withdraw from the study will be tabulated with reasons for withdrawal. Since the primary endpoint is defined using mRS, subjects deceased during study follow-up will be scored as mRS 6. Other subjects not completing the 180-day follow-up visit will be categorized for the primary endpoint using the mRS as of the last available follow-up visit or discharge (whichever is later). As a sensitivity analysis, we will also perform analysis after excluding subjects without 180-day follow-up evaluations. Additional details will be provided in the Statistical Analysis Plan (SAP).

7.4 Secondary Statistical Analysis

7.4.1 Secondary Endpoints

The secondary effectiveness variables:

- mRS at 30 and 90 days - The number and percentage of subjects who experience mRS 0 to 3 will be calculated along with the 95% confidence interval. Frequency counts and percentage of subjects within each category will be provided.
- Length of hospital stay - The median total length of stay and median ICU length of stay along with the inter-quartile range will be provided.
- Requirement for VPS - The number and percentage of subjects who have VPS placement will be calculated along with the 95% confidence interval.

7.5 Safety Analysis

7.5.1 Safety Outcomes

Several specific adverse events are monitored throughout the study. However the primary safety outcome to be assessed at completion of the trial will be death within 30 days.

The proportion of deaths for any reason through 30 days will be calculated and a 95% confidence interval will be presented. Survival estimates will be generated to evaluate the time-to-death using the Kaplan-Meier methodology for all deaths through 30 days.

All adverse events will be summarized by showing the number and percent of patients which report the event. Events will also be reported by relationship to the procedure or device.

7.5.2 Interim Safety Monitoring

7.5.2.1 Stopping the Trial Based on Interim Safety Data

The EOC and DSMB will receive periodic safety reports of all AEs and SAEs. In addition, the following specific endpoints will be assessed by the medical monitor and presented:

- Death (all cause) within 30 days of enrollment
- Death within 7 days of enrollment: Immediate peri-procedural death
- Symptomatic Re-Hemorrhage or New Hemorrhagic Event: any new intracranial hemorrhage or increase in size of pre-existing hemorrhage (IPH, IVH or extra-axial bleed) within 30 days associated with an increase of 4 or more points on the NIHSS or GCS increase ≥ 2 persisting for at least 24 hours, and/or requiring emergency surgical decompression or resulting in death.
- Symptomatic Evolution of Peri-hematomal Edema: Edema with increased mass effect or uncontrolled ICPs within 30 days requiring emergency surgical decompression NOT related to new or increased hemorrhage (i.e. edema related) associated with an increase of 4 or more pointon the NIHSS or GCS increase ≥ 2 persisting for at least 24 hours and/or requiring emergency surgical decompression or resulting in death.
- Symptomatic Ischemic Stroke: A new ischemic stroke (ipsilateral, contralateral; contiguous with bleed/operative site or remote; cortical, subcortical or perforator distribution) within 30 days associated with an increase of 4 or more points on the NIHSS or GCS increase ≥ 2 persisting for at least 24 hours and/or requiring emergency surgical decompression or resulting in death.
- Surgical complications related to Apollo / Artemis MIES: Surgical site infection, brain abscess or confirmed meningitis, or documented complication(s) deemed specifically related to the procedural anesthetic (medication, access or intubation related) within 30 days.

Additional details of the monitoring plan will be included in the study SOP and DSMB charter.

7.6 Blinding

This single-arm treatment registry is not blinded. Blinding the study is not required for interpretation of outcomes.

8. Study Withdrawal

Subjects may be terminated or withdrawn from the study for the following reasons:

- Voluntary withdrawal of consent— meaning that a subject voluntarily chooses not to participate further in the study. All data collected up to the withdrawal of consent will be maintained in the study database.
- Lost to follow-up — defined as a subject who is more than one month late to a study visit and for whom 5 documented telephone attempts to contact the subject and at least one certified letter were unsuccessful.
- Subjects may also be withdrawn at the investigator's discretion if within their best interest.

8.1 Unattended Visits

Any study subject who does not attend a scheduled follow-up visit should be contacted by site personnel to determine the reason for the missed appointment(s). If the missed visit was due to a serious adverse event, (e.g., re-hospitalization) an AE Case Report Form (CRF) must be completed and any reporting requirements met.

9. Data Safety Monitoring Board (DSMB)

A DSMB will be comprised of 4 members not participating in the trial and will include neurovascular specialist physicians and a statistician. The DSMB will exercise review of the overall safety of the trial, periodically review all adverse events occurring in the trial, and make recommendations to adjustments in the study protocol, should any be considered necessary for safety or other related reasons.

10. Trial Operating Committee

The TOC will consist of the study PIs, statistical PI, project managers, data managers, and others deemed necessary in overseeing the day-to-day operations of the trial. The TOC will review study progress, study conduct at individual clinical sites, other clinical site performance measures, and blinded DSMB reports.

11. Steering Committee (SC)

The steering Committee will be comprised of the trial PI's and selected principal investigators from participating centers. The SC will be responsible for overall supervision and execution of the trial including adherence to protocol, progress of enrollment, patient safety and consideration of new information. Daily trial management is the responsibility of the TOC. It will provide key input to the SC for study planning, execution and data presentation.

12. Study Management

As the study Principal Investigators, J Mocco MD, David Fiorella MD PhD, and Adam Arthur MD, have overall responsibility for the conduct of the study according to 21 CFR 812, 21 CFR Part 50, Good Clinical Practice (GCP) Guidelines (Guidance for Industry, E6 Good Clinical Practice Consolidated Guidance, ICH, April 1996), ISO 14155: Part 1 and 2, the Declaration of Helsinki, Medical Device Directive, Annex X, FDA and all applicable regulatory requirements. For this study, the PIs will have certain direct responsibilities and will delegate other duties to appropriately qualified individuals. All personnel participating in the conduct of this clinical trial will be qualified by training, education, and experience to perform his or her respective tasks.

*NOTE: A complete list of participating investigators will be maintained and will be available upon request.

13. Investigator Responsibilities

The Investigator(s) shall be responsible for the day-to-day conduct of the investigation as well as for ensuring that the investigation is conducted according to all signed agreements, applicable elements of ISO 14155, the Clinical Investigational Plan, applicable FDA regulations, and the principles that have their origin in the Declaration of Helsinki.

The investigator is also responsible for having control of the device under investigation, for protecting the rights, safety and welfare of subject's under the investigator's care and for obtaining informed consent in accordance with 21 CFR Part 50. Each Investigator must sign the Investigator Agreement (or an equivalent and a Financial Disclosure) prior to becoming eligible to enroll subjects in this trial.

Responsibilities of the Investigator include, but are not limited to:
Ensuring that IRB approval is obtained prior to undertaking the trial at a clinical site; and, that participation of a subject in a clinical trial includes obtaining written informed consent prior to randomization, and/or other non-standard of care study-related assessments;

Providing the study TOC with accurate and complete financial information per 21 CFR Part 54; Ensuring that all personnel assisting with the clinical trial are adequately informed and understand their trial-related duties and functions;

It is recommended that each site identify a study coordinator for this study. Working with and under the authority of the clinical site Principal Investigator, the study coordinator assures that all study requirements are fulfilled, and is the contact person at the site for all aspects of study administration.

The Investigator will allow direct access to source data/documents for trial related monitoring, audit, IRB/EC review and regulatory inspection. Also, the investigator will allow auditing of their clinical investigational procedure(s).

14. Required Documents from the Investigator

1) At a minimum, the investigational site will provide the following documents to the TOC:
2) Signed Investigator Agreement,
3) Investigators Agreement
4) Written and dated IRB/EC approval,
5) Written and dated IRB/EC approval for ICF document,
6) IRB/EC approval for any other written documents to be provided to the study subject (e.g., advertising),
7) HIPAA documentation,
8) *Investigator and Co-Investigators' current Curriculum Vitae,
9) Current medical licenses,
10) Any other relevant documents requested by the TOC or the reviewing IRB/EC or other regulatory authorities,
11) FDA Form 3454 or 3455 (or equivalent) regarding financial interests
12) Fully executed contract.
13) Ongoing IRB approval documents
14) Source Documents for data verification
15) Site Delegation of Authority Log

A site may not begin study participation until all of the above listed documents have been provided to the study management team.

* With regard to the Sub-Investigators current CVs, the study may begin once the CV of the site PI, IRB approval and IRB approved consent and privacy statement, the investigator's agreement, Medical License, and financial disclosures, fully-executed contract, and others listed above, have been received. No additional Investigators may participate in the study, however, until a copy of their CV and all other required documents have been provided to the TOC.

15. Investigator Records

The Investigator must ensure that all study subject records are stored for at least 6 years after the end of the clinical study. To avoid error, the study site should contact J Mocco MD prior to the destruction of study records to ensure

that they no longer need to be retained. In addition, J Mocco MD should be contacted if the Investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study records.

The Investigator will also maintain original source documents from which study-related data are derived, which include, but are not limited to:

Clinic progress notes recording subject's medical history and medications;

Medical charts with operative reports and condition of subject upon discharge;

Medical records regarding AEs/SAEs, including treatment and clinical outcome;

Results of diagnostic examinations, imaging (such as x-rays, MRIs), as well as the report of the radiologist's reading/interpretation of diagnostic imaging;

Signed notes of phone calls and/or correspondence indicating investigational site's attempts to follow study subjects at the required follow-up visits until subject's participation in the study is complete or terminated;

Records relating to patient death (e.g., death certificate, autopsy report, if available, or terminal medical records).

15.1 Data Collection

15.1.1 Data Management Overview

Data management will be handled by the MSMC Stroke Clinical Research Group, which is housed in the Department of Neurological Surgery at the Mt. Sinai Medical Center (MSMC). All activities will be conducted in coordination with the study PI, the sites, and the TOC. The data validation procedure will be implemented in two stages. First, the automated data checks will flag items that fail a rule, and the rule violation message will appear on the data entry screen at the time of data entry. The Study Coordinator at a site will see these rule violations and will be required to provide a response. His/her choices are to: (1) correct the entry immediately; (2) correct the entry at a later time; or (3) if the entered data are confirmed to be correct, dismiss the rule by checking that option provided by the REDCap system. Any changes made to the data will have a full audit trail. Second, for some checks that are more complicated, additional consistency checks will be run periodically after data entry occurs at the site. All data items that fail the programmed consistency checks will be queried via the data clarification request (DCR) process initiated by the MSMC data managers. Site Monitors will also be able to generate DCRs when discrepancies are found during source document verification. The DCRs will be generated, communicated to the sites, and resolved on the secure study website.

In addition to the study database, MSMC will provide the site staff password protected access to a standard set of web-enabled tools, including subject visit calendar, subject accrual status, case report form completion status, and outstanding DCR status pertaining to their respective sites.

15.1.2 Data Acquisition and Central Study Database

The entire study will be conducted using an electronic data acquisition method where all clinical data on enrolled subjects will be data entered (single-keyed) by the site personnel into a web-based data management system, REDCap. In order to provide user-friendly and easy-to-navigate interfaces, the REDCap data capture screens are designed based upon individual CRFs. Additionally, REDCap provides 24/7 technical support should difficulties arise. Prior to study start, the system is validated to ensure the data entry screens mirror the CRFs and that the pre-programmed data rules appropriately detect incorrect data. The data will be managed after data entry via data queries

from the MSMC.
The latest version of each CRF and source documents will be available as a PDF file on the REDCap website for use by study personnel. This process facilitates version control of these study related documents, particularly since documents may evolve over the course of the study.

This user friendly web-based database system, developed and validated by the MSMC, will be used for subject randomization, data entry, data validation, project progress monitoring, subject tracking, user customizable report generation and secure data transfer.

15.3 Reporting Module

The REDCap system also has a real-time reporting component that allows authorized users to view protocol specific reports as data listings and in a summary format, overall and by site, at any time during the study via the password protected system. The Reporting Module is developed based on input from the TOC and includes reports on enrollment, SAEs, CRF processing, and subject progress. The reports are presented in a manner that protects the integrity of the study (e.g., blinded).

MSMC will provide the TOC and authorized study personnel access to a standard set of web-enabled tools within REDCap. These tools allow the authorized research personnel to receive regular updates on accrual status and CRF status of enrolled subjects. Examples of available reports include subject enrollment logs, basic subject demographics, CRF completion rate and number of data queries outstanding and resolved. Like all reports generated on the system, data reported are in real time.

15.4 Security, Privacy, and Confidentiality

The MSMC employs several layers of data protection to ensure data security.

The first part of security is physical protection of the hardware systems employed by the MSMC. The facility housing the MSMC hardware is protected 24/7 by multiple layers of security. By limiting access, ensuring only authorized personnel have access, and tracking all entry, we can ensure this risk is minimal. All communication with the web server and client is encrypted. To help protect and secure the data stored in REDCap's back end database, the software application employs various methods to protect against malicious users who may attempt to identify and exploit any security vulnerabilities in the system. In REDCap, all incoming data gets intentionally filtered, sanitized, and escaped. Server environment variables that are vulnerable to forgery by end-users are also checked and sanitized. To specifically protect against Cross-Site Request Forgery (CSRF), which is another method of attack, REDCap utilizes a "nonce" (a secret, user-specific token) on every web form used in the application. The nonce is generated as a unique value for each new REDCap session

To maintain electronic records in the database as adequate and accurate, REDCap system tracks all changes made to any study patient-related and dynamically managed electronic records. REDCap has a built-in audit trail that automatically logs all user activity and logs all pages viewed by every user, including contextual information (e.g. the project or record being accessed). The logging record can itself be viewed within a project by users that have been given privileges to view the Logging page. The Logging page allows such users to view or export the entire audit trail for that project, and also to filter the audit trail in various ways based upon the type of activity and/or user. This audit-trail information is created with a computer generated time-stamp and the user name in chronological order, when the original data is modified or deleted.

16. Adverse Events

Adverse events (AEs) may occur at any time after randomization. Pre-existing conditions (existing prior to randomization) will be documented in the subject's medical record as part of prior medical history but will not count against either study procedure unless there is a worsening of the condition during the study. Adverse events (serious and non-serious) will be documented on an Adverse Event CRF. Non-serious adverse events will be recorded from randomization through hospital discharge or 7 days whichever is earlier. Serious adverse events will be recorded from randomization through the end of study (i.e., 180 day follow-up).

Investigators will record characteristics of each adverse event on an Adverse Event CRF. Each adverse event will be judged by the Investigator as to its level of relatedness to the investigational devices and investigational procedure. In addition, the Investigator will identify the date of onset, severity and duration. Severity will be judged using the scale noted in Table 10. All adverse events will be monitored until they are adequately resolved or explained or until the subject reaches the end of the study.

Table 10. Definition of event severity for judgment by Investigator.

Term	Definition
Mild	Patient is aware of a sign or symptom, but that sign or symptom does not interfere with normal activity or symptom is both transient and resolved
Moderate	Symptoms interfere with the subject's usual activity or symptoms require treatment
Severe	Symptom(s) cause either severe discomfort or have a significant impact of the subject's usual activity and symptoms require treatment

16.1 Serious Adverse Events

An adverse event is considered serious if it is life-threatening, prolongs hospitalization, requires a re-hospitalization, inpatient hospitalization, results in significant disability, or leads to death. Additionally, an important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include (but are not limited to): allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or, the development of drug dependency or drug abuse. Serious adverse events should not be reported for hospitalization or prolonged hospitalization in the following scenarios: for a diagnostic or elective surgical procedure related to a pre-existing condition; to allow for an efficacy measure for the study; or, for a planned surgical procedure that was not the result of a condition worsening due to participation in the study.

An assessment should be made regarding the seriousness, severity and relationship to the investigational devices and investigational procedure. The following factors should be considered when evaluating causality of adverse events: 1) the temporal sequence from the study procedure; 2) patient's response after discontinuation or re-introduction; and, 3) severity of the event. The investigators, on the basis of their clinical judgment and guided by the following definitions, should determine the relationship of an adverse event to the administration of the investigational device, and/or study procedure(s) as: definitely related, i.e. following in a reasonable temporal sequence, known to be a complication, and having no other explanation; probably related, i.e. following in a reasonable temporal sequence and not reasonably explained by the patient's clinical state or other therapies; possibly related, i.e. could have been explained by other therapies or patient's clinical state; or not related.

16.2 Reporting and Review of Adverse Events

To provide for consistent reporting of adverse events, serious and non-serious adverse events will be recorded on the Adverse Event CRF. Non-serious adverse events will be recorded from randomization through Day 7 or hospital discharge (whichever occurs first). Serious adverse events will be recorded from randomization through the end of study (i.e., 180 day final follow-up visit, death, or withdrawal of consent).

In order to ensure prompt reporting of adverse events, we require that all adverse events (as well as all related study data) be entered into the REDCap web-based database (REDCap) within five working days of their becoming aware of the event during the initial admission. For all serious adverse events (SAEs), we require that they be reported in the REDCap within 24 hours of the study site staff first being made aware of the occurrence of the SAE. The 24-hour reporting requirement for SAEs applies to all study phases.

Reporting of serious or life-threatening adverse events will trigger notification of the event to the Medical Monitor (MM). The MM will conduct an independent review of these specific SAE. If the MM believes the adverse event is serious, unexpected and either definitely, probably, or possibly related to the investigational device(s) and/or study procedures, the TOC staff will forward a Safety Report (pre-filled with as much data as possible) to the clinical site Investigator to be completed with any additional information that may be relevant to the SAE. The Safety Reports will be included in the reports prepared for the DSMB. The principal investigator, at each clinical site, will be responsible for reporting to his/her own IRB/EC according to individual IRB/EC policies. After the submission of the initial Safety Report, the principal investigator at the corresponding clinical site will be responsible for obtaining follow-up information about the event, and reporting it to the TOC.

If it is determined that an unanticipated adverse device effect presents an unreasonable risk to subjects, the Principal Investigator will recommend the termination of all investigations or parts of investigations presenting that risk as soon as possible. The PI and SC shall make a determination regarding termination not later than 15 working days after the sponsor first receives notice of the effect. Termination of all investigations or the parts of investigations that have been deemed to present the risk(s) shall occur not later than 5 working days after the PI and SC makes this determination.

The trial will resume only after determining there is sufficient evidence to reinstate the trial, and after each clinical site obtains IRB/EC approval.

17. Ethical Considerations

The rights, safety and well-being of clinical investigation subjects shall be protected consistent with the ethical principles laid down in the Declaration of Helsinki. This shall be understood, observed and applied at every step in this clinical investigation.

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The Sponsor and the Investigator(s) shall avoid improper influence or inducement of the subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

18. Protection of Patient Confidentiality

At all times throughout the clinical investigation, confidentiality will be observed by all parties involved. All data shall be secured against unauthorized access. Privacy and confidentiality of information about each subject shall be preserved in study reports and in any publication. Each subject participating in this study will be assigned a unique identifier.

The Investigator will maintain a confidential study subject list identifying all enrolled subjects. This list will contain

the assigned study subject's unique identifier and name. The Investigator bears responsibility for keeping this list confidential.

Monitors and auditors will have access to the study subject list and other information that personally identifies study subjects to ensure that data reported in the CRF corresponds to the person who signed the ICF and the information contained in the original source documents. Such personal identifying information may include, but is not limited to the subject's name, address, date of birth, and medical record number.

19. Ethics Committee/Institutional Review Board Approval

Institutional Review Board (IRB) / Ethics Committee (EC) approval is required prior to study commencement. The Investigator must also obtain renewal of IRB/EC approval as dictated by local requirements (but at least annually) during the entire duration of the study. The Investigator is responsible for fulfilling any conditions of approval imposed by the reviewing IRB/EC, such as regular reporting, study timing, etc. Study data required to be included in IRB/EC reports (e.g., Continuing Reviews) must be obtained from the SDMC; in order to ensure that accurate and consistent data are presented.

The Investigator will provide the Project Management (PM) team with copies of such approvals and reports. Withdrawal of IRB/EC approval must be reported to the PM team immediately following the investigator's knowledge of the withdrawal.

The reviewing Independent Review Board (IRB) / Ethics Committee (EC) must review and approve an Informed Consent Form (ICF) specific to this study. Prior to the start of the trial, the PM team will provide each study center with a sample ICF. The study center, to meet specific requirements, may modify this sample ICF; however, the ICF must contain all of the elements required by the protocol, regulations, and GCP. Each investigational site will submit a copy of their ICF to the TOC prior to submission to their IRB; and, the IRB/EC approved ICF and renewal approvals to the PM team as required for the duration of the study. The original, signed and dated ICF should be retained by the investigational site for monitoring, and a copy provided to the subject.

20. Informed consent

Upon confirmation of patient's eligibility, a written informed consent document must be obtained prior to any study-specific evaluations being conducted. In accordance with US FDA regulations (21 CFR 50) and ICH-GCP Consolidated Guidelines (Federal Register, May 9, 1997, Vol. 62, Number 90), a witnessed, IRB-approved, informed consent will be required from all subjects or their legal representative (LAR) or family member, as defined in 21 CFR 50.3(m), prior to participating in this trial. At the initial contact with a potential candidate, the investigator(s) will provide an adequate explanation of the purpose, procedures, possible risks/benefits, and participant responsibilities; in addition to the fact that his/her participation is voluntary, that he/she may withdraw from the study at any time, and that the decision not to participate or to withdraw will not affect subject's care in any way. Potential participants or their legal representative or family member will be given ample opportunity to ask questions and to consider their decision. If the subject expresses a sustained interest, a signed and dated written informed consent will be obtained. A copy of the consent form will be given to the participant or their legal representative or family member, and another copy will be placed in his/her medical record. The informed consent must be obtained by either the clinical site PI or other members of the study team who have been delegated the authority to obtain informed consent. Each of the study team members with this delegation must be qualified in terms of education, experience, and training to obtain informed consent.

The written informed consent document (and any other written information to be provided to the study subject) should be updated whenever new information becomes available that may require significant revisions to the informed consent document previously signed by a subject. Any such revision or update must be approved by the reviewing IRB/EC before being provided to the study subject. Previously consented subjects will be made aware of the changes and depending on the extent and/or severity of the new information a subject may be asked to "re-

consent" to continued participation in the trial.

21. Quality Assurance

To ensure monitoring responsibilities are performed to the fullest extent possible on a real-time basis through the RedCap, an experienced clinical research group will perform on-site and centralized monitoring for the trial uploading of all source documents within the REDCap system. MSMC staff will manage the assignment of monitors to performance sites, the coordination of monitoring visits, and provide support to monitors while they are in the field. In addition to on-site monitoring, centralized monitoring (per the FDA's most recent monitoring guidance developed in August 2011) reflects a modern, risk-based approach. Centralized monitoring focuses on critical study parameters and relies on a combination of monitoring activities. In this recent guidance, the FDA has encouraged the implementation of centralized monitoring due to its ability to ensure quality and integrity of data. Centralized monitoring is also very effective at identifying data fraud, data fabrication, and data errors.

For the first subject enrolled at any site, 100% of the data will be verified to source documents. For subsequent subjects, a checklist of key outcome and safety data variables requiring source document verification (SDV) has been developed based on the trial's safety and efficacy endpoints. Source documents verifying each data point collected in the trial will be uploaded into REDCap for all study subjects. This will allow for data to be monitored in a real-time fashion and for any errors in data to be identified more quickly. A target of no less than 50% of the trial data submitted to the REDCap database will be verified against source documents from the performance sites prior to finalization of the database. Safety and efficacy variables represent approximately half of the data to be verified. The remaining half of source monitored data include: 100% of deaths and 100% of serious adverse events and all MSMC requested source data reviews based on the per-subject evaluation of safety parameters defined in the protocol. All data monitored are verified for accuracy and thoroughness using the most appropriate source documents for all subjects.

Signed informed consent documents and HIPAA are monitored for all subjects. Additional monitoring verification will include: ongoing evaluation of the adequacy of site facilities and staff, site recruitment, subject randomization, the presence of regulatory documents, and specific review of documents and data as requested by the MSMC staff. Each site will be monitored on a real-time basis through the uploading of all source documents into the REDCap system. Sites are evaluated in an ongoing manner by site monitors and MSMC staff to determine if there is a need to monitor more frequently or more thoroughly or via on-site evaluation.

Any omissions and corrections to data submitted to the database are noted and queries are generated by the monitor on site or immediately via REDCap's automated system. All queries will be stored in REDCap's logging and audit trail so that all data changes or questions regarding data accuracy are tracked and permanently recorded. The auditing trail will contain information regarding which monitor issued the query, which user was assigned the query at each site, the complete free text conversations discussing data questions and/or changes, and will provide time and date stamps for all query related processes.

Monitors will perform closeout-monitoring evaluations at the completion of subject enrollment. The monitor will again review all regulatory files and verify documents for accuracy and completeness as directed by the MSMC staff. Sites are instructed in the record retention of all trial documents. Principal Investigators are directed to close the trial and issue a final report to their IRB/EC following resolution of any and all outstanding issues at that site. Finally, any additional special considerations for the auditing of any additional safety issues will be made.

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the subject's privacy as far as reasonably practicable. Only users with password-protected REDCap access will have the ability to view study data within the secure REDCap database. The Primary Investigator, Sponsor and representatives of regulatory authorities are permitted to inspect the study documents (e.g., study protocol, CRFs, and original study-relevant medical records/files) as needed. All attempts will be made to preserve subject confidentiality.

22. Protocol Deviations

A protocol deviation is defined as any study action taken by the clinical Investigator or site personnel in conflict with the Study Protocol. All protocol deviations will be entered into REDCap within 48 hours of the deviation. These will be tracked within the REDCap system and queries will be made and recorded as will through REDCap.

Deviations must be reported to the PM team regardless of whether medically justifiable, or taken to protect the subject in an emergency. Investigators will also adhere to procedures for reporting study deviations to their IRB/EC in accordance with their specific IRB/EC reporting policies and procedures.

Good Clinical Practice Guidelines require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol.

23. Final Report

A final report will be completed, even if the study is prematurely terminated. At the conclusion of the trial, a multi-center abstract reporting the results will be prepared and may be presented at a major meeting(s). A multi-center publication may also be prepared for publication in a reputable scientific journal. The publication of results from any single center experience within the trial is not allowed until the aggregate study results have been published, unless there is written consent from the study PI.

24. Information Confidentiality

All information and data generated in association with this study will be held in strict confidence and remain the sole property of Principal Investigator. The Investigator agrees to use this information for the sole purpose of completing this study and for no other purpose without written consent from the Trial Operating Committee.

25. Trial Registration

The study will be registered in a publicly accessible trial database (e.g., clinicaltrials.gov) prior to study initiation.

26. Risk Analysis

A thorough risk analysis was performed as part of design control recommendations of the Quality System Regulation (21 CFR 820).

27. Publication Policy

Publication of the results of this trial will be governed by the policies and procedures developed by the Trial Operations Committee. The Publication Policy will be fully compliant with the voluntary NIH Public Access Policy mandated by the Consolidated Appropriations Act of 2008 (Division G, Title II, Section 218 of PL 110-161).

28. References

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