INVEST: A Single Arm, Feasibility Study of Minimally Invasive Endoscopic Surgical Treatment with Apollo / Artemis for Supratentorial Intracerebral Hemorrhage (ICH)
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INVEST: A Single Arm, Feasibility Study of Minimally Invasive Endoscopic Surgical Treatment with Apollo / Artemis for Supratentorial Intracerebral Hemorrhage (ICH)

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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.

Site Investigator Name: _____

Signature/Date: _____

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Study Synopsis:

Title: INVEST: A Single Arm Feasibility Study of Minimally Invasive Endoscopic Surgical Treatment with Apollo / Artemis for Supratentorial Intracerebral Hemorrhage (ICH)

Objective: The primary objective of this multicenter single arm feasibility study is to provide an assessment of enrollment and follow up feasibility for this patient population being treated with the Apollo or Artemis Minimally Invasive Surgical Treatment (MIES). Patients who do not qualify for the INVEST Feasibility Study will be referred to the INVEST Registry study.

Study Design: This study will be a prospective, multi-centered trial that will enroll 50 patients at up to 10 United States (US) centers

Patient Population: Patients with moderate-large volume (30-80 cc) supratentorial intracerebral hemorrhage (ICH) who present within 24 hours of symptom onset for which the treating physician feels that, in the course of best medical care, they will use the Apollo system or Artemis Device. Once enrolled, patients will receive minimally invasive endoscopic evacuation with the Apollo system or Artemis Device.

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 or cerebrum. In the present study, we propose to investigate the feasibility of studying this patient population for eventual implementation of efficacy trials.

Inclusion Criteria:

1. Patient age ≥ 22 and ≤ 80, or age < 85 with baseline mRS=0
2. Supratentorial ICH of volume ≥ 30 mL ≤ 80 ml (measured using A x B X C/2 method)
3. CT/MR demonstrates ICH stability (< 5 cc growth) at least 6 hours after admission scan. If the initial stability scan shows growth, a second stability scan can be performed q12h until stability is demonstrated or until eligibility for the study has lapsed.
4. NIHSS ≥ 6
5. Presenting GCS 5-15
6. Historical mRS 0 - 2
7. Symptom onset < 24 h prior initial CT
8. Apollo / Artemis MIES (minimally invasive endoscopic surgical treatment) can be initiated within 72h of ictus/bleed
9. SBP can be controlled < 180 mmHg and sustained at this level for at least 6 hours

Exclusion Criteria:

1. Imaging
    a. Expanding hemorrhage on stability CT/MR scan;
    b. "Spot sign" identified on CTA (may perform a second CTA at 12 hours to demonstrate resolution);
    c. Hemorrhagic lesion such as a vascular malformation (cavernous malformation, AVM etc.), aneurysm, neoplasm;
    d. Hemorrhagic conversion of an underlying ischemic stroke;
    e. Infratentorial hemorrhage;
    f. Large associated intra-ventricular hemorrhage requiring treatment for IVH-related mass effect or shift due to trapped ventricle (EVD (extraventricular drain) for ICP (intracranial pressure) management is allowed);
    g. Midbrain extension/involvement.

h. Absolute contraindication to CTA, conventional angiography and MRA

2. Coagulation Issues
    a. Absolute requirement for long-term anti-coagulation (e.g., Mechanical valve replacement (bio-prostatic valve is permitted), high risk atrial fibrillation);
    b. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency;
    c. Platelet count < 100 x 103 cells/mm3 or known platelet dysfunction;
    d. INR > 1.4, 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. Presenting GCS of 3 or 4;
    b. High risk condition for ischemic stroke (high risk Afib (e.g., mitral stenosis with Afib), symptomatic carotid stenosis);
    c. Requirement for emergent surgical decompression or uncontrolled ICP after EVD
    d. Unable to obtain consent from patient or appropriate surrogate (for patients without competence);
    e. 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;
    f. Evidence of active infection indicated by fever at or over 100.7 °F, and/or open draining wound at the time of enrollment;
    g. Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments through 180 days;
    h. 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;
    i. Active drug or alcohol use or dependence that, in the opinion of the site investigator would interfere with adherence to study requirements;
    j. Currently participating in another interventional (drug, device, etc) research project.

Primary Endpoints:

The primary objective is to provide an assessment of enrollment and follow up feasibility for this patient population being treated with the Apollo / Artemis MIES, with endpoints defined as:

- Rate of recruitment over a two-year time span following first patient enrollment
- Rate of successful 180 day follow up obtainment. Statistical details can be found in section 7.

Secondary Endpoints:

- Stroke Impact Scale – Mobility at 180 days
- Stroke Impact Scale – ADLs at 180 days
- EQ-5D-5L at 180 days
- Length of hospital stay
- 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
    - Predominantly or Only IVH: mGraeb score of ≤ 5 on day 7 CT scan
- Safety Endpoint: Rate of mortality at 90 days

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1. Introduction:

Intracerebral hemorrhage (ICH) is the most common subtype of hemorrhagic stroke, accounting for 10-15% of all strokes and affecting between 10 and 30 people per 100,000[1, 2]. The incidence of ICH is increasing, likely secondary to the increasing mean age of the population[3, 4].

ICH is a devastating disease with the poorest prognosis of all stroke subtypes[5]. The estimated mortality rate is 50% at 1 year and more than 70% at 5 years[6]. The majority of survivors are dependent at follow-up[7]. If there is a concomitant component of intraventricular hemorrhage and hydrocephalus, outcomes are even worse[8-11].

The high level of intensity and the duration of care required for these patients is manifest in astronomical costs, with ICH being ranked amongst the most costly of all neurological diagnoses[12]. Russell et al. reported that the average cost for patients experiencing mortality from their initial hemorrhage was greater than 16,500 US dollars (patients admitted between 1999 and 2002). These costs were much greater in survivors, increasing to more than 28,000 for the initial hospitalization with an additional 16,000 incurred during the first year after discharge[12].

Despite extensive study, no medical or surgical intervention has ever been demonstrated to reduce mortality or improve outcomes in patients with ICH. This lack of progress is reflected by the mortality rate of ICH, which has been relatively stable for the past several decades[13].

Medical management consists of admission to an ICU or monitored stroke unit, airway assessment and management, control of hypertension, and assessment for, and reversal/correction of, any inherent or pharmacologically induced coagulopathy. The presence of hydrocephalus or elevated intracranial pressures, secondary to mass effect or concomitant intraventricular hemorrhage (IVH), may require emergent placement of a ventricular drainage catheter. More pronounced mass effect or herniation may require a craniectomy/craniotomy for emergent evacuation of the hemorrhage and/or decompression[14].

In those patients lacking an unambiguous indication for life-saving surgical decompression, multiple randomized controlled trials of more aggressive medical management strategies as well as conventional surgical evacuation have failed to demonstrate an improvement in clinical outcomes or survival [8, 15-21].

Randomized Trials of Medical Management of Intracranial Hemorrhage:

In the Factor VII for Acute Intracerebral Hemorrhage Trial, 841 patients with ICH were randomized to receive placebo or one of two doses of recombinant factor VIIa (rFVIIa) within 4 hours of the onset of symptoms. Although the higher dose of rFVIIa was associated with a significantly lower rate of hematoma expansion, this effect did not translate to an improvement in clinical outcomes or mortality[10]. Moreover, it did not appear that an increased incidence of thrombotic complications in the rFVIIa group accounted for the failure of the trial demonstrate a clinical benefit.

Similarly, two small pilot trials of aggressive medical management of blood pressure INTERACT and ATACH, failed to demonstrate any benefit for survival or favorable clinical outcome when compared to more conservative medical management[15, 16]. INTERACT I did show a reduction in hematoma growth with aggressive BP management[16]. A larger trial of aggressive blood pressure control, INTERACT II, failed to demonstrate a reduced rate of death or major disability with aggressive management, but did show a significant, but modest, improvement with an ordinal analysis of modified Rankin scores (mRS) for the intensive management group.

Trials of aggressive management of cerebral edema with mannitol have also failed[17-19].

Randomized Trials of Conventional Open Surgical Management of Intracranial Hemorrhage

Two large randomized controlled trials of conventional open surgery for intracranial hemorrhage (Surgical Trial in Intracerebral Hemorrhage (STICH) I and STICH II) have both demonstrated no beneficial effect for hematoma evacuation[8, 20]. In STICH I, early surgical management was compared to standard medical management in a series of 1033 patients with supratentorial ICH. Three-quarters of patients in both arms of STICH I demonstrated poor clinical outcomes or died. Subgroup analyses of the STICH I cohort indicated a potential benefit for those patients with superficial ICH (within 1 cm of the cortical surface) without intra- ventricular extension. On the basis of this observation, the STICH II trial was designed specifically to assess the effects of conventional surgical management in this group of patients. In STICH II, 601 patients with superficial hemorrhages were randomized between early surgery and conservative management. 59% of patients in the surgical group and 61% of the patients in the medical management groups had unfavorable outcomes. A trend toward improved mortality at 6 months (18% in the early surgery group and 24% in the medical management group) failed to reach significance (p = 0.095).

Taken together, these data provide strong evidence that the conventional open surgical management of intracerebral hemorrhage is not beneficial in patients with ICH who are not in need of emergent, life-saving decompression.

1.1 Rationale for study

Why would the minimally invasive evacuation of ICH be beneficial?

ICH is thought to induce neurological injury in a biphasic manner. The primary neurological injury is caused by the direct mechanical destruction of neurons by the original bleed[1]. This form of injury is not treatable per se, with the exception perhaps of medical interventions designed to reduce or eliminate hematoma early expansion from re-bleeding. As discussed above, several medical interventions have been demonstrated to successfully limit hematoma growth, but none has been associated with a compelling clinical benefit.

Secondary injury to the brain surrounding the hematoma has been theorized to be the sequelae of locally increased pressure resulting in reduced regional perfusion as well as a direct cytotoxic effect of blood breakdown products on adjacent brain tissue (hemotoxicity)[22]. It is believed that this secondary injury is manifest as peri-hematomal edema (PHE) on imaging studies[23-25].

In patients with ICH undergoing serial CT studies over the course of several weeks, Zazulia et al. observed the progression of mass effect at two distinct time periods. Early exacerbation of mass effect (within 48 hours) was related to acute hematoma expansion. Later progression was the result of peri-hematomal cerebral edema, which occurred between 9 and 21 days after the original bleed23. This delayed progression of edema and mass effect days to weeks after ICH provides strong supportive clinical evidence of a secondary injury. Other investigators have also observed that mass effect and cerebral edema persists longer after ICH than ischemic stroke, with mass effect lasting for up to one month in some cases[26-29].

Studies of regional perfusion in humans have largely failed to demonstrate significant regions of ischemia in the brain surrounding ICH[30, 31]. On the contrary, a wealth of pre-clinical evidence has shown that thrombin, hemoglobin, iron and other hemoglobin breakdown products have a significant potential for direct toxic effects upon brain tissue [32-34].

Theoretically, the early evacuation of blood products could alleviate local mass effect and improve regional perfusion, and in addition, reduce the volume of blood products and substrate contributing to hemotoxicity, thus reducing or eliminating these potential mechanisms of secondary injury. At the same time, the procedure would be best done in the least invasive manner possible as to avoid inducing additional injury to the brain.

The Case for Minimally Invasive Hematoma Evacuation

The failure of conventional surgical evacuation to improve outcomes in ICH has been attributed to the morbidity associated with the craniotomy and surgical approach. Specifically, it has been proposed that the surgical approach to the hematoma may cause enough damage to surrounding brain to offset any potential benefits of surgery. Correspondingly, it is possible that the potential benefits of hematoma evacuation could be realized if the procedure could be performed through a minimally invasive access.

A large meta-analysis of surgical treatment strategies for ICH concluded that surgery could be beneficial in patients undergoing early surgery (within 8 hours), with moderately sized hemorrhages (20-50cc), of moderate age (50 – 69 years) and with moderate to severe clinical deficits (GCS 9 – 12). Incidentally, an evaluation of the contributing data sets indicates that a single study (Wang et al.) largely drove the clinical benefit in each of the cohorts[35].

Wang et al. conducted a randomized trial in 465 patients with intracranial hemorrhage, randomizing patients between medical management and minimally invasive craniopuncture therapy. The craniopuncture procedure consisted of the CT-guided placement of a puncture needle into the hematoma. Following the aspiration of hematoma fluid, a lysis fluid (containing urokinase) was injected under pressure into the hematoma. The drainage needle was secured into position and allowed to drain for 3-5 days after placement. Using this technique, the authors reported a significant improvement in clinical outcomes with 41% of the craniopuncture group and 63% of the medical management group being dependent (mRS > 2) 90 days[35].

This minimally invasive CT-guided craniopuncture technique is routinely practiced in China with over 150,000 patients undergoing this procedure yearly[35, 36]. Zhou reported a meta-analysis of 12 studies including 1955 patients randomized between medical management and minimally invasive surgery. These investigators reported robust reductions in both death (46% relative risk reduction) and death or dependence (47% relative risk reduction) at the end of follow-up in patients undergoing MIS (minimally invasive surgery)[36].

Recently, two small pilot randomized controlled trials of MIS for ICH have been completed in the United States – The Minimally Invasive Surgery plus tPA for ICH Evacuation (MISTIE) and the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR IVH)[37, 38].

In MISTIE, 96 patients were randomized between conventional medical management (n=42) and minimally invasive surgery (n=54). The minimally invasive surgical procedure consisted of the initial stereotactic placement of a sheath with manual aspiration of the hematoma followed by the placement of a flexible drainage catheter that was irrigated with t-PA for up to four days. These investigators reported a significant reduction in perihematomal edema as well as trends toward better clinical outcomes at 180 and 365 days[25, 37]. They also observed an improvement in mobility and independence in ADLs at follow-up, as well as a reduction in length of stay and healthcare expenditures. Moreover, the degree of improvement in clinical outcome appeared to be directly related to the volume of hemorrhage remaining at the end of the treatment, with those patients with < 10 cc's of residual hemorrhage having the best outcomes. Unfortunately, only a minority of patients in the MISTIE study achieved this level of residual hematoma volume. Moreover, it often took several days of treatment before this level of hematoma reduction was reached.

In the CLEAR IVH trial[38], 48 patients with small supratentorial hemorrhages and large associated intraventricular hemorrhages requiring ventricular drainage were randomized between saline infusion and intrathecal tPA (IT-tPA) through a ventricular drain. These investigators observed that IT-tPA infusion increased the rate at which the IVH cleared. Moreover, patients with more rapid and complete clearance of IVH demonstrated a more rapid and complete improvement in neurological status. Although a robust signal for a beneficial effect was observed in the IT-tPA group overall, 6 of 26 patients (23%) in this cohort experienced symptomatic re-hemorrhage, with four requiring craniotomy for management. This symptomatic re-hemorrhage rate was considerably higher than that observed for irrigation of parenchymal drainage catheters in MISTIE II. Moreover, it required an average of 10 days to achieve adequate clearance of IVH in the IT-tPA group.

Thus, the existing clinical evidence provides support to the pre-clinical data suggesting that the evacuation of blood products after ICH could prevent secondary injury and improve outcomes. However, the current techniques are relatively rudimentary and suffer several potentially important shortcomings.

First, it requires days to achieve an adequate evacuation of blood products using the craniopuncture and catheter drainage techniques. Optimally, the removal of blood products should be accomplished as efficiently as is feasible and safe to limit or eliminate the potential for secondary injury related to local hypoperfusion and/or hemotoxicity. Second, the requirement for an indwelling drainage catheter with periodic access for irrigation presents the potential for infection and also is labor and resource intensive. This irrigation is typically performed within an intensive care unit setting. In addition, patients undergoing tPA infusions require multiple serial scans to assess the reduction in hematoma volume and to survey for re-bleeding. Finally, re-bleeding with thrombolytic irrigation is not an insignificant risk, particularly with respect to intraventricular administration, as demonstrated in CLEAR IVH.

The Case for Minimally Invasive Hematoma Evacuation using a Mechanical Device

Several mechanical techniques have been devised for the minimally invasive evacuation of intracranial hemorrhage. A primarily mechanical approach offers several potential advantages. First, an effective mechanical approach provides a means by which to achieve an immediate, efficient and predictable reduction in hemorrhage volume. This is particularly true if the technique is performed with direct visualization and/or periodic active monitoring with cross-sectional CT imaging and/or ultrasound. It stands to reason that an immediate and substantial reduction in blood product volume may better reduce the cumulative secondary injury than would a gradual reduction over several days. Second, with some purely mechanical approaches, no post-procedural drainage catheter is required, eliminating the resources required for the maintenance of the catheter as well as the potential for infection or additional hemorrhage associated with catheter manipulation. Third, the avoidance of catheter irrigation with t-PA reduces the potential for re-hemorrhage secondary to the local thrombolytic effect.

Intra-operative CT-guided Endoscopic Surgery for ICH (ICES)

The ICES technique involves the stereotactic placement of an endoscopic sheath into the hematoma. The hematoma is then evacuated using suction and irrigation from two pre-specified depths. The endoscope is then used to make an assessment of the volume of residual hemorrhage as well as to assess, and potentially control, any active intracranial hemorrhage using cautery[39]. In a small, single-center series of six patients, the operators were able to achieve an 80% reduction in hemorrhage volume and a 60% reduction in midline shift. In a second small, single- center trial, ten patients were randomized between the ICES technique and medical management. In the ICES group (n=6), the operators achieved an 80% reduction in hematoma volume, while the medical management group demonstrated an 80% enlargement, both over a 24-hour period after treatment allocation[40]. The trial was ultimately halted due to slow enrollment and the recognition from the operators that the technique required optimization within the context of a single-arm study prior to the performance of a randomized trial.

The Apollo System and Artemis Device

The Apollo System received FDA clearance for the controlled aspiration of tissue and/or fluid during surgery of the ventricular system or cerebrum in March 17, 2016 and CE marking in May 10, 2016 and is commercially available in the United States and throughout Europe. The Artemis Neuro Evacuation Device received FDA clearance (K171332) on August 14, 2017.

The Apollo System is an aspiration-irrigation apparatus, which is coupled to a low-profile wand (2.1 and 2.6 mm diameter sizes). The Apollo Wand houses an internal vibrating element that, when actuated with a foot pedal, macerates clot material within the wand to maintain patency of the system during aspiration. This design allows a targeted evacuation of blood products through a minimally invasive access without clogging. The Apollo Wands fit through the working channels of commercially available neuroendoscopes (Lotta, Karl Storz, Tuttlington, Germany) such that clot evacuation can be performed under direct visualization[41, 42]. The technique is very similar to the ICES technique in that a sheath is placed within the hematoma and evacuation is typically performed under direct endoscopic visualization. In some settings, periodic evaluation of the remaining hematoma is performed using intra-procedural CT or ultrasound[42].

A successor to the Apollo System, the Artemis Device is a surgical instrument designed to aid a physician in the removal of tissue and/or fluid during image-guided neurosurgery. The Artemis Device has two functions. These functions are control and transfer of aspiration and generation of rotational energy. Aspiration is generated by a Penumbra Aspiration Pump, which the Artemis Device connects to through flexible tubing. The Artemis Device has a rigid cannula containing a wire to facilitate removing tissue and/or fluid with the assistance of rotational energy and aspiration. The Artemis cannula fits through the working channels of commercially available neuroendoscopes (e.g. Lotta, Karl Storz, Tuttlington, Germany) such that clot evacuation can be performed under direct visualization[41, 42]. The technique is very similar to the ICES technique in that a sheath is placed within the hematoma and evacuation is typically performed under direct endoscopic visualization. In some settings, periodic evaluation of the remaining hematoma is performed using intra-procedural CT or ultrasound[42]. The method of action of removal is first vacuum aspiration, which draws the tissue and/or fluid into the lumen of the Artemis cannula. Next, the wire inside the lumen of the Artemis cannula is rotated, facilitating movement of any tissue and/or fluid that may otherwise clog the cannula lumen.

The conceptual principles of operation remain the same for the Artemis Neuro Evacuation Device and the Apollo System, both of which are used for the controlled aspiration of tissue and/or fluid removal.

The Artemis Device utilizes rotational energy, rather than vibrational energy used for the Apollo System, to prevent clogging of tissue and/or fluid aspirated into the Artemis cannula. The helical wire prevents the Artemis cannula from clogging by interacting with the aspirated tissue and/or fluid throughout the entire length of the cannula. The electrical power to rotate the wire in the Artemis cannula is provided by a battery which drives a motor, both of which are contained in the disposable handle.

In an initial multi-center, retrospective series of 29 ICH patients undergoing treatment with the Apollo system, an average reduction in hemorrhage volume of 54% was achieved, with a reduction of the hemorrhage volume to $\leq$ 10 cc in 48% of patients treated. As opposed to the ICES technique, in most cases, no drainage catheters were placed following the initial evacuation[43].

Thus the Apollo System and the Artemis Device potentially provides a means by which to efficiently and reliably achieve a minimally invasive, mechanical evacuation of intracranial hemorrhage under direct visualization and control using a neuroendoscope without the requirement for subsequent catheter placement and thrombolytic

irrigation.

Conclusions

Intracranial hemorrhage is a devastating disease associated with poor clinical outcomes. To date, no surgical or medical therapy has been demonstrated to improve outcomes in these patients. Of all the strategies tested, the most encouraging data exist for minimally invasive strategies employed to achieve a reduction in hemorrhage volume. Initial data derived from 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. Apollo system, has been commercially available for over 3 years and early experience with the system in regards to its application to remove parenchymal hemorrhages has evolved. As such, now that the technical approach has matured, it is necessary to carry out a feasibility single arm study before proceeding to a randomized controlled trial with a larger patient population.

Rationale for the INVEST Feasibility Design

The INVEST feasibility study was designed to include those patients who theoretically hold the highest potential to benefit from the Apollo or Artemis MIES procedure and thereby assess our ability to recruit and follow this patient population, which has been identified to maximize the odds of potentially observing a treatment effect in subsequent RCTs. Specific components of the design are addressed below.

Patients with presenting GCS of $\underline{\leq}$ 4 have been excluded from the INVEST feasibility study. Patients with very low GCS (3-4) represent a heterogeneous group and many will have severe, unrecoverable injuries potentially involving the brain stem. While some in this group may, in fact, benefit from the Apollo or Artemis MIES procedure, it is likely that majority will not. Furthermore, this severely injured patient population will likely have substantial barriers to follow up and may limit long-term data collection. As such, these patients are excluded from the INVEST feasibility study so as not to include a population that might eventually dilute any evidence of a potential treatment effect in a subsequent RCT. At the same time, if experienced operators at INVEST centers identify individual patients in this group whom they feel will benefit from the Apollo or Artemis MIES procedure and intend to treat the patients outside of the INVEST feasibility study, these patients may be eligible for enrollment in the companion INVEST single-arm observational registry (see accompanying protocol).

Patients with hemorrhages less than 30 cc or greater than 80 cc are excluded from the INVEST feasibility study. Our preliminary experience has indicated that hemorrhages ranging between 30 and 80 cc are feasibly treated with Apollo/Artemis MIES[1]. A supratentorial hemorrhage of < 30 cc is not likely to create an injury great enough to reach an NIHSS of 6 or higher as required for inclusion. Patients with hemorrhages of < 30 cc also have a higher likelihood of making an excellent functional recovery without intervention as was referenced in Broderick, et.al.[2]. As such it is likely that including patients with small hemorrhages could obscure our ability to see a signal for a treatment effect. Also at this volume level, the hemorrhage represents a much smaller “target”, which increases the challenge of accurately placing the sheath into the hemorrhage. When hemorrhages are larger than 80 cc, patients are more likely to require very early open surgical evacuation or decompression due to the initial mass effect (even if they were thought to be non-surgical at presentation). To reduce (to the extent possible) the incidence of early open surgical “bail-out” (or cross—over to Apollo/Artemis MIES) for patients randomized into the medical management arm of the trial, these patients are excluded. Moreover, when lobar hemorrhages are larger than 80 cc, they tend to be irregularly shaped and multi-compartmental, with areas that are difficult to access with the Apollo system/Artemis Device -- thus reducing the potential to achieve the pre-determined surgical goal (> 60% reduction and volume < 15 cc) without requiring multiple access sites or a larger craniotomy with multiple sheath trajectories[1].

Vascular imaging is required in all patients being enrolled in the INVEST feasibility study. Computed tomographic angiography (CTA) (or MRA and conventional angiography) is very informative in patients with spontaneous supratentorial ICH – both lobar and deep. Vascular imaging is critical for excluding an underlying vascular lesion, and it is also important for identifying patients at-risk for early hematoma expansion (e.g., those with a "spot sign"). The new AHA ICH guidelines list CTA as a class IIa treatment effect (benefit >> risk)[3]. We feel that the requirement for CTA (or MRA in patients with contra-indication to CTA – i.e., history of severe contrast allergy) markedly increases patient safety and is critical to the study. High quality vascular imaging is particularly critical in patients who will undergo Apollo or Artemis MIES, which could be disastrous if undertaken in the presence of an underlying unsecured vascular lesion. MRA may be performed in patients who have absolute contraindications to CTA. Also, conventional angiography may be substituted for CTA or performed for further evaluation of selected patients at the discretion of the investigator.

2. Purpose and Hypothesis

The primary aim of minimally invasive surgery (MIS) for supratentorial intracranial 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. Currently no prospective study exists evaluating the efficacy of the minimally invasive endoscopic surgery (MIES) with the Apollo system or Artemis Device for this purpose. The purpose of this feasibility trial is to provide an initial assessment of the enrollment and follow up practicality within the patient population receiving MIES treatment.

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 or 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 mini-craniectomy and dural incision. An endoscopic sheath (19-22F) is then placed through this access site into the hematoma under imaging control using neuronavigation. Then, under endoscopic guidance, the hemorrhage is evacuated with the Apollo system or Artemis Device. Following the evacuation, the endoscope and Apollo system or Artemis Device are removed.

Control intraoperative (as specified in Section 5) CT imaging is performed to assess the remaining hemorrhage volume and to assess for immediate procedural complications. Based on the intra-operative control CT imaging, either an additional pass(es) is 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 American Society of Anesthesiologists (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 the Manual of Procedures

3. Objectives

3.1 Primary Objective

- The primary objective is to provide an initial assessment of enrollment and follow up feasibility for the patient population being treated with the Apollo / Artemis MIES. Primary Endpoint: rate of successful obtainment of modified Rankin score (mRS) at 180 days

3.2 Secondary Endpoints:

Secondary Endpoints:

- Stroke Impact Scale – Mobility at 180 days
- Stroke Impact Scale – ADLs at 180 days
- 5Q-5D-5L at 180 days
- Length of hospital stay
- 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 90 days

4. Trial design

This is a prospective, multicenter feasibility trial utilizing Apollo / Artemis MIES in patients with supratentorial intracerebral hemorrhages. Patients will be enrolled who meet the inclusion and exclusion criteria and consent to participate. Data on each patient will be collected at the time of enrollment and treatment, and at subsequent follow-up visits.

4.1 Inclusion criteria

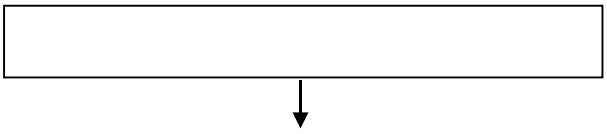
1. Patient age ≥ 22 and ≤ 80, or age < 85 with baseline mRS=0
2. Supratentorial ICH of volume ≥ 30 mL $\leq$ 80 ml (measured using A x B x C/2 method)
3. CT/MR demonstrates ICH stability (< 5 cc growth) at least 6 hours after admission scan
    a. If the initial stability scan shows growth, a second stability scan can be performed q12h until stability is demonstrated or until eligibility for the study has lapsed.
4. NIHSS ≥ 6
5. Presenting GCS 5 - 15
6. Historical mRS 0 - 2
7. Symptom onset < 24 h prior initial CT

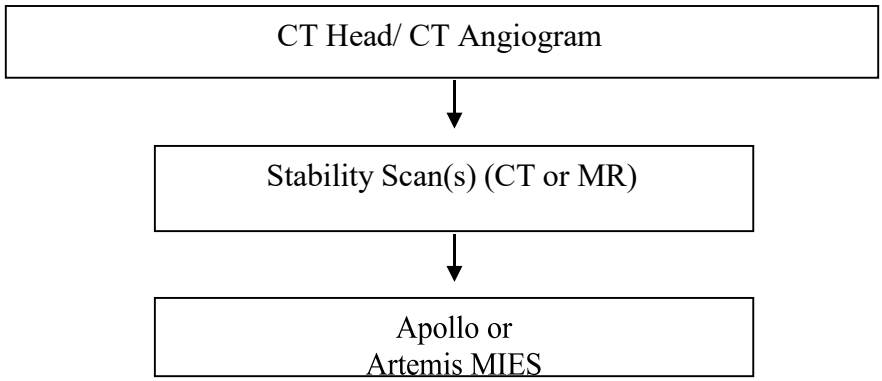
8. Apollo / Artemis MIES can be initiated within 72h of ictus/bleed
9. SBP can be controlled < 180 mmHg and sustained at this level for at least 6 hours

4.2 Exclusion criteria

1. Imaging
   a. Expanding hemorrhage on stability CT/MR scan
   b. "Spot sign" identified on CTA, MRI/MRA or conventional angiography
      i. May perform a second CTA (or MRI/MRA or angiography) at 12 hours to demonstrate resolution
   c. Hemorrhagic lesion such as a vascular malformation (cavernous malformation, AVM etc), aneurysm, neoplasm
   d. Hemorrhagic conversion of an underlying ischemic stroke
   e. Infratentorial hemorrhage
   f. Large associated intra-ventricular hemorrhage requiring treatment for IVH-related mass effect or shift due to trapped ventricle (EVD for ICP management is allowed)
   g. Midbrain extension/involvement
2. Coagulation Issues
   a. Absolute requirement for long-term anti-coagulation (e.g., Mechanical valve replacement (bio- prostatic valve is permitted), high risk atrial fibrillation)
   b. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency c
   c. Platelet count < 100 x 103 cells/mm3 or known platelet dysfunction
   d. INR > 1.4, 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. Presenting GCS 3 or 4
   b. High risk condition for ischemic stroke (high risk Afib (e.g., mitral stenosis with Afib), symptomatic carotid stenosis)
   c. Requirement for emergent surgical decompression or uncontrolled ICP after EVD
   d. Unable to obtain consent from patient or appropriate surrogate (for patients without competence)
   e. 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.)
   f. Evidence of active infection [indicated by fever (at or over 100.7 °F) and/or open draining wound] at the time of enrollment
   g. Any comorbid disease or condition expected to compromise survival or ability to complete follow- up assessments through 180 days.
   h. 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. i 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 ICH presenting within 24 hours of symptom onset but who are not enrolled into the study. Reason(s) for exclusion will be recorded. Logs will be entered by the clinical sites and reviewed on a consistent 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 impact of the therapy.

Patients with ICH or IVH who are not enrolled into the trial, but who undergo Apollo or Artemis MIES at the participating sites, will be eligible for a concurrent prospective, observational, registry for 180 days (see the Manual of Procedures).

4.4 Study Visits

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

- Pre-Treatment
- Procedure
- Post procedure (within 24 hours, Apollo / Artemis MIES patients)
- 7 days post-enrollment or Discharge (whichever comes first)
- Discharge (if beyond 7 days)
- 3 month follow-up (+/- 14 days)
- 6 month follow-up (+/- 21 days)
- 12 month follow-up (+/- 35 days)
-

4.5 Recruitment

The target population for the Apollo / Artemis MIES feasibility study are patients 22-84 years of age who have a diagnosis of spontaneous, non-traumatic, intracerebral hemorrhage (ICH) ranging in volume between 30 and 80cc, with an associated significant neurological deficit (NIHSS $\geq$ 6) who do not require emergent open surgical decompression related to uncontrolled intracranial pressure or mass effect.

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 10 United States sites centers will be included in this study to enroll 50 patients.

4.6 Screening and Baseline Evaluation

During screening and baseline evaluations consent is obtained, medical history screened, available clinical/neurological exams obtained, and laboratory work and imaging information per institutional standard of care are 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 perform a historical mRS determination). CT imaging must be performed to provide an initial diagnosis of IPH (intraparenchymal hemorrhage). Hemorrhage volume will be determined using the A x B x C/2 method. 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 (or MRA for CTA ineligible patients) must also be performed, as standard of care; either at presentation with the diagnostic CT or with the stability scan. 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, 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). In the case of a "spot sign", follow up CTA (or MRA if ineligible for CTA) can be obtained q12 hours to show resolution of the "spot sign" prior to enrollment. An NIHSS must be obtained prior to enrollment, and the score must be $\geq$ 6 for inclusion in the study. A pregnancy test will be conducted for applicable subjects (<50 years old and of child bearing potential). Once the patient meets all eligibility criteria, has undergone a stability scan, and the patient or LAR (legally authorized representative) has provided written informed consent, they will be considered enrolled in the study. Enrolled patients will be treated using Apollo / Artemis MEIS

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 (E6, E6(R1), E6(R2)), and 21 CFR Part 50, and will be approved by the site's reviewing IRB/EC prior to study initiation.

5. Study Screening and Treatment Procedure

The treatment procedure is described briefly below. The study procedure will take place within 72 hours of the clinical presentation of ICH -- after completion of the clinical baseline assessment, the presentation and stability imaging.

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. Hemorrhage volume will be measured using an A x B x C/2 algorithm. A Hemphill score will be assigned based upon the clinical presentation and imaging. 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 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).

Patients meeting all inclusion and no exclusion criteria will be eligible for enrollment after the stability scan.

5.2 Preparation for Treatment

Patients enrolled in the trial and receiving Apollo / Artemis MIES will also receive best medical management in addition to the procedure. 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 managing interventional team to manage ICPs.

Apollo / Artemis MIES will be performed under general anesthesia. The Apollo / Artemis MIES procedure must occur within 72 hours of clinical presentation (ictus). 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 trocar with a working channel which 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 Penumbra Aspiration Systems will be allowed in the study
CT Monitoring (within or outside of OR)	All FDA cleared computed tomography or cone beam computed tomography systems will be allowed in the study.

All medical therapy decisions are recommended to be in accordance with guidelines from the AHA or Critical care guidelines.

The specific types of devices used in each Apollo / Artemis MIES procedure will be recorded in the appropriate 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 that is both technically feasible and allows access to the longest possible axis of the hematoma.

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, Brainlab) 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. This technique of evacuating the hemorrhage from distal to proximal will be performed until the sheath has been withdrawn through the entire long axis of the hematoma as documented on the neuronavigation. At that point, further visualization of the evacuated cavity through the endoscopic may be performed to ensure there is no active bleeding or substantial residual hematoma. Once completed, the neuroendoscopic trocar and Apollo Wand or Artemis Device will be removed. An intra_operative CT (e.g. dynaCT, Siemens, Medical Imaging, Erlangen, Germany) will then be performed using cone_beam CT, an intra-operative 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. The surgical goal is to achieve a 60% reduction in hemorrhage volume AND a final hemorrhage volume of $< 15cc^4$.

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

Standardization of medical management will occur according to the following:

- General medical management according to AHA guidelines[44]
- Admission to monitored or intensive care unit for at least 24 hours
- Close monitoring of BP with treatment according to AHA guidelines[44]
- Follow-up imaging studies as indicated in any patient with neurologic deterioration

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

5.7 Recovery

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

5.7.1 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), a review of any adverse events, and a review of selected current medications. If discharge occurs before 7 days after enrollment, the discharge clinical examinations will also substitute for the 7-day clinical evaluation and a standard of care CT (preferred) or MR will be obtained at that time.

5.8 Hospital Costs

For each subject, overall costs will attempt to 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 collected and assessed, if possible.

5.9 Follow-Up Examination

5.9.1 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 electronic case report forms as well as within the medical record and/or in research source documentation as appropriate.

1. Modified Rankin Scale: 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. Barthel Index: The Barthel Index is an ordinal scale used to measure performance of activities of daily living. A historical Barthel Index score 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.
3. The National Institutes of Health Stroke Scale 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.
4. EQ-5D-5L 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.
5. Stroke Impact Scale: Additionally a quality of life scale outcome measure will be utilized in this study. Quality of life scales are designed to be sensitive to changes in outcome from mild and moderate stroke undetected by other outcome measures. Important parameters not fully interrogated by conventional outcome scales can be assessed byquality of life scales, including emotion, communication, cognition, and social role function. Standard measures, such as the mRS, primarily evaluate physical aspects of stroke outcome, not addressing more relevant quality of life measures. The Stroke Impact Scale is a validated assessment of quality of life specifically in patients with stroke. [45 45 45 45 45 45 4547]

All day 7, discharge, day 90, day 180 and day 360 clinical outcome measures will be assessed by a qualified member of the research or clinical team. The schedule of neurological assessments is listed in Table 1. At each visit, the patient 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.

5.9.2 Cross-Sectional Imaging

All scheduled CT and MR studies will be assessed by a central core lab neuroradiologist. The volume of hemorrhage on the diagnostic scan 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 calcualed either by multiplying the number of CT slices which depict the hematoma by the slide thickness or determined on coronal or sagittal reconstructions.

Hemorrhage volumes will also be assessed using a manual volume measurement technique on the diagnostic scan and all subsequent scans, as defined in the Imaging Manual. Intraventricular hemorrhage will be assessed on each scan and graded according to a modified Graeb score (see the Imaging Manual and Manual of Procedures).

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 post-presentation scan 7 day post presentation scan.

Table 1. Schedule of Events

ACTIVITY	SCREENING /BASELINE	STABILITY SCAN (at least 6 hours post initial CT)	TREATMENT	24 hour post - MIES (+/-12)	DISCHARGE AND /OR 7 DAYS (+/- 1 day)	3 MONTHS (+/- 14 days)	6 MONTHS (+/- 21 days)	1 YEAR or END OF STUDY (+/- 35 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		X			
CTA or MRA	X (or at stability)	X (if not done with Baseline)						
Barthel	Historic					X	X	X
NIHSS	X	X		X	X	X	X	X
GCS	X	X		X	X	X	X	X
mRS	Historic			X	X	X	X	X
Stroke Impact Scale (QOL)						X	X	X
ED-5D-5L						X	X	X
Pregnancy Test if childbearing potential	X	Or X						
Con Medications	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	within 48 hours of test			

5.9.3 Serious Adverse Events

All serious adverse events occurring during the 365 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. 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 90 days of enrollment
- Death within 7 days of enrollment: Immediate periprocedural 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 90 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 Perihematomal Edema: Edema with increased mass effect or uncontrolled ICPs within 90 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, 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 90 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 90 days.

A medical monitor will review these specific categories of events as they are reported. The DSMB will also function as the CEC and will review all of these specified categories of 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. Additional details of the monitoring plan will be included in the study MOP. Additional details regarding the DSMB structure and stopping rules will be included in the DSMB charter.

6. Study Primary Endpoints

The primary objective is to assess the impact of Apollo / Artemis MIES upon clinical outcomes in patients with supratentorial intracranial hemorrhage with primary endpoints defined as:

- Rate of recruitment over a two-year time span following first patient enrollment
- Rate of successful 180 day follow up obtainment.

- Statistical details can be found in section 7.2.

6.1 Analysis of Primary Endpoint

6.1.1 Definition of Analysis Samples

1. Target Population

   The target population for the Apollo / Artemis MIES trial are patients 22-84 years of age who have a diagnosis of spontaneous, non-traumatic, intracerebral hemorrhage (ICH) ranging in volume between 30 and 80 cc, with an associated significant neurological deficit (NIHSS $\geq$ 6) who do not require emergent open surgical decompression related to uncontrolled intracranial pressure or mass effect.

7. General Statistical Considerations

General Design

The Apollo / Artemis MIES Trial is a multicenter, single arm feasibility study investigating the potential efficacy of Apollo / Artemis MIES to improve clinical outcomes in patients with spontaneous, non-traumatic, ICH presenting within 24 hours. The primary hypothesis to be tested is that Apollo / Artemis MIS patients can be recruited and followed successfully for 180 days.

7.1 Sample Size Estimation for the Primary Outcome

Sample Size Calculation

The Apollo / Artemis MIES Trial is a prospective, multi-center, single-arm feasibility trial investigating enrollment of the Apollo / Artemis MIES in patients with spontaneous, non-traumatic, ICH presenting within 24 hours. Up to 50 subjects will be enrolled in this study. The primary outcome assessed at trial completion will be successful capture of 180 day modified Rankin score (mRS) for those 50 patients enrolled in the study. Additionally, we will analyze the proportion of patients achieving mRS of 0-3 and 90 day mortality.

7.2 Statistical Evaluation

Statistical Analysis of Primary Outcome

Two-sided 95% confidence intervals will be calculated for the proportion of subjects with captured mRS scores at the 180-day follow-up visit using the exact binomial distribution.

Statistical Analysis of Secondary Outcomes

Secondary efficacy analyses will include 180-day global disability assessed via mRS, analyzed as the proportion of patients achieving mRS of 0-3. Two-sided 95% confidence intervals will be calculated for the proportion of subjects with mRS scores of 0-3 at the 180-day follow-up visit using the exact binomial distribution. The Kaplan-Meier Curve will be generated to assess the 90 day mortality. With the date of enrollment set at day 0, and any death occurring on or before day 90 will be included as a death.

Subsequent Statistical Analysis

Statistical analysis of the SIS-ADL, SIS-mobility, EQ-5D-5L, and Length of Stay will be analyzed with confidence intervals.

Other pre-specified analyses will be performed as outlined in the statistical plan.

7.3 Missing Data and Imputation Methods

Every effort will 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. Additional details will be provided in the Statistical Analysis Plan (SAP).

7.4 Secondary Statistical Analysis

Statistical analysis of the raw Rankin outcome scores of 0 to 6 (with 5 and 6 collapsed) will be conducted with an adjusted ordinal logistic regression model (proportional odds model). This analysis will be adjusted using key baseline variables. The odds ratio and corresponding 95% confidence interval will be presented for the treatment effect.

Group differences will be analyzed by the non-parametric Wilcoxon rank sum test for the following:

- SIS-ADL
- SIS-mobility
- EQ-5D-5L
- Length of Stay

Other pre-specified analyses will be performed as outlined in the statistical plan.

7.5 Safety Analysis

7.5.1 Safety Outcomes

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 90 days.

7.5.2 Interim Safety Monitoring

7.5.2.1 Stopping the Trial Based on Interim Safety Data

The Trial Operating Committee (TOC) and Data Safety Monitoring Board (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 90 days of enrollment
- Death within 7 days of enrollment: Immediate periprocedural 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 90 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 Perihematomal Edema: Edema with increased mass effect or uncontrolled ICPs within 90 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 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 9s 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 90 days.

Additional details of the monitoring plan will be included in the study MOP. Additional details regarding the DSMB structure and stopping rules will be included in the DSMB charter.

7.6 Blinding

This study is not blinded. Blinding is difficult, if not impossible, from a clinical perspective. It is not possible to blind the Investigator who treats the patient, the clinical staff or the research team. Additionally, physicians treating subjects who experience an adverse event after must know how the hemorrhage was treated in order to effectively report the adverse event and plan further treatment. Blinding the study is not required for interpretation of study 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. Additional details will be specified in the DSMB charter.

10. Trial Operating Committee (TOC)

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 SC 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 enrollment, and/or other non-standard of care study-related assessments;

Providing the 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

At a minimum, the investigational site will provide the following documents to the TOC:

1) Signed Investigator Agreement
2) Written and dated IRB/EC approval,
3) Written and dated IRB/EC approval for ICF document
4) IRB/EC approval for any other written documents to be provided to the study subject (e.g., advertising),
5) HIPAA documentation,
6) *Investigator and Co-Investigators' current Curriculum Vitae,
7) Current medical licenses,
8) Any other relevant documents requested by the TOC or the reviewing IRB/EC or other regulatory authorities,
9) FDA Form 3454 or 3455 (or equivalent) regarding financial interests
10) Fully executed contract.
11) Ongoing IRB approval documents
12) Source Documents for data verification
13) 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), and its representatives. 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 Research Electronic Data Capture, 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 and/or their representatives. 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 within the secure study database.

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. 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 data entry, data validation, project progress monitoring, subject tracking, user customizable report generation and secure data transfer.

15.2 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 will be presented to the TOC 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 track trial progress by reviewing accrual status and CRF status of enrolled subjects. Other assistive tools and available information includes subject enrollment logs, basic subject demographics, CRF completion rate and number of data queries outstanding and resolved.

15.3 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, the risk of a security breach 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, the REDCap system tracks all changes made to any 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 enrollment. Pre-existing conditions 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 enrollment through hospital discharge or 7 days whichever is earlier. Serious adverse events will be recorded from enrollment through the end of study (i.e., 90 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, required treatment, relatedness and duration of the event. 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 enrollment through Day 7 or hospital discharge (whichever occurs first). Serious adverse events will be recorded from enrollment through the end of study (i.e., 90 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 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, in order for it to be reported 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 system, an experienced clinical research group will perform on-site and centralized monitoring for the trial. Sites will be responsible for uploading all applicable source documents into the REDCap system. MSMC staff and

their representatives 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 2013) 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, at minimum, key outcome and safety data will be reviewed against source documents. 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 final data analysis. 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 policies are monitored for all subjects. Additional monitoring verification will include: ongoing evaluation of the adequacy of site facilities and staff, site recruitment, the presence of regulatory documents, and specific review of documents and data as requested by the MSMC staff and their representatives. 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 and their representatives to determine if there is a need to monitor more frequently and/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 via the REDCap 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 and their representatives. 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 practical. Only users with password-protected REDCap access will have the ability to view study data within the secure REDCap database. The Primary Investigator, Sponsor, the Sponsor's representatives, 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.

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 the 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).

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