Chapter 13.0 Detailed Protocol (version 7; dated 22 DEC 09)

Table of Contents

13.1 Participating Centers

MISTIE Participating Centers (Stage 1: Tiers 1 and 2, and Stage 2 only)

	Institution	Principal Investigator(s)
1.	The Johns Hopkins University Johns Hopkins Bayview Medical Center Baltimore, MD	Judy Huang, MD
2.	The University of Cincinnati Cincinnati, OH	Mario Zuccarello, MD
3.	Medical University of South Carolina Charleston, SC	Dilantha Ellegala, MD
4.	Mount Sinai Medical Center New York, NY	Joshua Bederson, MD
5.	Virginia Commonwealth University Richmond, VA	William Broaddus, MD, PhD
6.	Loyola University Medical Center Maywood, IL	Michael Schneck, MD
7.	The University of Chicago Chicago, IL	Issam Awad, MD
8.	University of Maryland Baltimore, MD	E. Francois Aldrich, MD
9.	Montreal Neurological Institute at McGill University Montreal, QC Canada	David Sinclair, MD
10.	Stanford Medical Center Palo Alto, CA	Christine Wijman, MD
11.	New Jersey Neuroscience Institute at JFK Medical Center Edison, NJ	Martin Gizzi, MD, PhD
12.	Rush University Medical Center Chicago, IL	Richard Temes, MD, MS
13.	Bronson Methodist Hospital Kalamazoo, MI	Dean Kindler, MD, MA
14.	Georgetown University Washington, DC	Chelsea Kidwell, MD
15.	Baylor College of Medicine Houston, TX	To be determined
16.	Duke University Medical Center Durham, NC	Carmelo Graffagnino, MD

17.	St. Lukes Hospital Kansas City, MO	Paul Camarata, MD
18.	Temple University Philadelphia, PA	Christopher Loftus, MD
19.	University of Alabama at Birmingham Birmingham, AL	J. Ivan Lopez, MD
20.	University of Texas Health Sciences Center, San Antonio San Antonio, TX	Jean-Louis Caron, MD
21.	Mayo Clinic, Jacksonville Jacksonville, FL	Ronald Reimer, MD William Freeman, MD
22.	Hartford Hospital Hartford, CT	Inam Kureshi, MD
23.	Allegheny General Hospital Pittsburgh, PA	Khaled Aziz, MD, PhD
24.	Newcastle upon Tyne Hospital Newcastle, UK	A. David Mendelow, MD
25.	Cambridge University Cambridge, UK	Peter Kirkpatrick, MD
26.	University of Heidelberg Heidelberg, Germany	Thorsten Steiner, MD
27.	University of Goettigen Goettigen, Germany	Veit Rohde, MD
28.	Univeristy of Erlangen Erlangen, Germany	Juergen Bardutzky, MD

MISTIE-ICES Participating Centers (Stage 1: Tier 3 Only)

	Institution	Principal Investigator(s)
1.	University of California, Los Angeles Los Angeles, CA	Paul Vespa, MD Neil Martin, MD
2.	Massachusetts General Hospital Boston, MA	Christopher Ogilvy, MD Bob Carter, MD, PhD
3.	Pittsburgh Medical Center Pittsburgh, PA	Jonathan Engh, MD Lawrence Wechsler, MD
4.	Fairfax INOVA Fairfax, VA	James Leiphart, MD
6.	Columbia-Presbyterian Medical Center New York, NY	E. Sander Connolly, Jr., MD

7.	Thomas Jefferson University Philadelphia, PA	Jack Jallo, MD
8.	Case Western University Cleveland, OH	Alan Hoffer, MD
9.	Butterworth Hospital Grand Rapids, MI	Lawrence Foody, MD

13.2 Background Information

13.2.1 Investigational Product

The MISTIE arms are designed to investigate the safety of minimally invasive surgery plus aspiration followed by the administration of a low dose of recombinant tissue plasminogen activator (rt-PA; Activase, Genentech, Inc., San Francisco, CA) to intracerebral hemorrhage patients (ICH) via a catheter/cannula inserted directly into the clot versus medical management. The Study Chair holds an IND for clot lysis with this drug specific to this protocol.

Tissue plasminogen activator as found in tissue or in the melanoma cell line is a serine protease glycoprotein varying in molecular mass from 63,000 to 65,000 daltons. The molecular mass variation reflects heterogeneity due to different patterns of glycosylation. It contains an amino-terminal region that has a high degree of sequence homology with the "kringle" regions of plasminogen (Sottrup-Jensen et al. 1978) and prothrombin. A kringle is a characteristic triple disulfide structure originally described in the "pro" fragment of prothrombin (Magnusson et al. 1975). The amino-terminal region may be responsible for the fibrin-specific activation of t-PA. The carboxy-terminal end of the molecule contains a domain responsible for the protease activity of t-PA. t-PA is a mixture of one-chain and two-chain forms. The composition depends on the amount of proteolysis that takes place during manufacturing.

Activase® (Alteplase, recombinant; recombinant tissue plasminogen activator, rt-PA) is commercially available as a lyophilized powder for reconstitution in 100- and 50-mg vials and in 2-mg vials as Cathflo®.

In the ICES arm, twenty subjects will be randomized between endoscopic removal of the ICH (n=15) and medical management in tier 3 of the protocol at a select number of enrolling centers. These subjects will be compared to those subjects undergoing minimally invasive surgery plus aspiration followed by administration of rt-PA. The central aim of tier 3 is to demonstrate that **I**ntraoperative stereotactic **C**T-guided **E**ndoscopic **S**urgery **(ICES)** is a feasible, safe, and technically effective treatment for patients with acute intracerebral hemorrhage.

13.2.2 Clinical and Non-Clinical Findings

Intracerebral parenchymal hemorrhage (ICH) accounts for 10-20% of the 500,000 strokes per year in the United States.[1,7,8,21,36] Unfortunately the incidence of ICH has not decreased over the last 2 decades and the mortality rate in these cases ranges from 40-60%.[15,32,36,43] This mortality rate is up to six times higher than that for ischemic stroke.[11] Level of consciousness on admission and size of hematoma repeatedly correlate with outcome in ICH.[5,6,22] In an attempt to improve upon the dismal outcome many neurosurgeons have operated to evacuate or at least decrease the size of the hematomas. Unfortunately the early results were not shown to be beneficial and the option of medical versus surgical therapy remains controversial. Although past studies have shown no difference or even worsened outcome in surgical treatment careful scrutiny of the data shows that many of these studies are retrospective and that the hematoma sizes were often larger and the admission GCS scores worse in the surgically treated groups.[3,4,14,16,19,46,54] Additionally, timing of surgical evacuation was often delayed beyond 48 hours after the bleed.

More recent studies have revisited the issue of early surgical intervention with a more favorable result. Becker et al. reported that non-surgical therapy as well as size of hematoma was independently associated with intra-hospital death ($p<0.001$ and $P<0.025$ respectively).[5] In an attempt to improve mortality many authors have tried to decrease the size of the hematoma surgically. Morgenstern et al. randomized ICH patients to open craniotomy within 12 hours of bleed versus medical therapy.[35] They showed that at 1 month the mortality rate in the surgical group was 6% compared with 24% in the medical group and mortality at 6 months was 17% and 24% respectively. Zuccarello et al. were unable to find a difference in mortality rate.[57] However they did report a trend towards a higher percentage of patients having good outcome in the surgically treated group (56% surgical versus 36% medical) at 3-month functional outcome assessment as measured by the Barthel Index, Rankin Scale and NIH Stroke Scale.

Another factor that may account for the overall poor surgical outcome in prior studies may be location of hematoma. Hematomas of spontaneous ICH are centered mainly in the putamen (50-55%), thalamus (10-15%) or subcortical lobar locations (30-40%). Lampl et al. reported that in medically managed ICH, thalamic hematomas were associated with an overall worse outcome.[22] But Tuhrim et al. could demonstrate no effect of hematoma location on outcome.[51] From a surgical perspective, evacuation of deep hypertensive putaminal and thalamic hematomas necessitate the damage of normal overlying cortical tissue and possibly in itself can cause a worse outcome. Lobar hematomas usually damage some overlying cortex thus minimizing further surgical injury to cerebral cortex.

A study by Auer et al. showed that endoscopic surgical evacuation of subcortical bleeds resulted in a significant decrease in mortality (30% surgical vs. 70% medical) as well as a better functional outcome (40% surgical vs. 25% medical).[3] It is possible to postulate that endoscopic evacuation is less invasive and therefore resulted in less morbidity and mortality. Prasad et al.

in fact reported an increase in morbidity and mortality from craniotomy when compared with medical management and a decreased rate of poor outcome in those treated endoscopically.[41] Morganstern et al. demonstrated similar findings of increased surgery-related mortality in a cohort of ICH patients treated with ultra-early surgery.[35] In contrast, Peresedov reported that patients with hematomas evacuated by craniotomy had an overall mortality of 42.5% compared with a rate of 21.9% in those whose hematomas were drained stereotactically.[40] While it still remains unclear as to the overall benefit of surgery in relation to lesion location, what is clear from the literature is that surgery is definitely not helpful in improving outcome in patients with hematomas <9-10cm^3 in volume regardless of location.[3,17,24]

As a further adjunct to standard therapy, thrombolytics are being used increasingly with much reported safety and success for decreasing clot size in intracranial hemorrhage conditions. The safety and efficacy of urokinase has been well documented in cases of IVH including those with large hematomas casting all 4 ventricles.[2,9,48,50] Following craniotomy and aneurysm clipping several authors have also instilled rt-PA intrathecally for the treatment of SAH without complications. This treatment results in a rapid resolution of hematoma size and a significant decrease in clot associated complications.[47,49,53] Wagner et al. and Deinsberger et al. reported t-PA use in lysis and clot aspiration and reduction in cerebral edema in ICH porcine and rat models.[10,55] Recently similar findings have been reported for a series of ICH patients treated with thrombolytics as an adjunct to standard therapy. These studies have documented the feasibility and success of CT-guided / stereotactic catheter aspiration of intracerebral hematomas with and without the use of low-dose thrombolytics although no controlled studies have yet been reported.[18,20,26,29,33,34,45,52] Procedure-related mortality for image-guided catheter placement is less than 5% mortality. Thrombolytics instilled via a small catheter placed under CT scan stereotactic guidance (or MRI image-based guidance) into the ICH in patients followed by clot aspiration may provide an effective way of minimizing cortical injury as well as rapidly decreasing the size of the hematoma. This would occur without subjecting the patient to the risks of general anesthesia and craniotomy. This in turn could facilitate more rapid and complete recovery of function and decreased mortality from this condition.

Addition of the MISTIE-ICES arm (Tier 3): The MISTIE study leadership agreed to partner with the ICES Surgical Center investigators in order to compare the safety profiles of endoscopic surgery (immediate clot removal via a larger operation) with that of stereotactic thrombolysis (slower removal via a smaller operation). This partnership and the addition of the ICES arm as tier 3 were approved by the MISTIE DSMB and the NINDS. Imaging biomarkers (computerized tomography and magnetic resonance imaging (MRI)) and clinical determinants will be used to determine if minimally invasive endoscopic hematoma removal results in immediate harm to the brain. Patient outcomes will be compared between ICES and MISTIE cohorts.

13.2.3 Potential Risks

The adverse events associated with systemic use of Activase are well described and consist

primarily of bleeding complications, including serious major hemorrhagic events and ICH. The incidence of these bleeding complications has been quantified in patients receiving relatively large doses of Activase for acute myocardial infarction, acute ischemic stroke, and pulmonary embolism. Any potential bleeding attributable to Activase is most likely to occur within 24 hours of treatment and is unlikely to occur after 72 hours.

Subjects assigned to the surgical intervention have an increased risk of death, infection, hemorrhage extension, and new hemorrhage as compared to subjects assigned to conventional medical management. These risks may increase in the endoscopic group because of the increased number and surgical vigor of the attempts to extract clot from brain tissue.

To minimize these risks, all subjects will be stabilized for at least 6 hours prior to the initiation of the surgical intervention, all surgical instruments and cannula/catheters will be inserted and manipulated for clot removal and/or drug administrations using the standard intensive care unit (ICU) infection risk-reduction protocol, and blood pressure will be controlled during the 72-hour treatment period.

13.2.3.1 Potential Benefits

There is no controlled evidence at this time to support the use of endoscopic surgery or combined stereotactic surgery and rt-PA induced clot lysis as beneficial for ICH. Some case series suggest these approaches have a beneficial effect on mortality.

13.2.4 Choice of Thrombolytic and Dose

Three agents were approved for systemic fibrinolysis therapy: streptokinase, urokinase, and rt-PA. Urokinase has been used in the most detailed animal model of intraventricular thrombolysis.[37,39] There were no hemorrhagic complications or long term pathologic or histology changes on postmortem evaluation. Mayfrank has demonstrated similar clot resolution using rt-PA in pigs. Clinical studies with urokinase and rt-PA exist and have been summarized under Section 2.2.[2,12,13,32,44,48,50] We are not aware of any animal models of ICH treatment with streptokinase or of any clinical studies of intracerebral streptokinase injections. Moreover, antigenicity is another consideration. Streptokinase is a foreign substance that can cause a systemic allergic reaction; urokinase and rt-PA are human proteins and are not considered antigenic. For these reasons rt-PA was selected.

A dose finding protocol will be performed first to evaluate successive doses of rt-PA (0.3 mg in tier 1 and 1.0 mg in tier 2) administered via a soft catheter inserted into the core of the ICH. In a previous clinical trial of IVH thrombolysis, a dose of 3 mg every 12 hours was used as the initial baseline dose to test safety for the following reasons. No studies have evaluated the kinetics of rt-PA activity in the normal human CSF or the ICH cavity. Indeed such a study cannot be ethically performed in an individual without disease-related access to the ICH or IVH. Animal

model data have not been available to definitively establish dose. The best available animal study of intraventricular thrombolysis was performed by Pang et al.,[37,39] in which 20,000 IU of urokinase was administered every 12 hours until evidence of clot resolution was obtained. The clots treated in that study had a mean volume of 6.9 cc,[38] clots that were present in the patients with IVH in our natural history study (n = 17) who had treatment with EVD (n=9, 53%) had a mean volume of 38.6 cc. Although it is difficult to translate dosing in the canine model to this study, the proposed doses appear to be conservative, given the differences in clot volumes expected to be treated. The proposed doses are also within the range of dosages reported in the clinical series cited previously,[2,12,13,30,44,48,50] none of which reported substantial rates of hemorrhagic complications. The proposed doses are also significantly less than the recommended dose for use in acute ischemic stroke (0.9 mg/kg intravenously over 1 hour; not to exceed 90 mg for a 70-kg adult). The usual dose of rt-PA for coronary artery thrombolysis is 100 mg IV (AHFS Drug Information) while the usual dose of urokinase for coronary artery thrombolysis is 500,000 to 1,000,000 IU.[27,28] This implies an approximate efficacy ratio of 1 mg of rt-PA to 5,000-10,000 IU of urokinase for coronary thrombolysis. If this ratio is applied to the indication of ICH clot lysis, the proposed doses of up to 3 mg of rt-PA is consistent with a previously approved dose for urokinase, which was 25,000 IU.

The half-life of rt-PA in the ICH clot cavity or the CSF in the ventricles is currently undefined. It is unknown whether rt-PA is totally and immediately bound to fibrin clot or whether free rt-PA exists for some time after administration. Since bulk CSF flow is much slower than blood flow, the CSF half-life is probably significantly longer than the 26.5-minute half-life in the terminal elimination phase of rt-PA from the peripheral arterial circulation, but it is almost certainly much shorter than the 12-hour dosing regimen we have previously used (AHFS Drug Information). The only study of rt-PA half-life in the CSF was performed in subarachnoid hemorrhage patients not dissimilar to our ICH patients and demonstrated a half-life of 2 to 3 hours.[56] The optimal method of delivering a drug with a short half-life is by constant infusion, which is used most often for rt-PA in the peripheral and coronary circulation (AHFS Drug Information), in which we have tested for safety. Constant infusion of any agent into the CSF or ICH cavity, however, poses several difficult problems. The risk of ventriculitis and cerebritis would be significantly increased by a constant infusion versus an intermittent injection; the infusion rate would have to be extremely slow to avoid raising the ICP; and the consequences of an unintended increase in the rate of the infusion due to pump malfunction or human error could be disastrous. Thus, intermittent injections appear to be the safest route of administration. The optimal interval between injections is unknown. The worthwhile attempt to achieve a constant state of drug saturation with more frequent injections must be balanced by the risk of a catheter-related infection, which is potentially increased by the number of times the catheter is manipulated.[32] The dosing interval of 8 hours balances potential efficacy against the most frequent complication, infection. Because the study is limited to three or less days the total number of catheter openings will be similar to those in our previous IVH treatment safety study, which has a 5.9% rate of ventriculitis.

Clot lysis will be attempted by administering rt-PA through a catheter directly into the middle of the ICH. Depending on dose tier assignment, a dose of 0.3 mg or 1.0 mg of rt-PA will be injected into the catheter every 8 hours for up to 9 doses or until the residual clot approaches 10 cc in size or is reduced to 20% of the initial clot volume as measured on the stability CT scan. After each injection, the system will be flushed with normal saline. The drainage system is then clamped closed for 60 minutes before opening to spontaneous drainage at the level of the head until the next injection. The optimal dose of rt-PA will be administered to patients randomized to the surgical intervention in the safety study (n=25) using the same administration protocol compared to medical management (n=25).

Subjects enrolled in tier 3 of the protocol will be randomized between endoscopic surgery (n=15) and medical management (n=5). These subjects will not receive rt-PA administrations. All other aspects of the protocol remain the same in respect to data collection, stability protocols, and safety and outcome assessments. Study centers enrolling subjects in tier 3 are excluded from enrolling subjects in tiers 1 and 2 of the protocol.

If residual hematoma volume on daily CT scan continues to exceed 10 cc or 20% of the initial volume as measured on the stability CT scan, then instillation of the next dose of rt-PA will occur every 8 hours until hematoma volume falls to one of these thresholds or 9 injections (approximately 72 hours) have been performed. In the ICES arm, aspiration will stop at the surgeon's discretion when the aspirate volume is equal to 80% of the baseline clot volume or approaches 10 cc in size.

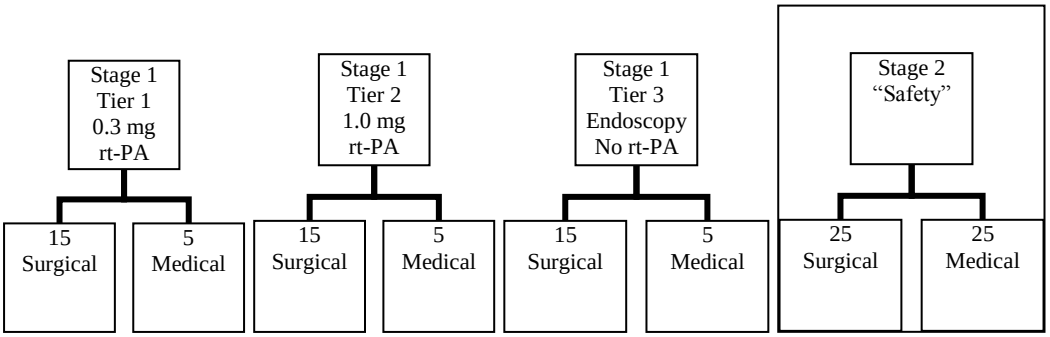
13.2.5 Regulatory Compliance

The administrative and clinical aspects of the study will be conducted to ensure compliance with the protocol and Title 21 of the United States Code of Federal Regulations (CFR) Good Clinical Practices (GCP) and International Conference on Harmonization (ICH) GCP Guideline E6, Section 5 as well as local applicable regulatory requirements.

13.2.6 Study Population

The study population will include 110 subjects and approximately 36 run-in subjects, (approximately 1 per study center); dose finding study, n=40 subjects: 3:1 randomization in each of two tiers (15 surgical and 5 medical); 3:1 randomization in one tier of endoscopy (15 surgical and 5 medical); and safety study, n=50 subjects: 1:1 randomization (25 surgical and 25 medical) across approximately 36 study centers with supratentorial ICH without suspected underlying structural etiology (tumor, vascular malformation or aneurysm). Subjects will be identified and recruited through the Emergency Department, clinical stroke service, and direct admissions to the Neurocritical Care Unit at each study center.

Minimally Invasive Surgery plus rt-PA for ICH Evacuation
MISTIE



13.2.7 Background Literature and Data

Two overviews of this issue are Qureshi et al.[42] and Lapointe et al.[23]

13.3 Trial Objectives and Purpose

The purpose of this trial is to determine the safety of using either endoscopic surgery or a combination of minimally invasive surgery and clot lysis with rt-PA to remove ICH. The procedures are to use image-based surgery (MRI or CT) to provide catheter access to ICH for the intervention, which is either a one-time clot aspiration followed by instillation of rt-PA over approximately 72 hours or two clot aspirations using endoscopic technique. We propose to test if these interventions facilitate more rapid and complete recovery of function and decreased mortality from this condition compared to conventional medical management without subjecting the patient to craniotomy. The specific objective of this trial is to test the safety of these interventions and assess their ability to remove blood clot from brain tissue.

13.4 Trial Design

13.4.1 Study Endpoints

The primary endpoints of the trial are safety related and are as follows:

1) 30-day mortality
2) Procedure related mortality
3) Incidence of cerebritis, meningitis
4) Rate of symptomatic rebleeding

The secondary endpoints of the trial will determine surrogate efficacy and are as follows:

1) Rate of clot size reduction at Days 4-5 determined by CT scans; absolute clot size reduction at Day 4-5

2) 30, 90,180, 270, & 365 day GOS, extended GOS, modified Rankin Scale, Stroke Impact Scale
3) Post-operative size reduction

13.4.2 Trial Design and Procedures

This study is a multicenter evaluation of minimally invasive surgery and ICH lysis with rt-PA versus endoscopic removal of ICH vs. medical care. The dose finding stage (n=40) will be done in two tiers and evaluate the safety of minimally invasive surgery plus one of two doses of rt-PA, 0.3 mg (tier 1) or 1.0 mg (tier 2), administered every 8 hours for up to 9 doses. Tier 3 will determine the risks and benefits of early, aggressive mechanical removal of hematoma. These results will be combined with those of tiers 1 and 2 to determine the optimal protocol for the final safety evaluation. There will be an interruption of enrollment between tiers 1 and 2 to evaluate safety and rate of clot resolution. The safety study stage (n=50) will compare the optimal minimally invasive surgery technique and/or the optimal dose from the dose finding tiers with conventional medical management. Endpoint assessment will be performed by blinded investigators.

Trial procedures are diagrammed in sections 13.17.1.a and 13.17.1.b.

13.4.3 Bias

All eligible patients who agree to participate in the study will be randomized to either medical or surgical management to minimize treatment bias. To avoid bias during the collection and analysis of the data related to the primary endpoints, an examiner (investigator, coordinator, or designee) blinded to treatment assignment will perform the 30, 90, 180, 270 and 365-day follow-up visits.

13.4.4 Treatment Protocol

Subjects in both groups, medical management and surgical management, will be treated medically using standard ICU protocols. This includes but is not limited to the following guidelines:

1. Intracranial pressure (ICP) management. The American Academy of Neurological Surgery's (AANS) Head Injury Guidelines will be used as the standardized approach for both the medical and surgical treatment groups. This approach has been previously employed. (Clifton GL, Miller ER, Choi SC, et al: Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 344:556-563, 2001) Intracranial hypertension is defined as pressure within the cranial vault elevated $\geq$ 30 mm Hg for five or more minutes. A patient will be monitored if he or she demonstrates obtundation, which we define as GCS less than or equal to 8 on a minimum of two observations over eight hours of time. All eligible patients will be monitored, independent of

medical or surgical treatment. The treating surgeon will use standardized clinical criteria to select the ICP monitoring device. The Camino parenchymal catheter has been pre-specified as the device of choice. However the intraventricular catheter could be a choice, if it offers clinical advantage in the presence of non-compressed ventricles, or a subarachnoid screw could be chosen, if there is risk of infection. The ICP monitor would ideally be placed prior to tPA administrations or at least three hours after dosing. A new CT scan must be obtained after ICP monitor placement to assess stability of the current hemorrhage and to monitor for any new bleeding. Nursing assessments and ICP monitoring will be performed on an hourly basis, as will routine zeroing and recalibration of the system. The goals of ICP management are to sustain intracranial pressure below 20 mm Hg and to improve the patient's level of consciousness. Interventions include: 1) head positioning (usually 30^o elevation HOB), 2) euthermia with core temperature $\leq 38^o$, 3) normoxia and normocapnia, and 4) sedation and analgesia, to maintain HR $\leq$ 120 with concurrent absence of agitated motor activity. When standard interventions are not effective, mannitol in doses of 1 gm/kg load and 0.25 gm per kg maintenance will be administered. In response to acute sustained ICP elevation ($\geq$ 40 mm Hg or refractory ICP elevation), hyperventilation to a $PaCO_2 \leq 25$ mm Hg will be performed. Ventilation parameters, including F_iO_2 and tidal volume, respiratory rate, and ventilation mode, will be set to produce $SaO_2 > 90\%$ saturation and mean airway pressures $\leq$ 20 cm H_2O. Prolonged sedation with propofol will be used for transient or sustained ICP $\geq$ 30 mm Hg, where agitation is deemed a possible factor. Surgical management of uncontrollable ICP to control ICP is allowed but not encouraged in the absence of full medical therapy. Surgery may be considered if hemorrhage extension or rebleeding occurs, if ICP $\geq$ 30 mmHg, with optimal medical management, for acute compartment syndrome, or other life-saving consideration. When ICP is controlled at $\leq$ 20 mm Hg for one or more days, sequentially withdraw treatment modalities from highest level of intervention to lowest level of intervention. Every effort will be made to avoid long term hyperventilation, in keeping with the AANS head injury guidelines (American Association of NS: Guidelines for the management of severe head injury. Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care. J Neurotrauma 13:641-734, 1996) and the ASA ICH treatment guideline statement.(Broderick JP, Connolly S, Feldman E: Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 38:2001-2023, 2007). ICP treatment will be scored using the validated American Brain Injury Consortium Therapeutic Intensity Level (TIL). The TIL will be assessed hourly or as clinically indicated.

2. Neurological status will be assessed hourly using GCS scoring. The GCS goal is 15 or 10T sustained for 8 hours of observation. A neurological deterioration (neuroworsening) will be defined as any GCS decrease of 2 or more points on the motor scale sustained for 8 hours without sedation. Sedation will be used for agitation. The sedations of choice are Propofol or Lorazepam 0.5 mg, IV, q 1-2 hr., to maintain a sedation score of 1. Daily attempts to discontinue sedation will be made. A daily neurologic exam is recommended to be coordinated with this attempted sedation withdrawal. Sedation will be discontinued when ICP is successfully

controlled. ICP monitoring devices will be removed when ICP is maintained < 20 mm Hg without pharmacological therapy.

3. Cardiovascular management will be directed towards the goal of maintaining BP ≤ 160/90 with long acting oral and supplementary IV medications. Beta-blockade with Metoprolol, 20 to 80 mg IV q 8 hrs, will be the primary therapeutic modality. Transient elevations of BP > 160 mm Hg will be treated with labetalol 5-10 mg IV. A second agent will be initiated where coronary artery disease is suspected by EKG or by historical criteria. Where renovascular hypertension appears likely, the angiotension converting enzyme inhibitor enalapril will be administered. When necessary for sustained BP control, a constant infusion of esmolol will be the first line drug, heart rate permitting (HR ≥ 90 beats per min).

4. Respiratory care will be directed at promoting adequate oxygenation without airway compromise, with full pulmonary inflation, and with oxygenation ≥ 90% on room air or supplemental O_2 by face mask of 28% or less. A trial of independent breathing will be undertaken and/or the level of mechanical ventilatory support will be diminished, when no pooled secretions exist, the LOC is ≥ 10 GCS points, and oxygenation is sustained. The absence of ongoing ICP elevation and the presence of independent sustained mechanical ventilatory activity for > 12 hours will be considered sufficient criteria to consider removal of the endotracheal tube in all patients with intact airway reflexes.

5. Nutritional support will consist of optimal calories, defined as ≥ 30 kcal/kg and 1.5 gm protein/kg. Feeding will be achieved by the least invasive means necessary, but with the goal of reaching full nutritional support by no later than day 7 of illness. Ranitidine and/or reglan may be used to suppress gastric acid. For patients with persistent ileus, after pharmacologic motility enhancement for > 48 hours, a trial of parenteral nutrition will be undertaken. The presence of established independent ventilation and the absence of aspiration on bedside swallowing tests will be considered the necessary prerequisites for a trial of oral feeding. Enteral or parenteral feeds will not be discontinued until a minimum of 80% of daily caloric needs is consistently met by oral intake.

6. Deep venous thrombophlebitis and pulmonary embolus prophylaxis will be undertaken on the day of admission with the use of sequential compression devices (SCDs). For patients at high risk of thromboembolism, low dose subcutaneous heparin (criteria established by the American Orthopedic Association) can be initiated 48 hours after termination of intracerebral t-PA therapy for those subjects randomized to surgical management.

7. Withdrawal of care discussions of prognosis and decisions to continue or limit, or to withdraw, life-sustaining interventions will be conducted according to each institution's policies for end-of-life decision-making, as well as their institutional codes of medical ethics. These discussions are the sole responsibility of the attending physician. In those circumstances where the subject's attending physician is also an investigator on this protocol, a conflict-of-interest for the attending physician may exist. In these situations, the investigator is encouraged to select a

colleague to serve in the clinician role or request a review by the hospital's ethics committee or other knowledgeable expert.

Subjects randomized to the MIS management arm in tiers 1 or 2 of the study will receive injections of rt-PA every 8 hours up to 9 doses via a catheter inserted into the ICH. After each injection the system will be flushed with normal saline. The drainage system is then clamped closed for 60 minutes before opening to spontaneous drainage at the level of the head until the next injection.

If residual hematoma volume on daily CT scan continues to equal or exceed 10 cc or 20% of the initial clot volume as measured on the stability CT scan, then instillation of the next dose of rt-PA will occur every 8 hours until hematoma volume falls below this threshold and/or 9 treatments have been performed. Injections should be discontinued if the catheter side ports no longer engage the clot.

CathFlo® (rt-PA, Genentech, Inc., San Francisco, California) is a sterile, white to pale yellow, preservative-free lyophilized powder for intracatheter administration after reconstitution with sterile water for injection, USP. CathFlo® is supplied in 2.2-mg vials; each reconstituted vial will deliver 2 mg of Alteplase. It is important that CathFlo® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing Alteplase 1mg/ml at approximately pH 7.3. The rt-PA will be prepared in a syringe labeled for investigational use that will be delivered to the ICU. See the CathFlo® Package Insert for information on the use of CathFlo® and for additional product information.

Lyophilized CathFlo® is stored refrigerated at temperature 2-8 degrees C and protected during extended storage from excessive exposure to light.

Subjects enrolled in the ICES arm (tier 3) of the study will not receive injections of rt-PA.

13.4.5 Study duration

The study is proposed to require 6 years. All subjects will be followed daily for 5 days post test intervention (6 days for medical intervention) regardless of treatment assignment. Subjects randomized to receive the surgical intervention in tiers 1 and 2 will undergo a one-time aspiration of clot followed by up to 9 drug administrations. Subjects randomized to receive the surgical intervention in tier 3 will undergo aspirations at two locations to remove as much of the visible clot as possible. Aspiration will stop when the aspirate volume is equal to 80% of the baseline clot volume. All subjects will be required to attend follow-up clinic visits at 30, 180, and 365 days after onset of ICH. A telephone follow-up will occur at 90 and 270 days.

13.4.6 Early Stopping Rules

A subject will have rt-PA administrations discontinued (tiers 1 and 2) or additional aspirations discontinued (tier 3) for any of the following reasons:

1) The ICH volume is reduced to 10 cc or 20% of the initial clot volume as measured on the stability CT scan. (surgical endpoint)
2) The subject receives 9 doses of rt-PA. (surgical endpoint; tiers 1 and 2 only)
3) Clinically significant rebleeding. (treatment failure)
4) Uncontrolled coagulopathy defined as INR > 1.3 (treatment termination)
5) In the investigator's judgment, withdrawal from the trial would be in the patient's best interest. (treatment failure)
6) The patient withdraws consent.

13.4.7 Drug Accountability (Tiers 1 and 2 only)

The following measures will be taken for drug accountability of study medications:

1. The investigational product is Recombinant Tissue Plasminogen Activator (CathFlo Activase®), which is manufactured by Genentech, Inc. CathFlo Activase® is stored refrigerated at 2-8° (36-46°F). Refrigerator temperature monitoring logs must be maintained for the time period that investigational product is stored at the site.

2. Each drug kit will be individually labeled; accountability for each kit will be emphasized at the training sessions.

3. Investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from the official study sites by authorized personnel according to local regulations.

4. All drug shall be dispensed in accordance with the authorized prescriber's prescription.

5. A drug accountability form will be provided to the site. This form will be used to document all investigational product transactions (i.e., receipt of drug, dispensings, wasted doses, etc.). This documentation will be maintained at the site however, copies will be requested at the end of the study.

6. Drug accountability will be checked during monitoring visits and via telephone pharmacy audits;

7. The study site will return all unused study medication to the Sponsor or its designee;

8. The total of amount of rt-PA administered will be recorded on the case report forms.

13.4.8 Randomization Codes

Patients will be randomized using a web-based enrollment system. Periodic monitoring of gender specific rates of recruitment will be carried out and recruitment criteria will be adjusted if necessary to ensure that women make up approximately one-half of all subjects. Dose-finding study: Patients will be randomized using a 3:1 schedule to receive the surgical intervention plus injections of 0.3 mg (tier 1) or 1.0 mg (tier 2) of rt-PA (depending on the dose-tier open at the time of enrollment) every 8 hours for up to 9 doses or to receive conventional medical management only. In tier 3, subjects will be randomized using a 3:1 schedule to receive the surgical intervention of endoscopic removal of the ICH or to receive conventional medical management only. Within each tier, clot size specific randomization schedules will be used: one for ICH greater than or equal to 20 cc and less than or equal to 40 cc; and one for ICH greater than 40 cc as measured on the initial (diagnostic) CT. Blocks of 4 patients will be employed within each schedule to ensure a 3:1 ratio. Safety Study: Patients will be randomized using a 1:1 schedule to receive the optimal surgical intervention plus the optimal dose from the dose-finding study or to receive conventional medical management only. Within each group, clot size specific randomization schedules will again be used: one for ICH greater than or equal to 20 cc and less than or equal to 40 cc; and one for ICH greater than 40 cc as measured on the initial (diagnostic) CT. All treatments are unblinded. It is impossible to blind the treatment assignment for subjects due to the nature of the protocol. The examiner performing the 30, 90, 180, 270, and 365 day follow-up assessments will be blinded to the treatment assignment of each subject.

13.4.9 Source Data

All data related to the initial surgical procedure, the reading of all image scans, and all follow-up visits will be recorded directly onto the electronic CRF and considered source data. All rt-PA administrations will be recorded in the patient's permanent medical record.

13.5 Selection and Withdrawal of Subjects

13.5.1 Inclusion Criteria

1. Age 18-80
2. GCS $\leq$ 14 or a NIHSS $\geq$ 6;
3. Spontaneous supratentorial ICH $\geq$ 20cc;

4. Symptoms less than 12 hours prior to diagnostic CT scan (an unknown time of symptom onset is exclusionary);
5. Intention to initiate surgery within 48 hours after diagnostic CT;
6. First dose can be given within 54 hours after diagnostic CT (delays for post surgical stabilization of catheter bleeding or because of unanticipated surgical delay are acceptable with approved waiver from the coordinating center) [Does not apply to Tier 3: ICES];
7. Six-hour clot size equal to the most previous clot size + 5 cc (as determined by additional CT scans at least 6 hours apart (A*B*C)/2 method);
8. SBP < 200 mmHg sustained for 6 hours recorded closest to the time of randomization;
9. Historical Rankin score of 0 or 1;
10. Negative pregnancy test.

13.5.2 Exclusion Criteria

1. Infratentorial hemorrhage (any involvement of the midbrain or lower brainstem as demonstrated by radiograph or complete third nerve palsy);
2. Patients with platelet count < 100,000, INR > 1.3, or an elevated PT or APTT (reversal of coumadin is permitted but the patient must not require coumadin during the acute hospitalization). Irreversible coagulopathy either due to medical condition or prior to randomization (patient must have a sustained INR ≤ 1.3 using short- and long-acting procoagulants [such as but not limited to NovoSeven, FFP, and/or vitamin K]);
3. Clotting disorders;
4. Any concurrent serious illness that would interfere with the safety assessments including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic, and hematologic disease;
5. Patients with a mechanical valve;
6. Patients with unstable mass or evolving intracranial compartment syndrome;
7. Ruptured aneurysm, AVM, vascular anomaly, Moyamoya disease;
8. Irreversibly impaired brainstem function (bilateral fixed, dilated pupils and extensor motor posturing), GCS less than or equal to 4;
9. Intraventricular hemorrhage requiring external ventricular drainage;
10. Internal bleeding, involving retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts [Does not apply to Tier 3: ICES];
11. Superficial or surface bleeding, observed mainly at vascular puncture and access sites (e.g., venous cutdowns, arterial punctures) or site of recent surgical intervention [Does not apply to Tier 3: ICES];
12. Known risk for embolization, including history of left heart thrombus, mitral stenosis with atrial fibrillation, acute pericarditis, or subacute bacterial endocarditis [Does not apply to Tier 3: ICES];

13. In the investigator's opinion, the patient is unstable and would benefit from a specific intervention rather than supportive care plus or minus endoscopic or MIS+rtPA removal of the ICH;
14. Prior enrollment in the study;
15. Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated;
16. Participation in another simultaneous trial of ICH treatment.

13.5.3 Criteria for Discontinuation of rt-PA Administrations/Aspiration Protocol

A subject will have rt-PA administrations discontinued (tiers 1 and 2) or additional aspirations discontinued (tier 3) for any of the following reasons:

Tiers 1 and 2:

1. The ICH volume is reduced to 10 cc or less or 20% of the initial clot volume as measured on the stability CT scan. (surgical endpoint)
2. The subject receives 9 doses (surgical endpoint; tiers 1 and 2 only)
3. Clinically significant rebleeding. (treatment failure)
4. Uncontrolled coagulopathy defined as INR > 1.3. (treatment termination)
5. In the investigator's judgment, discontinuation of dosing would be in the patient's best interest. (treatment termination)
6. The patient withdraws consent.

Tier 3:

1. Aspiration volume equals 80% of the stability ICH volume.
2. Clinically significant rebleeding. (treatment failure)
3. Uncontrolled coagulopathy defined as INR > 1.3. (treatment termination)
4. In the investigator's judgment, discontinuation of the aspiration protocol would be in the patient's best interest. (treatment termination)
5. The patient withdraws consent.

All subjects will be monitored daily for 6 days from the date or randomization regardless of treatment assignment. Monitoring includes blood pressure, GCS, neuroworsening, temperature, and serum labs for a minimum of 6 days. We will record and analyze all CT scans required by protocol and ordered as standard of care regardless of treatment assignment.

Subjects who withdraw consent or are lost to follow-up will not be replaced.

All consenting subjects will be asked to return to clinic for all scheduled follow-up assessments including the 30, 90 (telephone contact), 180, 270 (telephone contact) and 365 day visits.

13.6 Treatment of Subjects

13.6.1 Investigational Product and Procedures

13.6.1.1 Overview

This study is a multicenter evaluation of endoscopic removal of ICH or minimally invasive surgery plus ICH lysis with rt-PA vs. medical management. The dose finding study stage will consist of three tiers to evaluate the safety of minimally invasive surgery plus doses of rt-PA, 0.3 mg (tier 1) or 1.0 mg (tier 2), administered every 8 hours for up to 9 doses. A third tier will be devoted to exploring the effect of varying the mechanical extraction portion of the protocol using endoscopic technique. The safety study stage will compare the optimal minimally invasive surgery procedure and/or the optimal dose from the dose finding stage with conventional medical management. Determination of dose will be based on the initial two tiers.

13.6.1.2 Screening Procedures (All Tiers)

1. Diagnostic CT scan (Standard of Care). This scan is defined as the first CT scan performed that is used to diagnose the ICH. At each study center ICH volume will be determined in the following manner: On the CT slice with the largest area of ICH, the largest diameter (A) of the hematoma will be measured in centimeters. The dimension of the hemorrhage perpendicular to the largest diameter will represent the second diameter (B) in centimeters. The height of the hematoma will be calculated by multiplying the number of slices involved by the slice thickness, providing the third diameter (C). The three diameters will be multiplied and then divided by two (AxBxC/2) to obtain the volume of ICH in cubic centimeters. For the purpose of determination of (C) diameter, the first and last slices where hematoma is first and last noted are not counted (20).

2. Stability CT scan (Standard of Care). This scan will be done at least 6 hours after the diagnostic CT scan to determine clot stability. If this CT is not done per standard medical care at a participating study center, informed consent must be obtained prior to ordering the CT. The clot volume measured using the technique described above must not differ from the volume measured on the diagnostic CT scan by more than 5cc. Fiducials or their cutaneous location(s) should be placed at the time of this scan if the patient appears to be eligible. Fiducials should remain in place until after the post catheter insertion CT scan for those subjects randomized to surgical management.

If the clot volume measured on the initial stability CT scan differs by more than 5 cc, a second stability determination is allowed by repeat CT scan at least 6 hours after the initial stability scan. Additional CT scans are permitted as needed at least every 6 hours to continue to monitor for stability up until the eligibility time window closes.

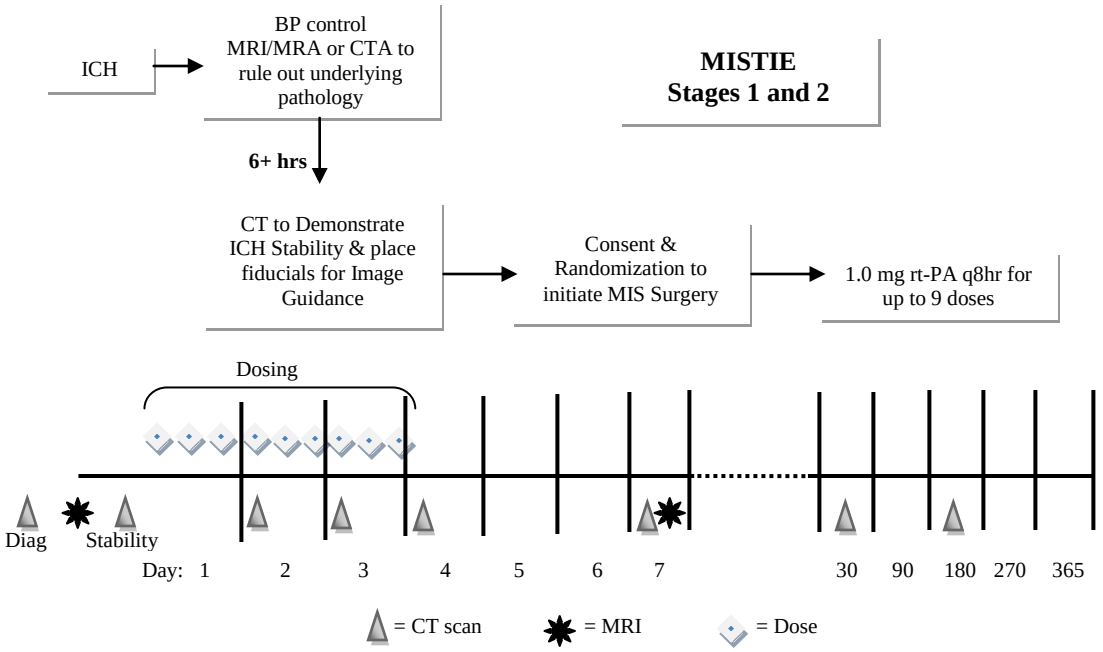
3. Imaging to rule out underlying pathology. A MRI (FLAIR)/MRA will be performed to rule out underlying pathology and to assess edema and cerebral ischemia. If the time window does not permit this imaging, or if MR is contraindicated, a CTA should be done at the time of the stability CT scan and an MRI done, if possible, before first dose of rt-PA for patients randomized to surgical management or at a complimentary time for patients randomized to medical management.

4. Blood pressure. Blood pressure stability is defined as SBP < 200 mmHg sustained over 6 hours prior to randomization. The long-term control goal is MAP < 110 or 160/90.

5. NIHSS. If not done as standard of care, a NIHSS score must be obtained and must be $\geq$ 6 (or a GCS of $\leq$ 14) for the patient to be eligible (using distal arm scoring). The NIHSS must be done by a certified examiner. The NIHSS must be done at or as close to time of presentation for screening and then repeated at time of enrollment to confirm eligibility.

Patients who meet all of the inclusion and exclusion criteria using the above screening procedures will be randomized to conventional medical management or surgery (minimally invasive surgery plus rt-PA or endoscopy). The operative procedure should occur as close as possible to the time of randomization for those subjects randomized to surgery (MIS plus rt-PA or endoscopy). If the surgical procedure is postponed to accommodate scheduling (i.e., it is preferable to wait until 6 am instead of midnight), a CT scan should be repeated to confirm stability of the ICH and blood pressure stability should be confirmed prior to beginning the surgical procedure. The first dose of study drug should be administered three or more hours after the surgical procedure for those subjects randomized to the MIS plus rt-PA procedure.

13.6.1.3 Experimental Intervention: MISTIE-Surgery (Stage 1: Tiers 1 and 2 and Stage 2)



A neurosurgeon certified by the Coordinating Center will perform the procedure. Viewing a PowerPoint presentation of the minimally invasive surgery procedure to insert the catheter is mandatory before credentialing a center's neurosurgery personnel. A PowerPoint presentation has been produced describing the catheter placement procedure and apparatus, sterile field techniques and the exact process for aspirating the clot. The presentation is available on the trial website. It will be used continuously to train and retrain personnel performing the surgery to assure the standardization of surgical procedure. This presentation will be edited as new safety data is developed. Each site will maintain a log of eligible surgeon(s) along with the date and time of viewing.

Optimal trajectory determination: The neurosurgeon will review the stability CT scan to determine the burr hole location and trajectory to be used during the operative procedure to place the catheter. Ideally, a 3-D reconstruction of this ICH on CT will be reviewed if this capability exists. The neurosurgeon will select the representative slices reviewed for trajectory determination and the coordinator will create from the DICOM viewer jpeg images using 4 slices across and 4 slices down to show the clot in the brain window. This image will be uploaded to the EDC system, the surgical review form will be completed by the neurosurgeon or coordinator in the EDC system and both will be reviewed by the Surgical Center. Trajectory determination will be coded as A, B, or C. Option A is used for a deep-seated ICH occupying the anterior third of the basal ganglia with a typical "oval" shape (football shape). A type A ICH should have an entry point in the low anterior frontal area frequently close to the midline near the eyebrow, and the trajectory of the catheter must be along the longitudinal axis of the clot. Option B is used for a deep-seated ICH

occupying the posterior third of the basal ganglia with a more roundish to elliptical shape. A type B ICH should have an entry point in the posterior parietal-occipital area, frequently several centimeters lateral from the midline to avoid the occipital ventricular horn, and the trajectory of the catheter has to be along the longitudinal axis of the clot. Option C is used for superficial (lobar) ICH with variable shape, but is often more spherical. A type C ICH should have an entry point at the superficial area closest to the clot. This is usually the widest "equatorial point" of a spherical-shaped clot. The trajectory of the catheter has to be along the widest, or "equatorial", axis of the clot.

Surgical Center review of optimal trajectory: The Surgical Center personnel will document the results of their review in a separate section of the EDC. The EDC will notify the site within 6 hours of data submission and share with the site personnel a summary report of the Surgical Center review instructing the site that the proposed burr hole location and trajectory is appropriate or that a different location/trajectory is recommended. The site neurosurgeon may then proceed with catheter placement using either the original proposed trajectory or the Surgical Center recommended trajectory. If there is disagreement between the two trajectories, the site neurosurgeon will document in the EDC the rationale for the chosen trajectory. See MOP Chapter 16: MISTIE Surgical Center for a detailed description of personnel involved, responsibilities, and contact information.

Catheter placement: The procedure will be performed in either the operating room or the ICU. After administration of the appropriate anesthetic, a Mayfield headrest is secured to the subject's head. A reference device is clamped to the Mayfield headrest. The image guidance system unit must be in direct line to the table with no line-of-sight obstruction. Registration is completed by correlating six points on the subject's head to six points on the previously loaded CT scan. Verification of accuracy is accomplished by testing various known landmarks on the subject's face to the image on the computer monitor. Re-registration during the case is accomplished by repeating the correlation of the six landmarks on the subject's head to the CT scan. The procedure is completed in the usual sterile manner for burr hole and catheter placement.

Either MRI or CT guided intraoperative catheter placement are allowed. The site of the entry burr hole is determined using radio-opaque dot localization if a standard frontal burr hole is insufficient. Standard frontal burr holes will be placed 3 cm lateral to the midline, anterior to the coronal suture for ipsilateral frontal, capsular and thalamic hematomas. If the subject has a deep brain hemorrhage, a large frontal burr hole will be used. If a lobar hemorrhage, the burr hole will be placed over the affected lobe. The position of the burr hole should be made posterior to the thickest portion of the hematoma. Surgical considerations regarding eloquent tissue and hematoma shape and location may require other burr-hole locations to optimize trochar/catheter trajectory to the target. A one-inch incision will be made in the scalp. The burr hole is drilled and the dura is opened with a small incision.

After the proper process of registration and localization with the image guidance system an introducer cannula will be placed stereotactically into the center of the hematoma. Up to two complete cannula placements will be allowed to minimize morbidity from the catheter implantation. The introducer portion is then removed and careful hematoma aspiration is performed free hand using a 10 cc syringe. Aspiration will continue until first resistance to gentle suction is appreciated. Volume aspirated will be documented. Aspirate fluids will be saved for pharmacokinetic/pharmacodynamic analyses. Following completion of hematoma aspiration, a soft ventriculostomy catheter is then passed through the rigid cannula and then the rigid cannula is removed leaving the soft catheter with all its perforations in the center of the residual hematoma. The catheter should be placed 2/3 of the way along the longest axis of the clot and in the middle of the width of the clot (i.e., within the middle 2/3 of the diameter). A CT scan should be done at this time to confirm correct placement, using windowing to view the side ports of the catheter, and measure clot size reduction as compared to the volume measured on the stability CT scan. If remaining clot volume is less than or equal to 10 cc or less than or equal to 20% of the initial clot volume, rt-PA should not be given. The catheter should remain in place for a minimum of 24 hours prior to removal.

Catheter adjustment: Correct catheter placement will be confirmed locally and measurements will be repeated centrally to document protocol compliance. Catheter adjustments will be made at this time if necessary. If the hematoma appears larger or the shape is altered on CT scan after the catheter is placed, the catheter may require repositioning and a CT scan must be repeated to confirm correct placement within the clot as well as stability of clot size. Repositioning can be defined as either 1) partial removal or "pull back," 2) remove the non-optimally placed catheter and replace with a better targeted catheter using the introducer method described above with either the same or a different trajectory of insertion, or 3) place a second catheter into the portion of the clot unengaged by the first catheter while maintaining the first catheter. There is a one-time allowance for a new catheter placement. "Soft pass" catheter replacements using the original trajectory do not count against this one-time allowance. The catheter is then tunneled subcutaneously, connected using sterile technique to a three-way stopcock and then to a closed drainage system. Level the drainage bag to zero while the catheter is in place. If the catheter must be repositioned or replaced after dosing has begun, the procedure must be done greater than or equal to 12 hours after the most recent dose and all stability protocols must be repeated as if this were the original catheter placement.

Antibiotic therapy should be administered pre-operatively (hospital protocol or 1 to 2G Ancef IV, dose is subject-weight dependent), then repeated every 8 hours until the catheter is removed (hospital protocol or Ancef IV 1G q 8hrs). If the subject has a known or suspected penicillin drug allergy, then antibiotic coverage will be administered pre-operatively and continued with each institution's non-penicillin drug of choice until the catheter is removed.

13.6.1.4 Experimental Drug Treatment: Drug Therapy (Stage 1: Tiers 1 and 2 and Stage 2)

A three-hour stabilization period post initial catheter placement and any repositioning or replacement of the catheter is mandated to re-assess patient clinical status and minimize rebleeding prior to rt-PA instillation. The first dose of rt-PA will then be injected into the catheter to dissolve the hematoma (i.e., three hours or more after the placement of the catheter).

Before initial dosing and subsequently after every 3 doses (daily), the investigator will be required to view the most recent CT scan to measure clot size and decide continuation/discontinuation of dosing. As clot size decreases and approaches the target reduction, the next CT may be obtained earlier than after 3 doses. This process allows the PI and team to confirm that: 1) remaining clot is greater than 10 cc or greater than 20% of the initial clot volume as measured on the stability CT scan, 2) the blood clot is in direct contact with the catheter, and 3) that the catheter is placed in the center of the clot to be dissolved. Bone windows must be done when obtaining any CT scan in order to confirm that the catheter side ports have contact with the clot. If none of the side ports are in contact with the clot, drug should not be given. Partial contact with the clot should be reviewed by the PI on a daily basis, prior to further dosing.

If these criteria are not met, the catheter must be repositioned. Repositioning to allow for the correct catheter to clot relationship may be performed once under direction of the investigator as needed during the dosing time of the protocol. After repositioning, wait 12 or more hours, and then obtain a repeat CT scan to confirm stability. Stability must be demonstrated in the following ways on all CT scans: 1) no expansion of ICH greater than 5cc as compared to the most previous CT scan, 2) no catheter tract bleed greater than 5mm, and 3) no new IVH or new expansion of IVH. If the clot is stable, dosing may resume.

Complete replacement of the catheter is allowed if the catheter to clot relation has been disturbed by inadvertent catheter movement or partial clot reduction. A second option is to place a second catheter into the portion of the clot unengaged by the first catheter while maintaining the first catheter. In this situation dosing would be alternated between the two catheters until a catheter is removed. Complete replacement should be performed only once (i.e., in any subject only two, new catheters may ever be placed). If repositioning does not correct the catheter-clot relation and the catheter has already been replaced once during the trial, rt-PA administration must be stopped and the catheter removed. This requirement will control the delivery of rt-PA into tissue space containing clot that can be lysed. In addition, an unscheduled CT scan must be performed should the subject clinically deteriorate or significantly improve his or her GCS score. These additional safety provisions will keep under surveillance the most ideal time for stopping drug after clot is fully lysed.

The drug will be administered as a sterile solution and in a sterile manner every 8 (± 2) hours for up to 9 doses. The total volume of injectate (t-PA plus normal saline flush) is standardized among the dose tiers to keep the drug concentration within a stable range and to keep the total volume per injection the same between each dosing tier using the most appropriate drug solubility volume recommended by the drug manufactuer. The injectate volumes are as follows:

Tier 1: 0.3 mg @ 0.5 mg/mL = 0.6 mL t-PA + 3.4 mL flush: total volume of 4 mL

Tier 2: 1.0 mg @ 1 mg/mL = 1 mL t-PA + 3 mL flush: total volume of 4 mL

Stage 2: 1.0 mg @ 1 mg/mL = 1 mL t-PA + 3 mL flush: total volume of 4 mL

A neurosurgeon, neurocritical care physician, or their trained designee will perform hematoma catheter injections under standard sterile technique. Viewing a video demonstration of the catheter injection protocol is mandatory before credentialing a center's physicians and coordinators. Study personnel will control the procedures for preparing the injection and for rt-PA administration. A training video has been produced describing the injection procedure and apparatus, sterile field techniques and the exact process for delivering the drug. The training video is available on the trial website. It will be used continuously to train and retrain personnel administering the injections. Great care and time has been and will be expended to assure the standardization of safe drug administration. This presentation will be edited as new safety data is developed.

Repeat CT scans will be performed earlier than every 12 to 24 hours if or when the treating physician determines that there is a sustained worsening of neurological condition. Therapy will be stopped at this time if there is any increase in hematoma volume on CT or emergence of systemic bleeding disorders.

The catheter should be left open to drain for 24 hours after the last dose of rt-PA prior to removal. The catheter must be closed at the time of removal and not open to air to avoid pnuemocephalus.

Only after 24-36 hours after the last rt-PA administration can the catheter be removed at the bedside, the tip is sent for culture, and sutures are placed for skin closure. Removal soon after 24 hours is strongly encouraged to limit infection risk (i.e., within the next 12 hours or between 24 and 36 hours post last dose). A CT scan must be done 24 hours post catheter removal and examined for new bleeding or hemorrhage extension.

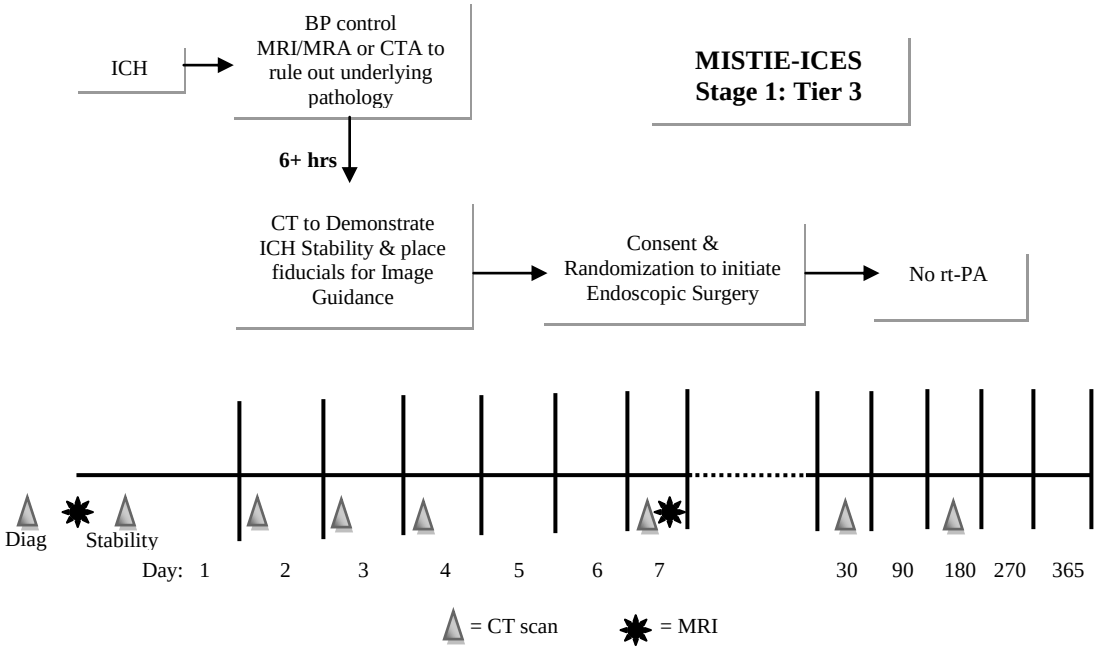
All subjects will be followed daily for 5 days post test intervention (6 days for medical intervention) regardless of treatment assignment. All subjects will have an MRI with FLAIR performed at Day 7 to compare with the baseline MRI to measure edema.

All subjects will be required to return for a follow-up clinic visit at days 30, 180, and 365. A telephone follow-up will be done at days 90 and 270.

13.6.1.5 Experimental Drug Treatment: Pharmacokinetic Sampling (Stage 1, Tiers 1 and 2, and Stage 2)

Pharmacokinetic samples will be taken from the fluid collected in the OR during the catheter placement procedure for subjects randomized in Stage 1, tiers 1 and 2 and Stage 2. Samples will not be collected from run-in subjects. If the surgeon is unable to aspirate any fluids in the OR, an attempt should be made to obtain a fluid sample prior to dose 1. Subjects will have additional samples taken, by the investigator or designee, using gentle aspiration of the clot before dose 4 and at 1 hour, 3 hours, and 7 hours and 50 minutes after dose 1 and dose 4. A total of 2 ml of fluid is needed per tube at each collection point. Please see MOP chapter 9 for more detailed instructions on sample collection and processing. All samples will be immediately centrifuged at 3000 rpm for 15 minutes and stored at -70 degree Farenheit. Samples will be batch shipped to Dr. Denise Rhoney at the Wayne State University for final PK analysis.

13.6.1.6 Overview of MISTIE-ICES Intra-operative Procedures (Stage 1: Tier 3)



A neurosurgeon certified by the Coordinating Center will perform the procedure. Viewing a video and PowerPoint presentation of the endoscopic procedure to remove the hematoma is mandatory before credentialing a center's neurosurgery personnel. A video and PowerPoint presentation have been produced describing the endoscopic procedure and apparatus, sterile field techniques and the exact process for aspirating the clot. The video

and presentation are available on the trial website. It will be used continuously to train and retrain personnel performing the surgery to assure the standardization of surgical procedure. These presentations will be edited as new safety data is developed. Each site will maintain a log of eligible surgeon(s) along with the date and time of viewing.

The procedure will be performed in the operating room. After administration of the appropriate anesthetic and a formal time out to determine the correct surgical side, a preliminary assessment of endoscopic trajectory is made based on the location of the hematoma, in accordance with the pre-study training module. The initial scan (CT or MRI) is also carefully evaluated to define the long axis of the intracerebral hemorrhage and to evaluate the various cranial entry points which allow introduction of the endoscope sheath most closely aligned to the long axis of the hematoma. The subject is then positioned with head up 20 degrees, supine, for most cases. Alternative positions are acceptable if needed to determine the optimal endoscopic surgical trajectory. The subject's head will be turned in the appropriate direction and fixed in the Mayfield head holder using sterile pins/standard technique.

The subject is then registered in the stereotactic image guidance system. This requires a stereotactic reference guide that must be applied using sterile technique. The image guidance probe is positioned over the candidate entry point. The virtual extension of the probe tip is employed to interrogate the candidate entry points to assess whether or not the endoscope sheath will transgress any critical functional areas. This strategy is also used to identify the entry point which provides optimal access to the central long axis of the hematoma.

The skin is prepped and draped in sterile fashion, preoperative antibiotics are administered within 60 minutes of skin incision time, and local anesthesia is applied. A 2.5 to 3.0 cm scalp incision is made. A 1.5 to 2.0 cm burr hole is made. The dura is opened and the cortical surface coagulated and incised to allow passage of the Frazee endoscope sheath with obdurator in place. The frameless stereotactic image guidance system registration device (the three-ball star for the BrainLab system) is affixed to the end of the endoscope sheath close to the junction point for the camera and endoscope. The endoscope sheath with obdurator in place and registration "star" affixed is then registered to the image guidance system in standard fashion for additional tools. This allows the endoscope sheath with obdurator then to become a frameless stereotactic "probe." This will be accomplished by using the offset feature and a probe's eye view to best guide the surgeon. The trajectory that enables exact bisection of the largest diameter of the hematoma will be selected. The expected depth of the insertion will be between 6 to 8 cm for basal ganglia hemorrhages.

The 8 mm endoscope sheath (preferred, but 8.8 mm sheath is acceptable) will be supported freehand with assistance of the Mitaka pneumatic arm. The Frazee endoscope sheath with obdurator and image guidance "star" is then fixed to the Mitaka arm (or other endoscope holder). The Mitaka arm is released and the endoscope sheath with obdurator is introduced

through the cortex into the hematoma along its long axis. The endoscope sheath is introduced to a point approximately two-thirds of the way to the distal margin of the hematoma. The sheath is fixed in that location by locking the Mitaka arm. The obdurator is removed.

Suction is fixed to the suction port of the Frazee sheath. In line with the suction is a 50 cc luken trap. The irrigation port is kept closed at this point. The working channel of the endoscope sheath is entirely open at this point and no suction is applied to the hematoma yet. Suction will be applied to the endoscope sheath in a graduate manner, using a suction regulator starting at 50 mm Hg suction pressure for 30 seconds. Suction is increase by 50 mm Hg every 30 seconds to a maximum of 300 mm Hg. At each pressure step, the volume of the hematoma that is aspirated will be determined. If the hematoma is being suctioned adequately at a particular pressure step, or if 50% of the initial hematoma volume has been aspirated, no additional increments of pressure will be made. The effluent of the suction fluid is collected in a Luken's trap and an estimate the clot volume is made. This fluid is saved for clot analysis (see section 13.6.1.7. below). Unless bright red bleeding is seen at depth 1, the Mitaka arm is released and the endoscope sheath is backed out to a point approximately one-third of the way into the hematoma cavity. The suctioning process is repeated at the second location. (Note: a second attempt at suctioning is only carried out if the first attempt does not remove 75 or 80% of the estimated volume of the hematoma. If the hematoma has virtually entirely been removed at the first suction location site, the second suctioning site is not necessary). The endoscope is introduced and the endoscope sheath is then irrigated at this location to be sure that there is no evidence of active bleeding. If active bleeding is detected, irrigation is continued until the bleeding stops. If the bleeding does not stop adequately, the bleeding point will be identified endoscopically either with or without ongoing irrigation. Once the bleeding point is identified, the Storz endoscopic bipolar is employed to coagulate the bleeding point. If there is continued low volume bleeding and no demonstrable identifiable discreet bleeding point, then DDAVP in a dosage of 0.3 mcg/kg can be administered to promote hemostasis. Once the irrigation comes back free of any evidence of ongoing bleeding, the endoscope sheath is removed entirely.

A volumetric assessment of the amount of hematoma removed is determined by the surgeon and recorded. The cortical surface is inspected carefully to be sure that there is no ongoing bleeding coming from the corticotomy. Generally, the cortical surface is not bulging through the dural opening as it would if there were recurrent hematoma or severe brain swelling. Cortical surface is generally pulsatile and has dropped a few mm below the inner surface of the dura. During the evacuation a patient is observed closely for changes in heart rate or blood pressure. If there has been time and with availability, the EEG and evoked potentials are monitored carefully to be sure that these have been maintained at an acceptable level, without signs of progressive deterioration, particularly on the side of the hematoma. At this point, the cannula and endoscope will be removed. Next, a 3 mm ventriculostomy will be passed into the hematoma cavity just created at a depth equivalent

to evacuation depth 1 (2/3 depth into the original hematoma). The catheter can usually be passed down the endoscope sheath tract. The wound is closed in the standard fashion and the hematoma drain is passed out with a separate trocar incision and fixed to the scalp. The hematoma drain is connected to a closed sterile drainage system. Level the drainage bag to zero while the catheter is in place. The drainage catheter is placed in the hematoma cavity at the time of surgery and left in place for up to 48 hours postoperatively. The catheter should be removed 24 to 36 hours post placement to allow for post-surgical drainage and to limit the risk of infection. The catheter is left open to drain at positive 5 cm from atmospheric pressure. This catheter may be used for additional hematoma removal to reach the 80% goal. A CT scan must be done 24 hours post catheter removal and examined for new bleeding or hemorrhage extension.

The surgeon will complete a structured surgical experience report form, to document feasibility and performance characteristics in the following domains: 1) time taken for initial intraoperative and subsequent stereotactic set up; 2) number of endoscopic passes; 3) trajectory of endoscopic pass that bisects the long axis of the hematoma; 4) hemorrhagic volume reduction on each subsequent CT scan as compared with the initial CT scan; and 5) surgeon's volumetric measure of the amount of hematoma evacuated.

A post-evacuation volumetric CT scan, using the same imaging protocol as the preoperative CT scan will be performed within 60 minutes post-procedure to rule out early recurrent hemorrhage.

Correct cannula/catheter placement will be confirmed locally and measurements will be repeated centrally to document protocol compliance.

Antibiotic therapy should be administered pre-operatively (hospital protocol or 1 to 2 G Ancef IV; dose is subject-weight dependent), then repeated every 8 hours until the catheter is removed (hospital protocol or Ancef IV 1G q 8hrs). If the subject has a known or suspected penicillin drug allergy, then antibiotic coverage will be administered pre-operatively and continued with each institution's non-penicillin drug of choice until the catheter is removed.

13.6.1.7 Clot analysis sampling (Stage 1: Tier 3)

For subjects enrolled in Tier 3: MISTIE-ICES, samples will be taken from the fluid collected the Luken trap in the OR during the catheter placement procedure per the instructions in MOP chapter 9. Samples will be batch shipped to Dr. Victor Marder at the University of California, Los Angeles for final clot analysis.

13.6.2 "Run-In" Patient Enrollments

Each study center is required to demonstrate proficiency in the technical aspects of enrollment, stabilization, surgery, and drug administration. This proficiency must be demonstrated on at least one patient prior to randomization of the first patient in the investigational cohort of 110 randomized and approximately 36 run-in patients. Proficiency will be determined after review of the "run-in" patient's study data for days 1 through 6 by the Study Chair and the Neurosurgery Reading Center. Because of the complexity, the endoscopic protocol in tier 3 will require 1 run-in patient per site. All "run-in" patients will complete the protocol through the 365 day follow-up visit.

13.6.3 Concomitant Medications

Only those medications listed on the concomitant medications list or any medication not listed that is used to specifically treat an adverse event will be collected through Day 6. The 365-day visit marks the last tracking of stop dates. Subjects will be asked during the 30-, 90-, 180-, 270-, and 365-day follow-up visits if anti-hypertensive medications have been prescribed since the last visit and if the subject is compliant with those medications.

Permitted Medications for subjects, including but not limited to NovoSeven, fresh frozen plasma, plasma concentrate and vitamin K, are permitted singly or in combination (but not required) for reversal of anticoagulation.

Prohibited Medication: Antithrombotics and antiplatelets are prohibited until 72 hours post last dose. After 72 hours post last dose: Antiplatelet agents such as ASA, clopidogrel/Plavix, glycoprotein IIb/IIIa inhibitors, such as eptifibatide/Integrilin, abciximab/Reopro, tirofiban/Aggrastat, and low molecular weight (fractionated) heparins (enoxaparin/Lovenox) may be administered. During the follow-up period (72 h post last dose of study drug through the 12 month visit), avoid enoxaparin at therapeutic doses $\geq$1.0 mg/kg sc q12 h. Subsequently, use of enoxaparin for DVT prophylaxis in the ICU at the usual doses of 30 mg sc q12 h or 40 mg sc QD is permitted as long as the patient has good renal function (creatinine clearance of > 30 ml/min) or does not have an unusually low body weight (< 45 kg). Regular low dose heparin, 5,000 units subcutaneous twice daily may be used (or sooner if medically necessary to treat a clinical symptom). After Day 7, urokinase, retiplase, desmetoplase, systemic rt-PA may be used. Anticoagulants used in stroke and pulmonary embolus prophylaxis, such as warfarin, heparin (full dose) and thrombolytics may be instituted at or after the 30-day follow-up visit.

Particular caution needs to be observed with renal dialysis patients receiving rt-PA. Because this group of patients can experience wide variations in blood pressure with dialysis attendant cardiac volume changes, attention to long-term and intra-procedure blood pressure control is important. Similarly, attention to regional anti-coagulation management is important.

13.7 Assessment of Outcome

13.7.1 Outcome Parameters

1) Rate of clot size reduction at Day 4-5 determined by CT scans; absolute clot size reduction at Day 4-5
2) 30, 90, 180, 270, & 365 day GOS, extended GOS, modified Rankin Scale, Stroke Impact Scale
3) Post-operative size reduction

13.7.2 Outcome Analysis

The following outcome-related assessments will be performed by the investigator according to the schedules described in Chapters 13.17.1.a and 13.17.1.b.

- Head CT scans
- NIHSS
- Stroke Impact Scale
- Barthel Index
- Modified Rankin Scale
- Glasgow Outcome Scale
- Extended Glasgow Outcome Scale

13.8 Assessment of Safety

13.8.1 Safety Parameters

1) 30-day mortality
2) Procedure-related mortality
3) Cerebritis, meningitis incidence
4) Rate of symptomatic rebleeding

13.8.2 Safety Analysis

All safety-related assessments should be consistent with generally accepted medical practices and standards of care. The following specific assessments will be performed according to the schedule described in section 6.1 of the Operations Manual.

- Treatment-emergent AEs
- Physical and neurological examinations

- Vital signs (temperature, blood pressure, MAP, heart rate, respiratory rate)
- Laboratory assessments (to be performed locally)
  - Hematology panel
  - Plasminogen
  - Fibrinogen
  - D-dimer
  - Serum pregnancy test in women of childbearing potential
  - Urine drug screen
- Concomitant medications
- CT scans/MRI

13.8.3 Adverse Event Reporting

In the event of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report to the coordinating center any serious adverse event, whether expected or unexpected, and which is assessed by the investigator to be reasonably or possibly related to the surgical procedure or Activase. All events meeting these criteria will be reported for the time period beginning with randomization through the protocol-defined follow-up. Serious criteria, definitions, and guidance for reporting follow.

Adverse events must be recorded in the source documents and on the electronic case report form. All adverse events, serious or otherwise occurring after presentation to the emergency department but prior to randomization will be documented on the Medical History screen in the EDC system. All adverse events and serious adverse events that occur during the acute treatment phase (ending at Day 6) will be recorded on the Medical Event form along with all neurological AEs and SAEs that occur through the Day 365 follow-up visit. Due to the relatively short half-life of rt-PA, adverse events occurring more than 72 hours after completion of rt-PA administrations are not expected to be considered related to the rt-PA administration. An adverse event is any untoward medical occurrence in a patient entered into the study that does not necessarily have a causal relationship with this treatment. An adverse event can be any unfavorable and unintended sign (including an abnormal lab finding), symptom, or disease temporally associated with the use of the product whether or not related to the product. The investigator must follow adverse events to resolution whenever possible.

For patients who are entered into the study (qualifies, informed consent is obtained, and randomization is completed) but have either an obstructed flow pathway or where catheter patency cannot be established, safety data (AEs/SAEs) will be collected through 6 days. Final outcome of all events at Day 365 are to be recorded if not recorded earlier. Patients without incidence of drug exposure will not be included in intention-to-treat analyses for drug-related safety issues but will be included in all intention-to-treat analyses of surgical and medical subjects. Patients who receive a partial dose or more of rt-PA will be included in all primary safety and surrogate efficacy analyses.

Serious Adverse Events (SAE) must be immediately (within 24 hours of awareness) reported by study site personnel to the Coordinating Center.

If a subject is discontinued early from rt-PA administrations for any reason, study site personnel must clearly report and document the circumstances and data leading to any discontinuation using the electronic case report forms. It must be determined if the reason for stopping rt-PA administration is an adverse event, for example, sustained ICP above 30 mmHg during injection. For any untoward event(s) the subject should be followed until the event resolves or is explained with the frequency of follow up designated by the investigator.

Any serious and unexpected adverse events, inclusive of the follow-up period, whether or not thought to be related to study drug or the catheter insertion procedure, must be reported immediately (within 24 hours of learning of the event) to the coordinating center. The study Chair agrees to adhere to FDA-defined guidelines and submit an *expedited* report of any death that is *related* (even remotely) to study drug or the cannula insertion procedure and *unexpected*, if the death occurs within 30 days from the date of the original ICH event. Unexpected is defined as any death in which the severity or specificity is not consistent with the investigator's brochure or the package insert or by the risk information described in the protocol and/or informed consent form. The study Chair will report any death that is *unrelated* to study drug or the cannula insertion procedure, if the death occurs prior to study completion. The protocol describes as part of the expected events a high percentage of patients who die without rt-PA or cannula placement; therefore, unrelated deaths, deaths occurring after 365 days, or deaths expected as part of the natural history of ICH without the test interventions will be reported with the adverse events in the treatment effects summary generated for each DSMB meeting and annual report.

13.8.3.1 Clinical Adverse Events

An adverse event is any untoward medical occurrence in any consenting subject . This event does not necessarily have a causal relationship with treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product or treatment.

Adverse events will be reported and recorded in the source document and on the electronic case report forms defined by their duration (start/stop) and the intensity of each event will be graded using the AE dictionary codes in the EDC system. The grades range in intensity from 1 (mild) to grade 5 (death). Grades are specific to each event. Specific events will not have all five grades available. All AEs coded as a grade 4 or 5 will automatically require SAE reporting.

13.8.3.2 Serious Adverse Events Including Death

A Serious Adverse Event is an adverse event that results in any of the following outcomes. For purposes of this study, Regulatory Agency reporting responsibilities have been designated to the Coordinating Center.

1. Death. Study Chair agrees to adhere to FDA-defined guidelines and submit an *expedited* report of any death that is *related* (even remotely) to study drug or the cannula insertion procedure and *unexpected* if the death occurs within 30 days from the date of the original ICH event.

2. Life threatening: experience that places the study subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred.

3. Inpatient hospitalization or prolongation of existing hospitalization.

4. Persistent or significant disability or incapacity: a substantial disruption of a person's ability to conduct normal life functions

5. A congenital anomaly or birth defect

6. Important medical events may result in a Serious Adverse Event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.8.3.3 Unexpected Adverse Experience

Unexpected events are any serious adverse event in which the specificity or severity is not consistent with the natural history of ICH without the test intervention including catheter placement and rt-PA administration. Unexpected will be defined as the specificity or severity of an event that is not consistent with the risk information described in the general investigational plan.

The Medical Events listed below are published by the American Stroke Association and the European Stroke Initiative as natural history events of ICH/IVH or are found in the Investigator's Brochure or Activase® Package Insert for the use of rt-PA. These medical events are therefore expected in the disease process or with use of the test article. Please enter these on the Medical Event form as adverse events. Reports of these events will be analyzed and submitted as grouped data by the trial's statisticians.

Expected Medical Events			
Nervous System		**Other Events**	
Brain Edema	Hydrocephalus	Aspiration	Pneumonia (Including ventilator-associated)
Brain Stem Compression	Hypoxia	Catheter-related vascular infections	Pulmonary Embolus
Brain Herniation	Intracranial Abscess	Deep Vein Thrombosis	Sepsis/Bacteremia
Brain Rebleeding Near the Initial Hemorrhage Site	Mass Effect	Diaschisis	Sinusitis
Catheter Tract bleeding/ Hemorrhage Enlargement	Meningitis, Bacterial or Non-Bacterial	Elevated BP	Spontaneous Bleeding from Non-cerebral sites
Cerebral Infarction	Perihematomal Ischemia	Fever/Hyperthermia	Thromboembolic Complications
Coma	Seizures	Hypercapnia	Urinary Tract Infections
Death	Ventriculitis, Bacterial or Non-Bacterial	Hypertension, Induced or Not Induced	Vascular Injury/Puncture Site Bleeding
Decreased LOC	Cerebritis	Hypotension, Induced or Not Induced	Pericarditis
Delirium	Headache	Infectious Complications	
Elevated ICP		Nausea/Vomiting	

13.8.3.4 Attributability of Serious Adverse Events to the Test Intervention

The investigator and/or Medical Monitor will define whether the event is best described as UNRELATED, POSSIBLE, PROBABLE, or DEFINITELY RELATED to the test intervention including catheter placement and rt-PA administration, according to the following definitions.

- Unrelated: There is evidence that the adverse event definitely has an etiology other than that assigned to either the catheter, cannula, or endoscope placement or rt-PA. AEs with onset more than 72 hours post rt-PA administration are not expected to be related to the rt-PA administration.

- Possibly Related: The adverse event has a temporal relationship to the test intervention. However, an alternative etiology may be responsible for the adverse event. Information on drug withdrawal may be lacking or unclear.

- Probably Related: The adverse event has a temporal relationship to the test intervention. The event is unlikely to be related to an alternative etiology. There is a reasonable response on withdrawal (dechallenge). Rechallenge information is not required.

- Related: The adverse event has a temporal relationship to the test intervention and resolves when rt-PA administration is discontinued. An alternative etiology is not apparent. If the subject is rechallenged with rt-PA, the adverse event recurs. Rechallenge is not necessarily required.

Guidance for Reporting. Any alarming, serious, or unexpected adverse event, including death due to any cause, which occurs during this study, inclusive of the follow up period (day 365), and whether or not thought to be related to the administration of test article, must be reported immediately (within 24 hours of learning of the event) to the Coordinating Center. The CC will then notify the Study Chairman, Genentech, Inc., the Medical Safety Monitor, the ICU Complications Monitor, Health Canada, the UK and European QA Monitors, and the FDA. The UK and European QA Monitors will notify the MHRA and Competent Authorities in all other Member States concerned as well as to the Ethics Committees concerned as necessary.

Name	Title	Phone Number	Fax Number	Email Address
24-hour pager	Coordinating Center	410-283-8342	410-502-7869	
Daniel F. Hanley, MD	Principal Investigator	410-614-6996 Cell: 410-615-3749	410-502-7869	dhanley@jhmi.edu
Pat Reilly, RN, MSN	Sr. Medical Science Liaison, Vascular Medicine (Genentech)	717-566-7993	717-566-7994	patr@gene.com
J. Ricardo Carhuapoma, MD	ICU Safety Monitor	410-955-7481	410-614-7903	jcarhua1@jhmi.edu
Carlos S. Kase, MD	Medical Safety Monitor	617-638-5102	617-638-7758	cskase@bu.edu
Marc Lemieux	Health Canada	514-398-2667	514-398-8576	marc.lemieux@mcgill.ca
Barbara Gregson, PhD	QA Monitor, UK; MHRA	+44 191 233 6161 ext. 22175	+44 191 256 3268	barbara.gregson@ncl.ac.uk
Alan Cohen	QA Monitor, Europe	+32 4 738 650 91		alanscohen@skynet.be
Neha Gada	FDA/CBER (IND File)	301-796-3985	301-796-9842	Neha.Gada@fda.hhs.gov

General Reporting of Serious Adverse Events Associated with Test Article. The CC will report all AEs and SAEs to the Study Chairman as the IND Sponsor (in accordance with CFR 312.32: IND Safety Reports) and the DSMB either immediately or as a routine summary report depending upon the severity of the event.

The CC will submit events meeting the following criteria to the Food and Drug Administration (FDA) as expedited IND Safety Reports and to the UK and European QA Monitors according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report: The CC will notify the FDA and the UK and European QA Monitors of any **fatal or life-threatening** adverse event that is **unexpected** and assessed by the investigator to be **possibly, probably, or definely related** to the use of test article. Unexpected adverse events are any event in which the specificity or severity is not consistent with the natural history or ICH or IVH without test article administration. Unexpected will be defined as the nature, specificity, or severity of an event that is not consistent with the risk information described in this protocol, the Activase package insert (PI), or

investigator's brochure (IB). Such reports will be telephoned or faxed to the FDA, Health Canada, the MRC, and Genentech within 7 calendar days of the CC first learning of the event. The UK and European QA Monitors will submit the reports to the MHRA and Competent Authorities in all other Member States concerned as well as to the Ethics Committees concerned as necessary.

15 Calendar Day Written Report: The CC will notify the FDA, the UK and European QA Monitors, and all participating investigators, in a written IND Safety Report, of any **serious, unexpected** AE that is considered **possibly, probably, or definitely related** to the use of test article. An **unexpected** adverse event is one that is not already described in this protocol, the Activase PI, or IB. The UK and European QA Monitors will submit the reports to the MHRA and Competent Authorities in all other Member States concerned as well as to the Ethics Committees concerned as necessary.

Annual Written Report: The Data Management Center will notify the FDA and the European Member States in whose territory the clinical trial is being conducted and the Ethics Committees concerned as necessary with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety. Each Member State shall see to it that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are immediately entered in a European database to which, in accordance with Article 11(1), only the Competent Authorities of the Member States, the Agency and the Commission shall have access. The Agency shall make the information notified by the sponsor available to the Competent Authorities of the Member States.

• Written IND Safety reports will include an **Analysis of Similar Events** in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events will be analyzed and the significance of the new report in light of the previous, similar reports commented on.

• Written IND safety reports with Analysis of Similar Events will be submitted to the FDA, Health Canada, the MRC, Genentech and all participating investigators within 15 calendar days of the CC first learning of the event. The UK and European QA Monitors will submit these reports to the MHRA and Competent Authorities in all other Member States concerned as well as to the Ethics Committees concerned as necessary.

For questions related to safety reporting, please contact the CC.

13.8.4 Adverse Event Follow-up

Follow-up assessments should be repeated to document return of any abnormalities to normal, or to document other outcomes of any adverse events.

Methods for eliciting, recording and assessing adverse events

To elicit adverse events, simple questions with minimal connotations should be used as the initial questions at all evaluation points during the study. For example:

How have you felt since your last visit?
Have you had any health problems since you were here last?
Have you (or the patient) had any serious bleeding? Examples of this include blood transfusions, a sudden drop in blood pressure, blood in urine or stool, coughing or vomiting blood or any other internal or external bleeding.
Have you (or the patient) suffered bleeding on the brain, a stroke, or any other change in function of the brain or nerves?
Have you (or the patient) had any symptoms such as sudden onset of shortness of breath, coughing up blood, purple discoloration of the feet, loss of pulse in legs or feet or other problems with blood clots?
Have you had any unusual or unexpected worsening your underlying medical condition?

13.9 Statistics

13.9.1 Statistical Methods

Comparison of groups. Group characteristics will be compared with Fisher's exact test for categorical variables, and with Student's t-test for continuous variables. However, medians will be compared for variables such as blood counts and Glasgow coma scores, which are expected to have highly skewed distributions.

Safety analysis. The following set of rules will be used to evaluate the safety of the rt-PA dosing levels used in the surgical management group.

1) If rates of mortality, bleeding, and infection in each of the MIS+rt-PA management groups are lower than or equal to those in the medical management group after stage 1, MIS+rtPA will be considered safe at all the doses evaluated.

2a) If rates in any of the MIS+rtPA groups for mortality or bleeding events are higher than those observed in the medical management group after stage 1, then that surgical treatment dosing level will be considered safe with respect to that event if the one-sided

test of the null hypothesis (MIS+rtPA group event rate minus medical group event rate = 0) has a p-value that exceeds 0.20, AND the event rate in the MIS+rtPA group represents no more than a 25% increase relative to the current population estimates. The current best estimate for mortality is 57% and for all re-bleeding over the initial 7 days of treatment is 48%. These rules will undergo necessary refinement as more data to support different thresholds for insuring patient safety are available.

2b) If rates of infection in any MIS+rtPA group are higher than those observed in the medical group after stage 1, but do not exceed 15%, this will be considered safe. A p-value criterion will not be applied for this event as infection is expected to be a much less frequent event and event rates for both MIS+rtPA and medical management groups will be more variable.

If either of the safety decision rules specified in 2a or 2b above have to be applied and indicate relative safety for a MIS+rtPA treatment at a given rt-PA dose: the stage 1 results for that MIS+rtPA group will also be evaluated for evidence of beneficial treatment effects. Both the study Executive Committee and the DSMB must concur that treatment benefits exist. In situations where the data produced demonstrate a complex profile of benefits and risks, the net benefits of efficacy must outweigh the net adverse events in the opinion of both data review groups. Again, both the study Executive Committee and the DSMB must concur.

Endpoint analysis. The analyses described below will be carried out after completion of 110 randomized patients. No interim analysis of futility is planned. As appropriate, selected groups of patients will be combined to provide more precise estimates of the event rates. For example, emergency craniotomy for treatment of ICH mass effect will be considered as the worst outcome category in a per-protocol analysis of mortality and efficacy.

Mortality evaluation. The 30-day survival probability (P) for each patient will be calculated using the logistic regression model developed by Tuhrim, et al.[50] This is equivalent to:

$$P = \frac{e^{-3.3125 + 2.7859\,GCS + 0.0180\,ICH + .5832\,PP - .956\,7HYDRO + .0979\,IVH}}{1+e^{-3.3125 + 2.7859\,GCS + 0.0180\,ICH + .5832\,PP - .956\,7HYDRO + .0979\,IVH}}$$

where GCS (Glasgow Coma Scale score) can assume values of 0 (GCS> 8) or 1 (GCS $\leq$ 8); ICH = size of intraparenchymal hemorrhage size measured in cm^3; PP (pulse pressure) can assume values of 0 (PP $\leq$ 85 mm Hg) or 1 (PP > 85 mm Hg); HYDRO can assume values of 0 (absent) or 1 (present); and IVH represents the size of the intraventricular hemorrhage in cm^3.

For each group of patients the probability of obtaining the number of deaths observed, with an underlying mortality rate at the level predicted by the Tuhrim model will be calculated. If the probability of obtaining that number or fewer is less than 0.05 this will indicate that a reduction

in mortality from that expected has occurred. If the probability of obtaining that number or greater is less than 0.05, this will indicate that an increase in mortality from that expected has occurred. Rates of rebleeding and cerebritis/meningitis will be compared with the rates for these events from the current study and also with the rates observed in the groups of patients in this proposed study treated in the lower dose tiers of rt-PA. Fisher's exact test will be used for statistical comparisons. Additionally, generalized linear mixed models for binary data will be used to examine AE and SAE probabilities between treatment groups while accounting for potential confounders and center clustering effects.

Survival time analyses will be used to estimate time to hydrocephalus and time to final removal of the catheter. Hydrocephalus will be deemed to have occurred at the time of placement of a shunt, or when the increase in ventricle size exceeds the Lemay[25] ratio of 0.50. Patients who meet neither of these criteria will be treated as censored observations as of the last CT scan taken during the first 30 days.

Efficacy estimation. Efficacy evaluation will focus on the rate of percent clot resolution obtained and on the analysis of the PK data, for each group of patients. As described earlier, the intracerebral hemorrhage volume (V_t) estimated present at time t will be standardized as a percentage of the initial volume ($\%V_t$) by use of the equation $\%V_t = (V_t/V_o \times 100)$, where V_o is the volume of the hemorrhage on the baseline CT scan. Statistical analysis of the rate of clot resolution will be done using this standardized data. The percent clot resolution rate per day will be estimated using regression models, in which the standardized volume is regressed against time since baseline CT scan. These analyses will include the data from each CT taken between baseline and 96 hours for all patients in the group. Robust estimates of the standard errors will be calculated using the Huber/White/Sandwich estimator of variance, which adjusts for clustering of observations on patients. Evidence that clot resolution deviates from strictly first–order kinetics will be examined by using a higher order term, such as a quadratic, as well as a linear term, for the estimation of percent clot resolution rate by time from baseline CT scan.

Comparisons of the rate of clot resolution among two or more groups will be carried out by designating one patient group, such as the patients treated with 0.3 mg of rt-PA every 8 hours, as the reference group, creating an indicator or "dummy" variable for each other patient group in the comparison, creating a further variable defined as the product of "time since baseline CT" and the indicator variable (i.e. an interaction term), and adding this latter variable to the model as an independent variable. This is *equivalent to* estimating a separate clot resolution rate for each patient group, while keeping the estimates for any other covariates in the model identical for all patient groups. This method will be also used to compare the endoscopy group with the minimally invasive catheter placement groups. Furthermore, this approach provides a method for statistically testing for differences in clot resolution rates between patient groups. Statistical significance of the interaction term would signify that the rate of clot resolution differed between the group of patients indicated and the designated reference group of patients. Since prior observations by our group have suggested a possible effect of gender on clot resolution, gender will be examined as a possible explanatory variable.

Follow-up mortality and morbidity. Data on mortality and morbidity collected at 1, 3, and 6 months will be collected. Measures of central tendency, such as means or medians where more appropriate, as well as estimates of variability, will be calculated for each time point. While the scoring of the Stroke Impact Scale (and Barthel Index) provides for finer distinctions to be made between patients and for patients across time, the Glasgow Outcome Scale score includes two important features. First, it provides for a score to be assigned for patients who have died. Second, this GOS can be established by an observer as an estimate of function prior to the onset of disease. This makes comparisons easier when mortality may occur and allows for comparison between pre and post morbid states. Since the Stroke Impact Scale, Barthel Index, and GOS are ordinal measures, appropriate statistical tests such as the Wilcoxon matched-pairs signed-ranks test, for comparisons of measures within the same group of patients, for example at different times, and the Mann-Whitney two-sample statistic for comparisons across groups of patients, will be employed. A nonparametric multi (greater than 2)-sample test on the equality of medians will be used to test the null hypothesis that the samples were drawn from populations with the same median. Significance calculated by Fisher's exact test is available for this test in the statistical package, Stata that will be used for these analyses.

A P value of less than 0.05 will be considered to indicate statistical significance.

13.9.2 Sample Size

A total sample of 110 randomized patients is planned in addition to the one to two run-in subjects enrolled at each study center, as follows. In stage 1, 60 patients, consisting of 20 patients in each of three successive dosing tiers, will be enrolled using 3:1 randomization in each tier to receive the MIS+rt-PA or endoscopic intervention (n=15 per tier) or conventional medical management (n=5 per tier). In stage two 50 additional patients will be enrolled using 1:1 randomization to receive the MIS+rt-PA or medical intervention (n=25), using the dose selected as a result of the findings from stage 1, or conventional medical management (n=25). The recruitment of these patients will be achieved through the enrollment of six patients per year at each study center. Patients will be enrolled during a 66-month period with an additional six months allocated for initiation and termination procedures.

13.9.3 Level of Significance

Observations with a probability of 0.05 will be accepted as unlikely to be attributed to chance.

13.9.4 Criteria for Termination of the Trial

The DSMB will review the collected data following enrollment of the first 15 subjects and then at 20, 60, and 110 randomized subjects. All deaths will be reviewed. The most likely complications from this therapy are increased mortality, rebleeding, and cerebritis. We propose

to analyze the safety data in two groups to approximate complications attributable to surgery and to the ongoing drug irrigation. The first consists of bleeding and complications within the first 24 hours after catheter placement. The second consists of bleeding and procedure-related complications in the subsequent six days exclusive of surgical events. The minimally invasive surgical group and endoscopic group would also be compared. Any appropriate sub group of surgical subjects will be analyzed separately (such as minimally invasive surgery subjects achieving endpoint of clot resolution without the use of rt-PA). The FDA IND division will be notified according to FDA regulations, part 312.

Early Stopping Rules. In addition, the DSMB will perform an ad-hoc review after occurrence of any of the following serious adverse events. If at any time after the initial 10 patients, the rates of occurrence of 30-day survival fall below 30%, the symptomatic rebleed rate exceeds 35%, first week operative death rate of greater than 10% or the infection rate is greater than 15%, the DSMB will investigate the causes of these complications. If any of these events are related to the catheter insertion or manipulation, or related to rt-PA at a 95% confidence level, then the study will be suspended for a complete safety and efficacy review.

An added limit to excessive dosing is the requirement to analyze each dose tier of 20 subjects for safety before proceeding to the next higher tier. The underlying principles are as follows: 1) safety analyses for additional bleeding events, bacterial cerebritis and new serious adverse events (SAE) will occur by the DSMB before each change of dose tier. The pre-specified safety threshold for rates of symptomatic bleeding during the dose optimization phase is 35%. 2) Analysis for possible achievement of rapid clot lysis will occur at each tier. If the rt-PA associated clot lysis rate produces more than 80% clot lysis in the first 48 hours of treatment, the study may be expanded to 30 patients in the dose tier currently being investigated.

13.9.5 Procedure for Accounting for Missing, Unused, and Spurious Data

Standard procedures will be employed.

13.9.6 Deviations from the Statistical Plan

Changes in the pre-specified analysis plan will be reported to the IRB and FDA. Justification for any such changes should they need to occur will be supplied.

13.9.7 Selection of Subjects to be Included in the Analyses

Because the primary goal of this study is to establish the safety of the combined surgical and drug interventions, all dosed subjects will be included in the primary analyses. Secondary analyses of all randomized and evaluable subjects will be performed as needed to confirm or reject the study hypotheses.

13.10 Direct Access to Source Data/Documents

Investigator/Institution will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

13.10.1 Data Collection and Reporting

Data for each patient will be reported and recorded on electronic case report forms. Electronic case report forms (eCRF) must be completed for every randomized patient. This means all patients who have a signed informed consent, undergo screening procedures, and fulfill all eligibility criteria.

The electronic CRF (eCRF) will be completed by the site investigator(s) listed on the Form FDA 1572 or otherwise designated by the site Principal Investigator. If any entry on a source document requires change, a single line will be drawn throughout the incorrect entry, and the correction will be entered in ink, initialed and dated. Whiteout, erasures, or obliteration on source data are not permitted.

All time fields throughout the forms are military time format. Any entries occurring during the hours of midnight to 1 am will change from 00: _ _ to 0: _ _. For example, a time entered as 00:15 will change to 0:15. All date fields throughout the forms are dd/mmm/yyyy format.

13.10.2 Records Retention

For the purposes of this section, "original study documents" are defined as:

- Subject medical records created at or available to the enrolling center during the subject's participation in the trial, or any other document that supports entries in the EDC system and represents the original source of that information, including but not limited to applicable sections of medical charts, patient correspondence, laboratory data, pharmacy logs and drug accountability forms, as well as any forms or documents used to compile or maintain original subject data or study procedural information. Intermediary documents and worksheets used to organize and compile original records into a form that facilitates easier transcription into the EDC do not represent original study documents. Certain data may be entered directly into the EDC in which case the EDC system represents the original study document.

- All Essential Regulatory Documents (as defined under Good Clinical Practice Regulations) including: all material communications with the IRB; all communications with the sponsor (including the surgical center, reading center, outcomes committee, endpoint committee, safety monitor, Emissary's monitoring staff, etc.) that are related to

study subjects or which otherwise document material study-related procedures or safety issues; and, all training records and documentation that all participating staff are suitably qualified and authorized (CVs, 1572, Delegation Log, etc.).

- Archival copies of the data and electronic documents from the VISION-EDC system.

All study documents should be uploaded to the Electronic Trial Master File (eTMF) section of the VISION-EDC system. VISION will be used as the master repository for all site and sponsor regulatory documents, and all patient source documents with the exception of DICOMs and any records not uploaded to the EDC (perhaps for confidentiality reasons or do to specific site discretion, such as might be suitable for financial contracts), sites generally do not need to maintain duplicate local files unless otherwise mandated by local institutional requirements.

At the conclusion of the study, all entered patient data and uploaded documents (with the exception of Modified Rankin videos and DICOMs) in the VISION-EDC system will be archived and provided to the site on DVDs. Modified Rankin video interviews uploaded to the Glasgow outcomes center will be destroyed at the conclusion of the trial in accordance with informed consent commitments. Due to their extreme size, DICOMs submitted to the EDC system will not be maintained long-term in the EDC system, but rather will be promptly deleted once they have been reviewed by the reading and surgical centers. Sites will be responsible for retaining DICOMs via their local PACS system (or local copies of CDs).

Regulations require that study documents (including the archive CDs and any study documents not uploaded to the EDC) must be retained in the files of the responsible investigator for potential review by regulatory agencies. As this is an international study conducted under the jurisdiction of multiple regulatory bodies (FDA, NIH, Health Canada, ICH, etc.) and for not in support of any one specific regulatory application, retention requirements may be considerably longer than what may be required under local or regional regulations or other trials being conducted at the site. As such, the principal investigator must retain the study documents until otherwise instructed by the coordinating center. The expected retention period is a minimum of 15 years after the conclusion of the overall clinical trial, irrespective of any particular site's participation.

13.11 Quality Control and Quality Assurance

The Principal Investigators at The Johns Hopkins University and the Coordinating Center personnel involved in the clinical research have a good track record of cooperation with experienced stroke investigators. The organizational structure of the trial contains an Executive Committee, Medical Safety Monitor, and Data and Safety Monitoring Board (DSMB).

The Executive Committee (EC) consists of two site principal investigators, the Study Chair, the independent Medical Safety Monitor, the independent Chairman of the DSMB, and the trial's

biostatistician. The Chairman of the committee is the study principal investigator. This appointment is confirmed by mutual consent of the site study investigators. The EC is responsible for the selection of the sites and investigators.

The Medical Safety Monitor is independent of the Coordinating Center and experienced in the field of clinical stroke trial conduct and stroke therapies. The Executive Committee and the Medical Safety Monitor have determined issues of data flow and stopping rules. Recommendations from the Medical Safety Monitor will be made to the DSMB concerning clinical data and safety analyses regarding continuation or cessation of the trial. The Executive Committee will take the final decision concerning the status of the trial. The Executive Committee has the right to govern the activities of the Coordinating Center. The Medical Safety Monitor will also review the clinical history of all patients with SAEs. He will provide his interpretation of relationship of each SAE to the study intervention for the DSMB. The DSMB will provide all pre-planned data reviews and be available for any emergent reviews

The central Randomization Center is the Johns Hopkins University Investigational Drug Services (IDS) Pharmacy. It is external to the Coordinating Center and holds the treatment allocation codes. Where necessary, the site pharmacist will communicate with the central Randomization pharmacist external to the Coordinating Center and the site investigators.

13.11.1 Training and Communication

An investigator meeting will take place in Baltimore, MD at the start-up of Year 01. Study personnel from the Johns Hopkins University Coordinating Center will meet with the other investigator-coordinator teams. The meeting is expected to last one and one-half days. An investigator/coordinator operational manual will be developed for the meeting. Overhead images and slides will be presented during the start-up meeting. The visual aids provided to each site include slides on Background and Significance, Good Clinical Practices, Investigator Responsibilities, FDA requirements, surgical protocols, Case Report Forms, and other specifics of the protocol. This site initiation process will acquaint the center personnel with the design and methods of the trial, the study organization, treatment monitoring, and integrity of data collection.

We will instruct the coordinators on the use of remote data entry (RDE) electronic systems used to capture study data (eCRF), and on the relevant regulatory requirements. During the investigator meetings, formal certification will be required of each site investigator and coordinator prior to the start of the study. NIH Stroke Scale certification and Human Subjects training is also required of each site investigator and coordinator.

13.11.2 Study Monitoring

Study monitors will prepare periodic reports summarizing performance characteristics of the trial as it proceeds from design and development through its completion. The content of the performance monitoring report will emphasize the importance of data collection, quality data, and protocol adherence. Reports will be reviewed by the trial leadership and used to take corrective actions when appropriate.

The monitor report will include an assessment of each site's performance in protocol adherence, patient recruitment, thorough follow-up, and error-free reporting. Site visits may be made to participating study centers for the purpose of assessing performance or potential for performance. Monitoring visits will verify the accuracy and completeness of CRF's, source documents, applicable FDA or other regulatory files and requirements, and that the investigator's obligations are being fulfilled.

Study monitoring will be conducted by Emissary, an experienced CRA firm. There will be no "routine" interim monitoring of the clinical sites. The eCRF (EDC) entries are source-document verified in accordance with a pre-defined monitoring plan developed at the start of the project. Specifically, key primary efficacy and safety data points are reviewed at 100% (approximately) against faxed worksheets and procedure reports; secondary data points (such as demographics, Con-Meds, hourly vitals, etc) are reviewed at an agreed upon lower percentage. (Note, the eCRF system has extensive data validation and range checks to help assure data quality and to reduce transcription errors and missing/illogical/ inconsistent entries). The sites will be compliant in promptly making the EDC entries, faxing the source documents, and resolving the queries as prompted by the eCRF. The CC will continue to manage the sites and handle routine site communications. Emissary monitors will partner with the CC to help sites meet their data deadlines. Should any site exhibit a recurrent and comparatively high rate of queries during the review, or otherwise present a situation suggesting there may be problems at the site (such as lack of compliance with procedures, slow responsiveness, excessive protocol violations, undocumented adverse events, etc.), Emissary will notify the CC of the situation and together will determine a corrective action plan. (A site will be terminated if it does not comply with a corrective action plan.) All sites will have a close-out monitoring visit. In addition to the standard tasks of ensuring completeness of the regulatory files and long-term retention of the documentation, the focus of this visit will also include reviewing a representative number of actual medical charts to ensure the integrity of the previously faxed source documents and to assess that adverse events were appropriately reported. Emissary monitors are included in the investigator start up meeting training and site initiations subsequent to the start up meeting.

13.11.3 Radiographic Masking

Although determinations for routine patient care will be performed locally, radiographic determination needed for treatment comparisons will be made in a central radiological setting

and be part of the permanent data files. Centralizing the CT and MRI scan interpretations ensures that the required masks are maintained. Central reading will assure a high degree of uniformity and standardization of the measurement of the hemorrhage size and assessment of edema and mass effect. The central radiologist and radiology technician will be blinded to clinical information such as the response of the patient to minimally invasive surgery or endoscopy with or without rt-PA. All imaging studies will be catalogued and analyzed, and the results entered into the relational database.

13.12 Ethics

13.12.1 Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendment up to and including the WMA General Assembly, Edinburgh, Scotland (2000) as described in section 13.17.2.

13.12.2 Ethical/Institutional Review Board

The site investigator will provide the JHU Coordinating Center with documentation of institutional review board approval of the protocol and the informed consent document before the study may begin at the site. The ethical review board(s) will review the protocol as required.

The Investigator is to supply the following to the study site's institutional review board(s):

1. The current clinical investigator brochure (Genentech, Inc., San Francisco, CA)
2. The current protocol and informed consent document
3. All updates to the clinical investigator brochure during the course of the study
4. Relevant curriculum vitae
5. Human Subjects Training Certification
6. Any specific information the review board requires.

The Investigator must provide the following documentation to the JHU Coordinating Center:

1. The institutional review board's initial and annual re-approval of the protocol.
2. The institutional review board's approvals of any revisions of the informed consent document or amendments to the protocol or informed consent.

13.12.3 Informed Consent

The informed consent document will be used to explain the risks and benefits in simple terms to the patient or authorized representative before the patient is entered into the study. The informed

consent document must contain a statement that the consent is freely given, that the patient/authorized representative is aware of the risks and benefits of entering the study and the patient is free to withdraw from the study at any time. A sample informed consent for tiers 1 and 2 and tier 3 are included in Chapters 13.17.3 and 13.17.4.

The Investigator or designee is responsible for obtaining informed consent from each patient or their authorized representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug. Informed consent by an authorized representative of the patient should be obtained according to the clinical judgment of the investigator.

13.12.4 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) appointed by the NIH/NINDS will review the collected data yearly or following enrollment of the first 15 subjects and then after 20, 60, and 110 randomized subjects, whichever occurs first. All deaths will be reviewed. The most likely complications from this therapy are increased mortality, rebleeding, and cerebritis. Safety thresholds have been established and if reached will trigger the monitor committee to analyze the causes of these complications. If any of the complications are related to the catheter insertion or manipulation or related to rt-PA at a 90% confidence level, then the study will be suspended for a complete safety and efficacy review. In addition, the DSMB will perform an ad-hoc review after occurrence of any serious adverse events as listed above under "Stopping Rules."

Data safety and monitoring procedures will be in place before enrollment begins and monitoring will be performed on a regular basis throughout the subject accrual and treatment periods.

Dr. Carlos Kase, MD, a stroke physician not involved with the study, will serve as the Medical Safety Monitor. Dr. Kase is a neurologist with experience treating acute ischemic and hemorrhagic stroke as well as clinical trials. He is familiar with the proposed study intervention. He will be responsible for ongoing monitoring of reports of SAEs submitted by the clinical centers to ensure good clinical care and to quickly identify safety concerns. If necessary, he will suggest measures to be taken to prevent the occurrence of particular adverse events, e.g., modifying the protocol to require frequent measurement of laboratory values predictive of the event. With the assistance of the CC, the Medical Safety Monitor will prepare quarterly reports concerning SAEs for submission to the principal investigator, the DSMB, and, as appropriate, the FDA. In the event of unexpected SAEs or an unduly high rate of SAEs, he will be responsible for notifying the DSMB Chair.

Dr. J. Ricardo Carhuapoma, MD, a neurointensivist not involved with the study, will serve as the Critical Care Monitor. Dr. Carhuapoma is a neurologist/neurointensivist with extensive experience in the intensive care of subjects with ICH. He will review key elements of subject acute care management, specifically the interventions, ICU practices, and acute care

complications. He will assess individual subject data for intervention compliance, uniformity of ICU management, and accuracy of reporting serious adverse events related to the ICU experience. Dr. Carhuapoma will report any problems or significant trends to the DSMB, which will then advise the Study Chair, in blinded fashion, of any problems or issues necessary for the management of center performance and protocol compliance.

13.12.5 Inclusion of Women

Women will be included in the study. Periodic monitoring of gender specific rates of recruitment will be carried out and recruitment criteria will be adjusted if necessary to ensure that women make up approximately one-half of all subjects. The previous multicenter study coordinated by JHH made up of ICH subjects had almost 50% female subjects without any intervention strategies. Pregnant or lactating females will be excluded because of the likelihood of altered coagulation function associated with the high estrogen/progesterone state.

13.12.6 Inclusion of Minorities

Minorities will be included in the study. The frequency of minorities will depend upon the general characteristics of patients seen at the participating site. In the previous multicenter study coordinated by JHH, approximately 56% of subjects were African-American, 14% were Hispanic, 8% were Asian, and 22% were Caucasian. With similar recruitment at all sites, we anticipate approximately 75% of subjects to be minorities. The design of this clinical trial will enroll subjects who reflect the minority and gender composition of the United States population. We will target/plan on enrolling 13 Asian subjects, 63 black or African-American subjects and 40 white subjects, based on enrollment in our completed IVH-rtPA trial.

13.12.7 Inclusion of Children

Children under the age of 18 years of age will be excluded from enrollment because of the high incidence of occult vascular malformation in this group.

13.12.8 Human Subjects Research Training

Education in the protection of human research participants has been met by certified completion of the Johns Hopkins University School of Medicine Web-based Research Compliance course, "Human Subjects Research Training" by all relevant Key Personnel. The course consists of the University of Minnesota Web modules on Informed Consent, the Consent Process, and After Informed Consent, a Johns Hopkins University School of Medicine Module on local IRB requirements, and achievement of a passing score on the Knowledge Assessment module.

Education in the protection of human research participants will be met by certified completion of the "Human Subjects Research Training" by all relevant site investigators and coordinators at each participating site. The course must be equivalent to the University of Minnesota Web modules on Informed Consent, the Consent Process, and After Informed Consent, and Module on local IRB requirements, and participants must achieve a passing score on the Knowledge Assessment module.

13.12.9 Investigator Responsibilities

Each site investigator affirms that he or she is qualified by education, training & experience; thoroughly familiar with rt-PA and its use, and aware of and comply with Good Clinical Practice (GCP/ICP). The investigative team agrees to permit monitoring and auditing and maintain a current co-investigator list and information on delegated authority. Each site surgeon affirms he or she is qualified by education, training, and experience to perform minimally invasive surgery or endoscopic surgery.

Investigator responsibilities include being able to recruit required number of subjects; having time to conduct and complete the trial; having an adequate number of qualified staff and facilities for the safe and proper conduct of the trial. The investigator must ensure that all persons assisting with the trial know the protocol and trial functions. The principal investigator agrees to make all trial-related medical decisions, to ensure medical care for adverse events including clinically significant labs, to inform the subject's primary physician of the subject's participation in the trial, and to ascertain the reason(s), if subject withdraws prematurely from the trial. The investigator further agrees to obtain IRB approval, provide documents to the local IRB during the trial.

The investigator agrees to conduct the trial in compliance with the protocol, not to implement any deviation without Coordinating Center agreement, document and explain any deviation from the accepted protocol, account for use of rt-PA on site, and follow the trial's randomization procedures. The investigator will be responsible for his or her investigative team members as they obtain and document informed consent; ensure the accuracy, completeness, legibility, and timeliness of data; maintain source documents; change or correct edited data; maintain trial documents; and report all serious adverse events. The Principal Investigator agrees to record all temporally related adverse events, and inform the institution of trial completion and final reports.

13.13 Data Handling and Record Keeping

13.13.1 Coordinating Center Activities

Data analysis is approved by the Executive Committee to take place at The Johns Hopkins University. Full analysis will occur when the data has been cleaned and the database locked.

Unblinding as to treatment allocation will be made by the Randomization Center to the CC so that analysis according to treatment effect can occur. The results of the data analysis will be given first to the EC. Initial access to this information will be via its EC representative(s) so that early and inappropriate access to this information may be avoided. Futility analyses will not be conducted. Stopping rules have been established on safety and efficacy (See Section 13.9.4.).

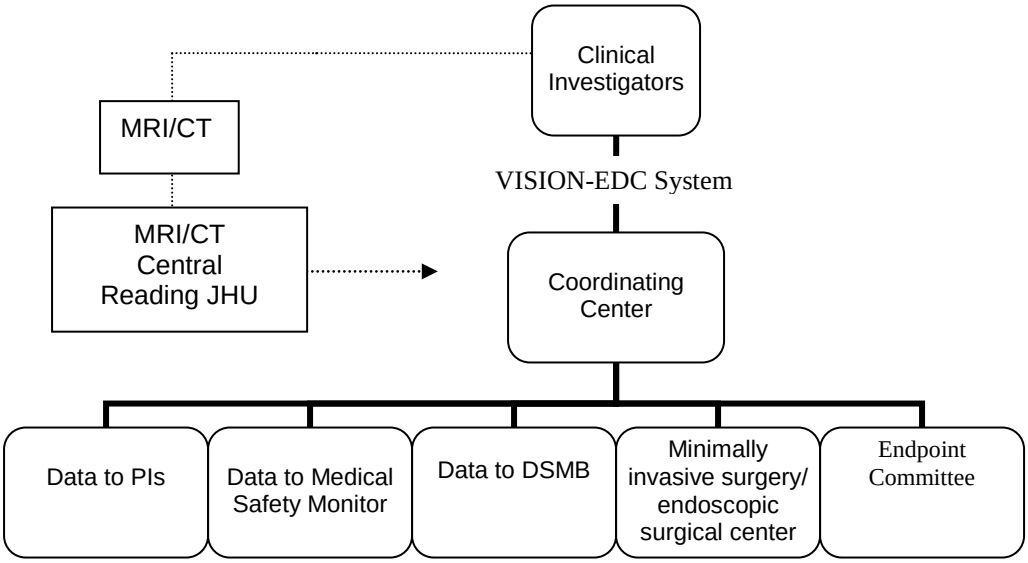
Crude data will be held at the Coordinating Center. Collations of this data will be supplied to the safety monitoring committee at pre-determined times requested by the DSMB, or at any other time the committee may so determine.

The CC, based at JHU, has been developed for data management, quality control, and statistical analysis and to assist in safety monitoring. The CC will be supervised by the Study Chair. The CC will collect data from the site clinical investigators as well as from the central MRI/CT readers, to ensure accuracy and completeness of data collection, to manage, edit and clean the data that has been entered into an electronic database designed for the study, and produce periodic data summaries for the PI and safety monitors. The CC will also be responsible for management of regulatory documentation, protocol compliance and budgetary issues. An outline of data flow in this study is provided below.

Biostatisticians for the project will work with the CC to function as the Analysis Center for the trial. The CC will receive the data on a regular basis, edit the data, and apply quality control and quality assurance procedures. The CC will maintain the accumulated database, create an accurate and secure library of reports and data files reflecting the accumulation of the study data and subject log data. The CC will insure accuracy and completeness of data and provide timely feedback on data quality. When data is ready, the biostatistician will analyze the data, working closely with the CC.

The EC, Medical Safety Monitor, and the DSMB shall remain blinded to outcome data throughout the conduct of the trial. Blinded data will be reviewed by the safety monitoring committee at pre-determined times and unblinded data at the discretion of the same committee. Unblinding will occur at the completion of the trial, or at its early termination. The unblinding sequence is described below.

Data Flow and Management



13.13.2 Quality Control and Management of Data

The CC will prepare reports summarizing patient selection and protocol adherence as well as data quality. At the patient closeout, the CC will develop and manage data analyses that summarize the study's findings. The CC will also prepare the final reports summarizing the overall performance of all sites with respect to the protocol and the quality of the data generated. Each performance center must demonstrate that it is properly staffed and equipped to support the protocol activities.

The protocol is supplemented with an organized operations manual containing performance standards, instructions for handling of the drug, surgical procedures, CT scans and MRI scans. Data forms associate directly to an electronic database. Before the trial begins, the CC and sites will have approved consent forms and IRB approvals, fully executed contracts and agreements, curriculum vitae for each investigator on file, and normal lab ranges for the local labs. The subject recruitment goal for each site is designated at 6 subjects per site per year. Site performance as well as detailed eligibility and exclusion criteria and reports will be generated with graphic representation of the trial's progress monthly. Subject eligibility logs will be transmitted via the EDC system to the CC daily. During monitoring, electronic data entry will be compared to source documentation to check for accuracy and completeness. Also, the CC will crosscheck all forms against each other for reporting accuracy. All discrepancies will be reported to individual sites by the CC. Sites will be required to make the necessary changes/clarifications directly into the electronic data entry system.

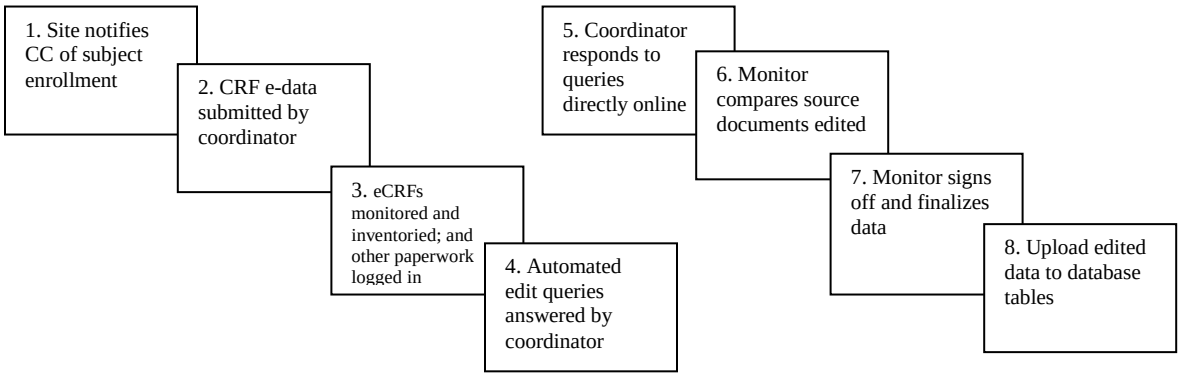
13.13.3 Data Collection

Each patient is assigned a unique study number, with a list of patient names, study numbers, and any identifying information kept in a separate file to ensure patient confidentiality. Daily data collection of ICP management, ICU care, catheter-monitoring, and neuroimaging will assess the patient's clinical response to treatment as well as the status of those subjects receiving medical management as part of the clinical trial. These data will be used to assess compliance with stopping rules and care directed at independence. The results of daily coagulation studies also will be collected. The Modified Rankin, Expanded Glasgow Coma, NIHSS, Barthel Index, and SIS scales are used to assess clinical outcome at one, three and six months. Data collection entries are completed daily electronically. CD ROM disks containing MRI and CT studies are sent to the CC no more than 7 days after the subject's discharge from the hospital. A paper bedside source document binder may be prepared locally to further document the existence of the subject and substantiate the data collected. An examiner blinded to treatment assignment will obtain the follow-up clinical data at 1, 3 and 6 months post-stroke.

Data will be entered directly into an electronic data collection system onto preformatted fields at hospital computer workstations. Data may first be entered onto parallel paper case report forms (CRF's) and bedside worksheets, according to the investigator and coordinator's preferences. Access to electronic CRF's will be via security passwords. At the CC, the data will be uploaded into database tables. The data will be secured using security commands and chronological audit links before and after electronic documents are received at the CC in compliance with HIPAA requirements. All data is anonymous with a unique identifier assigned at the study center.

Edit checks will be defined at each data point. These checks will include missing day warnings as well as out of expected range warning. The data will be transferred to a XML database server located in a secure area in compliance with HIPAA requirements. The file server will be backed up daily. Upon entry on site, the CC will complete a first data check and data query will be automatically generated to the site coordinator. The site coordinator will respond to the edits online until the data are corrected and locked to further changes. These data will be compared to source documents for every subject.

Statistical analyses will be done using STATA upon transfer from XML.



13.14 Financing and Insurance

The proposed study will be financed via a peer-reviewed research grant. A submission to the NIH is awarded. Finance and insurance is addressed in a separate agreement.

13.15 Conflict of Interest

Individuals who are aware of a potential or existing conflict of interest that may preclude them from committee involvement or investigator participation will disclose all potential conflicts to the EC so that appropriate action may be taken.

13.15.1 Publication Policy

The results of the trial will be published regardless of its outcome. A Publication Committee will be established. Publication regarding further analyses performed on the data will be by mutual agreement between the Executive Committee and the site investigators.

The investigator may publish or present at scientific meetings the results of this study, provided that confidential information is not disclosed, and only after obtaining advance written consent from the Executive Committee. Consent may be withheld at the sole discretion of Executive Committee.

In this regard, a copy of all public disclosures, including but not limited to publication manuscripts, abstracts, and seminar presentations, should be provided to the Executive Committee for review, at least 30 days before the manuscript is submitted to the publisher or a presentation is made.

The Executive Committee agrees that before it publishes any results of the study, a pre-publication manuscript will be provided to the investigator for review at least 30 days before being submitted to a publisher.

13.15.2 Data Disclosure

All information concerning the basic scientific data and information supplied by the investigator and not previously published are considered confidential. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the study's Executive Committee written consent. The Investigators understand that the information developed in this clinical study will be used by the trial Investigators in connection with the development of this protocol and therefore, may be disclosed as required to other clinical investigators, to the United States Food and Drug Administration, and to other U.S. and non-U.S. government agencies. In order to allow for the use of the information derived from the clinical

studies, it is understood that there is an obligation to provide the U.S. FDA and NIH with complete test results and all data developed in the study.

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13.17 Appendices

13.17.1.a Study timeline: MISTIE (Stage 1: Tiers 1 and 2)

	Baseline	Post Consent Screening	Post Randomization/ Pre Surgery	Day 1	Day 2	Day 3	Days* 4 - 6	Day 7	Day 30† ± 7 days	Day 90† ± 7 days	Day 180† ± 14 days
Diagnostic CT (SOC)	X										
Stability CT (6 hours after diagnostic CT)		X									
Blood pressure control sustained over a minimum of 6 hours	X	X									
Pregnancy test	X	X									
Medical History/Review of Systems			X								
Review of Systems (post surgery)				X							
MRI (FLAIR)/MRA (or CTA)				X				X			
Image-Guided Catheter Placement + Aspiration (Surgical Group Only)				X							
rt-PA administration (Surgical Group Only; every 8 hours for 72 hours)				X	X	X					
Dose Tier 1: 0.3 mg q8hrs				0.9 mg	0.9 mg	0.9 mg					
Dose Tier 2: 1.0 mg q8hrs				3.0 mg	3.0 mg	3.0 mg					
Post catheter placement CT scan				X							
PK Sampling at Dose 1 and Dose 4				X	X						
Daily CT Scan				§	X	X	X (Day 4)		X		X
				24 h post Catheter Removal							
Vital Signs				X	X	X	X				
Neurocheck				X	X	X	X				
Lab Assessments				X	X	X	X				
NIHSS		X	X					X	X		X
Barthel Index			X						X	X	X
Modified Rankin	Historic	X	X						X	X	X
Stroke Impact Scale									X	X	X
GOS									X	X	X
eGOS									X	X	X

*Assessments should be performed daily through Day 6 regardless of treatment assignment.
†An examiner blinded to treatment group assignment and acute care data must complete the Day 30, 90, and 180 follow-up visits.
§ Subjects enrolled to medical management: The Day 1 CT scan does not need to be repeated if enrollment occurs on the same calendar day as the stability CT scan (done 6h post the diagnostic CT scan).

13.17.1.b Study Timeline: MISTIE-ICES (Stage 1: Tier 3)

	Baseline	Post Consent Screening	Post Randomization/ Pre Surgery	Day 1	Day 2	Day 3	Days* 4 - 6	Day 7	Day 30† ± 7 days	Day 90† ± 7 days	Day 180† ± 14 days	Day 270† ± 14 days	Day 365† ± 14 days
Diagnostic CT (SOC)	X												
Stability CT (6 hours after diagnostic CT)		X											
Blood pressure control sustained over a minimum of 6 hours	X	X											
Pregnancy test	X	X											
Medical History/Review of Systems			X										
Review of Systems (post surgery)				X									
MRI (FLAIR)/MRA (or CTA)				X				X					
Image-Guided, Endoscopic Catheter Placement + Aspiration (Surgical Group Only)				X									
Post catheter placement CT scan				X									
Daily CT Scan				§	X	X	X (Day 4)		X		X		
				24 h p ost Catheter Removal									
Vital Signs				X	X	X	X						
Neurocheck				X	X	X	X						
Lab Assessments				X	X	X	X						
NIHSS		X	X					X	X		X		X
Barthel Index			X						X	X	X	X	X
Modified Rankin	Historic	X	X						X	X	X	X	X
Stroke Impact Scale									X	X	X	X	X
GOS									X	X	X	X	X
eGOS									X	X	X	X	X

*Assessments should be performed daily through Day 6 regardless of treatment assignment.
†An examiner blinded to treatment group assignment and acute care data must complete the Day 30, 90, 180, 270, and 365 follow-up visits.
§ The Post catheter placement CT scan will serve as the Day 1 CT scan. The Day 1 CT scan does not need to be repeated.

13.17.1.c Study timeline: MISTIE (Stage 2)

	Baseline	Post Consent Screening	Post Randomization/ Pre Surgery	Day 1	Day 2	Day 3	Days* 4 - 6	Day 7	Day 30† ± 7 days	Day 90† ± 7 days	Day 180† ± 14 days	Day 270† ± 14 days	Day 365† ± 14 days
Diagnostic CT (SOC)	X												
Stability CT (6 hours after diagnostic CT)		X											
Blood pressure control sustained over a minimum of 6 hours	X	X											
Pregnancy test	X	X											
Medical History/Review of Systems			X										
Review of Systems (post surgery)				X									
MRI (FLAIR)/MRA (or CTA)				X				X					
Image-Guided Catheter Placement + Aspiration (Surgical Group Only)				X									
rt-PA administration (Surgical Group Only; every 8 hours for 72 hours)				X	X	X							
Post catheter placement CT scan				X									
PK Sampling at Dose 1 and Dose 4				X	X								
Daily CT Scan				§	X	X	X (Day 4)		X		X		
				24 h post Catheter Removal									
Vital Signs				X	X	X	X						
Neurocheck				X	X	X	X						
Lab Assessments				X	X	X	X						
NIHSS		X	X					X	X		X		X
Barthel Index			X						X	X	X	X	X
Modified Rankin	Historic	X	X						X	X	X	X	X
Stroke Impact Scale									X	X	X	X	X
GOS									X	X	X	X	X
eGOS									X	X	X	X	X

*Assessments should be performed daily through Day 6 regardless of treatment assignment.
†An examiner blinded to treatment group assignment and acute care data must complete the Day 30, 90, 180, 270, and 365 follow-up visits.
§ Subjects enrolled to medical management: The Day 1 CT scan does not need to be repeated if enrollment occurs on the same calendar day as the stability CT scan (done 6h post the diagnostic CT scan).

13.17.2 WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This

does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

To further clarify the WMA position on the use of placebo controlled trials, the WMA Council issued, during October 2001, a note of clarification on article 29 (See Below).

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

NOTE OF CLARIFICATION ON PARAGRAPH 29 of the WMA DECLARATION OF HELSINKI

The WMA is concerned that paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

13.17.3 MISTIE Sample Consent Form

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Minimally Invasive Surgery plus rt-PA for ICH Evacuation: MISTIE

PROTOCOL NO.: Sponsor protocol number: ICH01
WIRB® protocol number: 20021602

SPONSOR OF RECORD: Daniel F. Hanley, MD
Director, Brain Injury Outcomes Division
Johns Hopkins University Department of Neurology
Baltimore, Maryland, USA

PRIMARY FUNDING: National Insitutes of Health/
National Institute of Neurological Disorders
and Stroke

ADDITIONAL SUPPORT: Genentech, Inc.
Johnson & Johnson (Company providing drain tubes)
FDA Office of Orphan Products Development

INVESTIGATOR:

FACILITY(S):

STUDY-RELATED PHONE NUMBER(S):

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain anything that you do not clearly understand. You may have an unsigned copy of this consent form to take home and think about or discuss with family or friends before making your decision.

A person who takes part in a research study is called a research or study subject. In this consent form, "you" always refers to the research subject. If you are a legally authorized representative (LAR), please remember that "you" means the research (study) subject.

SUMMARY

You are being asked to join a research study. The purpose of this consent form is to help you decide if you want to be in the research study. Please read this form carefully.

To be in a research study you must give your informed consent. Giving "informed consent" means:

- Reading this consent form,
- Having the study doctor or staff explain the research study to you,
- Asking questions about anything that is not clear, and
- Getting an unsigned copy of this consent form to take home. This gives you time to think about it and to talk to family or friends before you make your decision.

You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- No one can promise that a research study will help you.
- Taking part in a research study is entirely voluntary. No one can make you take part.
- If you decide to take part, you can change your mind later and withdraw from the research study.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study may involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- Other parts of this study may involve experimental (investigational) drugs or procedures that are being tested for a certain condition or illness. An investigational drug is one that has not been approved by the U.S. Food & Drug Administration (FDA).
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.
- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed, then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

After reading and discussing the information in this consent form you should know:

- Why this research study is being done;
- What will happen during the research;

- What drug or device or procedures will be used;
- Any possible benefits to you, if any;
- The possible risks to you;
- The other medical procedures, drugs or devices that could be used instead of being in this research study; and
- How problems will be treated during the study and after the study is over.

If you take part in this research study, you will be given a copy of this signed and dated consent form.

PURPOSE OF THE STUDY

You are being asked to join a research study looking at removing blood from the brain that happened without warning and which is not caused by a head injury. This unexpected bleeding in to the brain is called ICH or intracerebral hemorrhage. ICH typically occurs in patients with high blood pressure or in the elderly due to fragile blood vessels.

The rate of death in patients with ICH is still very high despite the best medical treatment. Also, the amount of recovery in those that survive are also very poor. It has been shown that the amount and success of recovery is related to the size of the blood clot in the head. However, extensive surgery to remove the blood clot has sometimes been shown to be more harmful. Therefore, the usual treatment for ICH is to avoid doing extensive surgery whenever possible. This usual treatment is called "standard medical care."

Recent studies have shown that a less aggressive method of removing the blood clot - by using a small drain tube surgically placed into the brain to give a medicine to break up the clot - can be of benefit. This study will allow us to see if this method of clot evacuation is safer than standard medical care which does not involve removing the clot.

The purpose of this study is to evaluate the safety of a study drug called recombinant tissue plasminogen activator (rt-PA) when used with minimal surgery for the removal of a blood clot from the brain. The study drug is approved in heart attacks or stroke for dissolving clots but is an investigational drug in this study. An investigational drug is one which has not been approved by the U.S. Food and Drug Administration (FDA) for this targeted use.

PROCEDURES

About 146 patients will be enrolled in this study over a 6-year period. With your consent, you will have the following screening procedures to find out if you are eligible for this study.

1. A CT scan will be done at least 6 hours after the first CT scan that diagnosed the bleeding in your brain. If this second CT scan shows more blood in the brain when compared to the first CT scan, another CT scan will be repeated at least 6 hours later. This is done to make sure the bleeding has stopped. A CT scan is a test that produces an image of your body using a small amount of radiation. The image shows the body tissues and structure in three dimensions ("3-D"). These CT scans may already have been done per standard medical care.

2. A MRI (magnetic resonance imaging) scan with FLAIR and a MRA (magnetic resonance angiogram) or a CTA (computed tomography angiogram) will be done. These procedures are standard medical care to see if the bleeding is caused by abnormal blood vessels, such as an aneurysm. You will not be eligible for this study if this is the cause for your bleeding.

3. A pregnancy test will be done if you are a female of childbearing potential. You must not be pregnant to be in this study.

If, after these tests, you are found to be eligible for this study, you will be randomly assigned (similar to flipping a coin) to one of the two methods being compared in this study. You will either continue to receive standard medical care, or a small tube will be surgically placed into the clot to allow it to drain. You will have 1 chance out of 2 to be selected to have surgery. The drug rt-PA may be given through this tube to help break-up the clot if the drain alone does not remove enough of it.

If you are randomly chosen or assigned to the group that will get the drain, you will be taken to an operating room or other designated area and given an appropriate anesthetic. A neurosurgeon will make a skin incision over the site of the blood clot after giving a local anesthetic. Following this, a hole will be drilled in the skull through the skin opening and an unbendable, hollow tube will be passed into the clot. When the tube is in the right place, suction will be applied to the drain using a syringe to remove as much of the blood clot as possible. A soft rubber drain tube (called a catheter) will be passed through the tube and the unbendable tube will be removed. The soft rubber drain tube will be left in the clot in the head and the skin will be closed it. Another CT scan will then be done to see how much clot is left and to make sure that the soft drain tube is in the middle of the remaining blood clot.

You will then be taken to the intensive care unit. If there is enough blood clot remaining in the brain after the surgery, rt-PA (a drug that breaks up blood clots) along with a saline (salt water) fluid will be given into the drain every 8 hours to break up the clot. In-between injections, the drain tube will be attached to a drainage system to allow the clot to come out on its own. Once a day you will be taken to have another CT scan. Injections

of rt-PA will stop after 9 doses have been given or when enough blood has been removed from the clot, whichever comes first.

We will remove four ½-teaspoons (a total of 2 teaspoons) of fluid directly from the drain using a syringe and gentle pressure once before and three times after drug treatments 1 and 4.

If you are randomly assigned to continue to receive standard medical care, you will have a CT scan every day for 4 days. Your vital signs and neurological condition will be monitored daily for the next 6 days. Labs will be drawn for the next 6 days to monitor natural chemical levels in the blood related to the bleeding in your brain.

Regardless of what group you are assigned to your vital signs, such as, heart rate, blood pressure, temperature, and neurological condition will be monitored daily for the next 6 days. Laboratory blood samples will be drawn for the next 6 days to monitor natural chemical levels in the blood related to the bleeding in your brain. CT scans will be done daily for the next 4 to 5 days to monitor the remaining blood clot in your brain. A MRI will be performed at day 7.

You will be asked to return to clinic 30, 180, and 365 days from today. During this clinic visit you will have a follow-up CT scan to look at how your brain is healing. Your neurological condition and blood pressure will be checked and you will be asked questions about how well you are doing.

You will be contacted by telephone 90 and 270 days from today. You will be asked questions about your condition and how well you are doing.

RISKS AND DISCOMFORTS

Approximately 48% of ICH patients receiving standard medical care will normally have further bleeding in the brain. This is called rebleeding. In this study, the risk of rebleeding could be higher than normal. Certain procedures such as inserting the drain tube into the clot, injecting the clot-dissolving drug, and removing the drain tube may increase the risk.

Approximately 10% to 20% of ICH patients receiving standard medical care will normally develop infection. In this study, the injection of the study drug (rt-PA) could increase this risk. The placement of the drain tube and leaving it in place for 3 days may further increase this risk. The removal of fluid from the drain may be associated with an increased risk of infection. We will try to reduce the risk of infection by using a standardized sterile technique to inject the drug and remove the fluid.

We do not yet know if your overall risk is higher or lower if you get the drain tube and the investigational medication. Other risks include possibly worsening your neurological

condition and potentially even death. An ICH patient receiving standard medical care is at risk for these events as well.

We will watch for problems by sampling the spinal fluid for infection, if necessary, testing the blood for bleeding disorders, and by CT scans of the brain to look for additional bleeding.

You will have to stay in bed while the drain tube is in place. All other medical care will be routine for subjects with your condition in the intensive care unit.

Drawing blood from your arm may cause pain, bruising, lightheadedness, and, on rare occasions, infection.

There may be risks or side effects, which are unknown at this time.

The radiation exposure from the CT scans you will receive by participating in this study is equivalent to an exposure of 1.08 rems to your whole body. For comparison, naturally occurring radiation from the environment exposes people to about 0.3 rems per year and people exposed to radiation in their occupations are permitted to receive whole body exposures of 5 rems per year.

Because of the need for head CT and MRI scans, you will have a pregnancy test if you are a female of childbearing potential. You may not take part in this study if you are pregnant or nursing.

Your condition may not get better or may get worse during this study.

NEW FINDINGS

You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

POSSIBLE BENEFITS

Your intracerebral hemorrhage (ICH) may improve while you are in this study; however, this cannot be promised. The results of this study may help people with ICH in the future. There is no guarantee that you will receive any medical benefits from being in this study.

There may be no benefit to you from use of the study drug. We hope to show that rt-PA in combination with minimal surgery, will decrease the size of the blood clot in your head allowing you to recover faster. If you are assigned to receive standard medical care, you may not have this benefit. If this study shows that the use of rt-PA in combination with minimal surgery is more effective than medical treatment, it could be of benefit to many

more patients who have bleeding into the brain.

It cannot be promised that you will receive any medical benefits from being in this study.

COSTS

Genentech Inc., based in South San Francisco, USA is the manufacturer of this drug. They will provide it free of charge during this study.

Procedures that are done only for the study, such as extra lab tests will not be billed to you or your insurance company.

You or your insurance company may be billed for:

- Any standard medical care given during this research study.
- The surgical procedure of placing the narrow tube into your brain. If your insurance company does not pay for this procedure, the study will pay for it.

Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include the costs of treating side effects. Otherwise, you might have unexpected expenses from being in this study.

You may want to talk with your insurance company about its payment policy for standard medical care given during a research study. If your insurance company does not pay, you may be billed for those charges.

COMPENSATION FOR INJURY

You will be responsible for payment of any treatment or hospitalization you require if you are injured as a result of being in the study. Your health insurance company will be billed for payment of any treatment or hospitalization. Your health insurance company may or may not pay for treatment of injuries as a result of your participation in this study. The sponsor, the federal government, and the study doctor do not have a program to pay for injuries that may result from participation in this research study.

By signing this consent form, you have not waived any of the legal rights which you otherwise would have as a subject in a research study. Your health insurance company may or may not pay for treatment of injuries as a result of your participation in this study.

PAYMENT FOR PARTICIPATION

You will not be paid for participation in the study. You will present receipts and be reimbursed for travel and or parking as part of the 30, 180, and 365 day follow-up visits only. All other visits will take place while you are in the hospital.

ALTERNATIVE TREATMENT

If you decide not to enter this study, there are no other specific treatments available. Ask the study doctor to discuss possible options with you. You do not need to participate in this study to receive general and intensive care treatments for your condition.

Currently the only alternative to this treatment is standard medical management without removal of the blood clot. Your decision to participate or not to participate in this study will not affect the quality of care you receive. If you decide not to enter the study, you will continue to receive all medical and surgical care appropriate for your condition.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?

The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Information gathered for this research about:
    - Physical exams
    - Laboratory, x-ray, and other tests results
- Records about any study drug you received

Who may use and give out information about you?

The study doctor and the study staff will use this information. They may also share certain information with agents for the study doctor who provide technical or administrative support.

Who might get this information?

For regulatory purposes, the sponsor of this study is Dr. Daniel F. Hanley, a neurologist and the director of the Brain Injury Outcomes Division at the Johns Hopkins University School of Medicine in Baltimore, Maryland. Dr. Hanley is coordinating this study on behalf of the doctors and staff at approximately 40 other hospitals and academic centers in the U.S. and Europe, including your doctor and hospital. He is assisted by a number of organizations and individuals who provide services in support of this trial. The term "sponsor" includes:

- Dr. Hanley;

- His staff at the Johns Hopkins University; and
- The other people and organizations who assist Dr. Hanley with this study.

Your information may be given to:

- The sponsor;
- The U.S. Food and Drug Administration (FDA);
- Department of Health and Human Services (DHHS) agencies;
- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported;
- Genentech, Inc. (the pharmaceutical company providing the drug for this study);
- Johnson & Johnson (the medical device company providing the drain tubes for this study);
- Wayne State University (fluid sample testing);
- The Johns Hopkins University; and
- *[Add local IRB and any additional names here]*.

Why will this information be used and/or given to others?

- To do the research,
- To study the results,
- To see if the research was done right, and
- To plan further research.

The doctors and scientists participating in this study intend to use the information to write medical papers and make presentations at annual meetings. Your identity will not be disclosed in these presentations and publications.

The people working on this study will collect information about you. This includes things learned from the procedures described in this consent form. They may collect other information including your name, address, date of birth, and other details. The research team will need to see your information. Sometimes other people at [YOUR INSTITUTION] may see or give out your information. These include people who review the research studies, their staff, lawyers, or other [YOUR INSTITUTION] staff.

People outside of [YOUR INSTITUTION] may need to see your information for this study. Examples include government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study, and companies that support the study.

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. Information, which may include copies of your medical records, will be delivered by mail, courier, fax transmission, e-mail attachment, or by submission to a secure website.

Release of your records is necessary for you to participate in this investigational study. If you do not wish to participate, you will still receive full standard medical care.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
Yes, but this permission will not stop automatically.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

Use the following Confidentiality section instead of the above Authorization section if the site is not *a covered entity under HIPAA of if the site* is *using a separate HIPAA authorization form.*

Confidentiality

Study information collected about you will be given to the sponsor.

For regulatory purposes, the sponsor of this trial is Dr. Daniel F. Hanley, a neurologist and the director of the Brain Injury Outcomes Program at the Johns Hopkins University School of Medicine in Baltimore, Maryland. Dr. Hanley is coordinating this trial on behalf of the doctors and staff at approximately 40 other hospitals and academic centers in the U.S. and Europe, including your doctor and hospital. He is assisted by a number of organizations and individuals who provide services in support of this trial. The term "sponsor" includes:

- Dr. Hanley;
- his staff at Johns Hopkins; and
- the other people and organizations who assist Dr. Hanley with this study.

It will also be given to the U.S. Food and Drug Administration (FDA). It may be given to governmental agencies in other countries where the study drug may be considered for approval.

Medical records which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by:

- The sponsor;
- The U.S. Food and Drug Administration (FDA);
- Department of Health and Human Services (DHHS) agencies;
- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Genentech, Inc. (the pharmaceutical company providing the drug for this study);
- Johnson & Johnson (the medical device company providing the drain tubes for this study);
- Wayne State University (fluid sample testing);
- Johns Hopkins University; and
- *[Add local IRB and any additional names here]*.

The people working on this study will collect information about you. This includes things learned from the procedures described in this consent form. They may collect other information including your name, address, date of birth, and other details. The research team will need to see your information. Sometimes other people at [YOUR INSTITUTION] may see or give out your information. These include people who review the research studies, their staff, lawyers, or other [YOUR INSTITUTION] staff.

The doctors and scientists participating in this study intend to use the information to write medical papers and make presentations at annual meetings. Your identity will not be disclosed in these presentations and publications.

People outside of [YOUR INSTITUTION] may need to see your information for this study. Examples include government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study, and companies that support the study.

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. Information, which may include copies of your medical records, will be delivered by mail, courier, fax transmission, e-mail attachment or by submission to a secure website.

Release of your records is necessary for you to participate in this investigational study. If you do not wish to participate, you will still receive full routine medical care.

VOLUNTARY PARTICIPATION/WITHDRAWAL

Taking part in this study is voluntary. You may decide not to take part or your may leave the study at any time. Your decision will not cause any penalty or loss of benefits to which you are entitled.

The study doctor or the sponsor may stop your participation in this study at any time without your consent for any of the following reasons:

- it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan; or
- for any other reason.

If you leave the study before the planned final visit, you may be asked by the study doctor to have some of the end-of-study procedures done.

SOURCE OF FUNDING FOR THE STUDY

The U.S. National Institutes of Health (NIH) is providing the primary funding for this study.

QUESTIONS

Contact [NAME] at [NUMBERS] for any of the following reasons:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, you may contact:

[YOUR LOCAL IRB/EC NAME AND ADDRESS]

The IRB/EC is a group of people who independently review research.

The IRB/EC will not be able to answer some types of questions, such as questions about appointment times. You may contact the IRB/EC if you cannot reach the research team or if you want to talk to someone else.

Minimally Invasive Surgery plus rt-PA for ICH Evacuation
MISTIE

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers.

CONSENT

I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form I have not given up any of my legal rights.

Consent and Assent Instructions:

Consent: *Subjects 18 years or older and able to provide consent must sign on the subject line below.*

Consent is provided by the Legally Authorized Representative for adult subjects unable to consent.

Assent: *Is required for adult subjects unable to consent.*

_____
Subject Name

CONSENT SIGNATURE:

_____ _____
Signature of Subject (18 years and older) Date/Time

_____ _____
Signature of Legally Authorized Representative (when applicable) Date/Time

_____
Authority of Subject's Legally Authorized Representative or Relationship to Subject (when applicable)

_____ _____
Signature of Person Conducting Informed Consent Discussion Date/Time

ASSENT SIGNATURES, For Adult Subjects with a Legally Authorized Representative:

Assent:

For subjects who have a legally authorized representative, I confirm that:

☐ I have explained the study to the extent compatible with the subject's understanding, and the subject has agreed to be in the study.

OR

☐ The subject is not able to assent due to lack of mental capacity.

_____ _____

Signature of Person Conducting Assent Discussion Date/Time

13.17.4 MISTIE-ICES Sample Consent Form

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Minimally Invasive Surgery plus rt-PA for ICH Evacuation: MISTIE Intraoperative Computerized Tomographic (CT)-guided Stereotactic Endoscopic Surgery (ICES)

PROTOCOL NO.: Sponsor protocol number: ICH01
WIRB® protocol number: 20021602

SPONSOR OF RECORD: Daniel F. Hanley, MD
Director, Brain Injury Outcomes Division
Johns Hopkins University Department of Neurology
Baltimore, Maryland, USA

PRIMARY FUNDING: National Insitutes of Health/
National Institute of Neurological Disorders
and Stroke

ADDITIONAL SUPPORT: Johnson & Johnson (Company providing drain tubes)
Karl Storz (Company providing endoscope equipment)
FDA Office of Orphan Products Development

INVESTIGATOR:

FACILITY(S):

STUDY-RELATED PHONE NUMBER(S):

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain anything that you do not clearly understand. You may have an unsigned copy of this consent form to take home and think about or discuss with family or friends before making your decision.

A person who takes part in a research study is called a research or study subject. In this consent form, "you" always refers to the research subject. If you are a legally authorized representative (LAR), please remember that "you" means the research (study) subject.

SUMMARY

You are asked to participate in a research study. The purpose of this consent form is to help you decide if you want to be in the research study. Please read this form carefully.

To be in a research study you must give your informed consent. Giving "informed consent" means:

- Reading this consent form,
- Having the study doctor or staff explain the research study to you,
- Asking questions about anything that is not clear, and
- Getting an unsigned copy of this consent form to take home. This gives you time to think about it and to talk to family or friends before you make your decision.

You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- No one can promise that a research study will help you.
- Taking part in a research study is entirely voluntary. No one can make you take part.
- If you decide to take part, you can change your mind later and withdraw from the research study.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study may involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- Other parts of this study may involve experimental (investigational) drugs or procedures that are being tested for a certain condition or illness. An investigational drug is one that has not been approved by the U.S. Food & Drug Administration (FDA).
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.
- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed, then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

After reading and discussing the information in this consent form you should know:

- Why this research study is being done;
- What will happen during the research;
- What drug or device or procedures will be used;
- Any possible benefits to you, if any;
- The possible risks to you;
- The other medical procedures, drugs or devices that could be used instead of being in this research study; and
- How problems will be treated during the study and after the study is over.

If you take part in this research study, you will be given a copy of this signed and dated consent form.

PURPOSE OF THE STUDY

You are being asked to join a research study looking at removing blood from the brain that happened without warning and which is not caused by a head injury. This unexpected bleeding in to the brain is called ICH or spontaneous intracerebral hemorrhage. ICH typically occurs in patients with high blood pressure or in the elderly due to fragile blood vessels.

The rate of death in patients with ICH is still very high despite the best medical treatment. Also, the amount of recovery in those that survive is also very poor. It has been shown that the amount and success of recovery is related to the size of the blood clot in the head. However, extensive surgery to remove the blood clot has sometimes been shown to be more harmful. Therefore, the usual treatment for ICH is to avoid doing extensive surgery whenever possible. This usual treatment is called "standard medical care."

Recent studies have shown that a less aggressive method of removing the blood clot - by using a small drain tube surgically placed into the brain to give a medicine to break up the clot - can be of benefit. This study will allow us to see if this method of clot evacuation is safer than standard medical care which does not involve removing the clot.

The purpose of this study is to determine if a surgical procedure using CT scans to guide blood removal is an effective therapy to treat bleeding in the brain.

PROCEDURES

About 146 patients will be enrolled in this study over a 6-year period. With your consent, you will have the following screening procedures to find out if you are eligible for this study.

1. A CT scan will be done at least 6 hours after the first CT scan that diagnosed the bleeding in your brain. If this second CT scan shows more blood in the brain when compared to the first CT scan, another CT scan will be repeated at least 6 hours later. This is done to make sure the bleeding has stopped. A CT scan is a test that produces an image of your body using a small amount of radiation. The image shows the body tissues and structure in three dimensions ("3-D"). These CT scans may already have been done per standard medical care.

2. A MRI (magnetic resonance imaging) scan with FLAIR and a MRA (magnetic resonance angiogram) or a CTA (computed tomography angiogram) will be done. These procedures are standard medical care to see if the bleeding is caused by abnormal blood vessels, such as an aneurysm. You will not be eligible for this study if this is the cause for your bleeding.

3. A pregnancy test will be done if you are a female of childbearing potential. You must not be pregnant to be in this study.

If, after these tests, you are found to be eligible for this study, you will be randomly assigned (similar to flipping a coin) to one of the two methods being compared in this study. You will either continue to receive standard medical care, or a small tube will be surgically placed into the clot to allow it to drain. You will have 3 chances out of 4 to be selected to have surgery. The first patient at every participating hospital will be assigned to get this drain tube instead of being randomized.

If you are randomly chosen or assigned to the group that will get the drain, you will be taken to an operating room or other designated area and given an appropriate anesthetic. A neurosurgeon will make a skin incision over the site of the blood clot after giving a local anesthetic. Following this, a hole will be drilled in the skull through the skin opening and a special instrument called an endoscope will be passed into the clot. The endoscope is a 10 mm diameter fiberoptic catheter similar to that used by doctors to look into the colon. When the endoscope is in the right place, suction will be applied to the drain to remove as much of the blood clot as possible. This blood/fluid will be collected and sent to a lab at another hospital for testing. A soft rubber drain tube (called a catheter) will be passed through the tube and the unbendable tube will be removed. The soft rubber drain tube will be left in the clot in the head and the skin will be closed it. Another CT scan will then be done to see how much clot is left and to make sure that the soft drain tube is in the middle of the remaining blood clot. This technique usually takes about 1 hour to perform and the tube stays in for 2 days to remove any additional blood. Your vital signs and neurological condition will be monitored daily for the next 6 days. Labs will be drawn for the next 6 days to monitor natural chemical levels in the blood related to the bleeding in your brain.

If you are randomly assigned to continue to receive standard medical care, you will have a CT scan every day for 4 days. Your vital signs and neurological condition will be monitored daily for the next 6 days. Labs will be drawn for the next 6 days to monitor natural chemical levels in the blood related to the bleeding in your brain.

Regardless of what group you are assigned to your vital signs, such as, heart rate, blood pressure, temperature, and neurological condition will be monitored daily for the next 6 days. Laboratory blood samples will be drawn for the next 6 days to monitor natural chemical levels in the blood related to the bleeding in your brain. CT scans will be done daily for the next 4 to 5 days to monitor the remaining blood clot in your brain. A MRI will be performed at day 7.

You will be asked to return to clinic 30, 180, and 365 days from today. During this clinic visit you will have a follow-up CT scan to look at how your brain is healing. Your neurological condition and blood pressure will be checked and you will be asked questions about how well you are doing.

You will be contacted by telephone 90 and 270 days from today. You will be asked questions about your condition and how well you are doing.

RISKS AND DISCOMFORTS

Blood Removal Surgery

The risks or discomforts associated with having surgery to treat bleeding in your brain include wound infection, headache, scalp pain, and post-operative bleeding. In some cases, severe post-operative bleeding could cause neurological deficits, (including weakness or paralysis on one or both sides of your body, loss of sensation on one or both sides of your body, difficulty hearing or speaking, double vision, loss of vision, or other vision problems, or problems with your thinking) and/or death. Any tube placed in the body carries the risk of infection, bleeding, bruising and swelling. The procedure may involve risks that are currently unforeseeable.

CT and MRI

The risks or discomforts associated with CT and MRI scans include anxiety of being in a tight, enclosed space. You may experience claustrophobia and associated anxiety when in the MR scanner.

The magnets in the MRI make loud clanging noises and you will be given ear plugs to soften the noise.

In addition, the magnet attracts certain metals. People with metallic objects in or on them

(pacemakers, infusion pumps, aneurysm clips, metal prostheses, joints, rods, plates, dental braces, etc.) should not participate. You will be screened for this and excluded if you have any such metal devices. The "metal" in dental fillings is less susceptible, and is, therefore allowed.

NEW FINDINGS

During the course of the study, you will be informed of any significant new findings (either good or bad) that might cause you to change your mind about continuing in the study. If significant new information is provided to you, your consent to continue participating in this study will be re-obtained.

POSSIBLE BENEFITS

Participation in the study may decrease the amount of injury to your brain caused by the bleeding. You may receive no benefit at all.

Anticipated Benefits to Society
The knowledge gained may help doctors determine if patients benefit more from surgery as opposed to standard medical care. In addition, this study may lead to better ways to identify whether a patient should receive surgery or standard medical care.

COSTS

Procedures that are done only for the study, such as extra lab tests will not be billed to you or your insurance company.

You or your insurance company may be billed for:

- Any standard medical care given during this research study.
- The surgical procedure of placing the narrow tube into your brain. If your insurance company does not pay for this procedure, the study will pay for it.

Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include the costs of treating side effects. Otherwise, you might have unexpected expenses from being in this study.

You may want to talk with your insurance company about its payment policy for standard medical care given during a research study. If your insurance company does not pay, you may be billed for those charges.

COMPENSATION FOR INJURY

You will be responsible for payment of any treatment or hospitalization you require if you are injured as a result of being in the study. Your health insurance company will be billed for payment of any treatment or hospitalization. Your health insurance company may or may not pay for treatment of injuries as a result of your participation in this study. The sponsor, the federal government, and the study doctor do not have a program to pay for injuries that may result from participation in this research study.

By signing this consent form, you have not waived any of the legal rights which you otherwise would have as a subject in a research study. Your health insurance company may or may not pay for treatment of injuries as a result of your participation in this study.

PAYMENT FOR PARTICIPATION

You will not be paid for participation in the study. You will present receipts and be reimbursed for travel and or parking as part of the 30, 180, and 365 day follow-up visits only. All other visits will take place while you are in the hospital.

ALTERNATIVE TREATMENT

If you decide not to enter this study, there are no other specific treatments available. Ask the study doctor to discuss possible options with you. You do not need to participate in this study to receive general and intensive care treatments for your condition.

Currently the only alternative to this treatment is standard medical management without removal of the blood clot. Your decision to participate or not to participate in this study will not affect the quality of care you receive. If you decide not to enter the study, you will continue to receive all medical and surgical care appropriate for your condition.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?

The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Information gathered for this research about:
    - Physical exams
    - Laboratory, x-ray, and other tests results

- Records about any study drug you received

Who may use and give out information about you?

The study doctor and the study staff will use this information. They may also share certain information with agents for the study doctor who provide technical or administrative support.

Who might get this information?

For regulatory purposes, the sponsor of this study is Dr. Daniel F. Hanley, a neurologist and the director of the Brain Injury Outcomes Division at the Johns Hopkins University School of Medicine in Baltimore, Maryland. Dr. Hanley is coordinating this study on behalf of the doctors and staff at approximately 8 other hospitals and academic centers in the U.S., including your doctor and hospital. He is assisted by a number of organizations and individuals who provide services in support of this trial. The term "sponsor" includes:

- Dr. Hanley;
- His staff at the Johns Hopkins University; and
- The other people and organizations who assist Dr. Hanley with this study.

Your information may be given to:

- The sponsor;
- The U.S. Food and Drug Administration (FDA);
- Department of Health and Human Services (DHHS) agencies;
- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported;
- Johnson & Johnson (the medical device company providing the drain tubes for this study);
- Karl Storz (the medical device company providing the endoscopy equipment for this study);
- Wayne State University (fluid sample testing);
- The Johns Hopkins University; and
- *[Add local IRB and any additional names here]*.

Why will this information be used and/or given to others?

- To do the research,
- To study the results,
- To see if the research was done right, and
- To plan other research

The doctors and scientists participating in this study intend to use the information to write medical papers and make presentations at annual meetings. Your identity will not be disclosed in these presentations and publications.

The people working on this study will collect information about you. This includes things learned from the procedures described in this consent form. They may collect other information including your name, address, date of birth, and other details. The research team will need to see your information. Sometimes other people at [YOUR INSTITUTION] may see or give out your information. These include people who review the research studies, their staff, lawyers, or other [YOUR INSTITUTION] staff.

People outside of [YOUR INSTITUTION] may need to see your information for this study. Examples include government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study, and companies that support the study.

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. Information, which may include copies of your medical records, will be delivered by mail, courier, fax transmission, e-mail attachment, or by submission to a secure website.

Release of your records is necessary for you to participate in this investigational study. If you do not wish to participate, you will still receive full standard medical care.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
Yes, but this permission will not stop automatically.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

Use the following Confidentality section instead of the above Authorization section if the site is not *a covered entity under HIPAA of if the site* is *using a separate HIPAA authorization form.*

Confidentiality

Study information collected about you will be given to the sponsor.

For regulatory purposes, the sponsor of this trial is Dr. Daniel F. Hanley, a neurologist and the director of the Brain Injury Outcomes Program at the Johns Hopkins University School of Medicine in Baltimore, Maryland. Dr. Hanley is coordinating this trial on behalf of the doctors and staff at approximately 40 other hospitals and academic centers in the U.S. and Europe, including your doctor and hospital. He is assisted by a number of organizations and individuals who provide services in support of this trial. The term "sponsor" includes:

- Dr. Hanley;
- his staff at Johns Hopkins; and
- the other people and organizations who assist Dr. Hanley with this study.

It will also be given to the U.S. Food and Drug Administration (FDA). It may be given to governmental agencies in other countries where the study drug may be considered for approval.

Medical records which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by:

- The sponsor;
- The U.S. Food and Drug Administration (FDA);
- Department of Health and Human Services (DHHS) agencies;
- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Johnson & Johnson (the medical device company providing the drain tubes for this study);
- Karl Storz (the medical device company providing the endoscopy equipment for this study);
- Wayne State University (fluid sample testing);
- Johns Hopkins University; and
- *[Add local IRB and any additional names here]*.

The people working on this study will collect information about you. This includes things learned from the procedures described in this consent form. They may collect other information including your name, address, date of birth, and other details. The research team will need to see your information. Sometimes other people at [YOUR INSTITUTION] may see or give out your information. These include people who review the research studies, their staff, lawyers, or other [YOUR INSTITUTION] staff.

The doctors and scientists participating in this study intend to use the information to write medical papers and make presentations at annual meetings. Your identity will not be disclosed in these presentations and publications.

People outside of [YOUR INSTITUTION] may need to see your information for this study. Examples include government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study, and companies that support the study.

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. Information, which may include copies of your medical records, will be delivered by mail, courier, fax transmission, e-mail attachment or by submission to a secure website.

Release of your records is necessary for you to participate in this investigational study. If you do not wish to participate, you will still receive full routine medical care.

VOLUNTARY PARTICIPATION/WITHDRAWAL

Taking part in this study is voluntary. You may decide not to take part or your may leave the study at any time. Your decision will not cause any penalty or loss of benefits to which you are entitled.

The study doctor or the sponsor may stop your participation in this study at any time without your consent for any of the following reasons:

- it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan; or
- for any other reason.

If you leave the study before the planned final visit, you may be asked by the study doctor to have some of the end-of-study procedures done.

SOURCE OF FUNDING FOR THE STUDY

The U.S. National Institutes of Health (NIH) is providing the primary funding for this study.

QUESTIONS

Contact [NAME] at [NUMBERS] for any of the following reasons:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, you may contact:

[NAME AND ADDRESS OF YOUR IRB/ETHICS COMMITTEE]

The IRB/EC is a group of people who independently review research.

The IRB/EC will not be able to answer some types of questions, such as questions about appointment times. You may contact the IRB/EC if you cannot reach the research team or if you want to talk to someone else.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers.

CONSENT

I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form I have not given up any of my legal rights.

Consent and Assent Instructions:

Consent: *Subjects 18 years or older and able to provide consent must sign on the subject line below.*

Consent is provided by the Legally Authorized Representative for adult subjects unable to consent.

Assent: *Is required for adult subjects unable to consent.*

Minimally Invasive Surgery plus rt-PA for ICH Evacuation
MISTIE

Subject Name

CONSENT SIGNATURE:

_____ _____
Signature of Subject (18 years and older) Date/Time

_____ _____
Signature of Legally Authorized Representative (when applicable) Date/Time

_____
Authority of Subject's Legally Authorized Representative or Relationship to Subject (when applicable)

_____ _____
Signature of Person Conducting Informed Consent Discussion Date/Time

ASSENT SIGNATURES, For Adult Subjects with a Legally Authorized Representative:

Assent:

For subjects who have a legally authorized representative, I confirm that:

☐ I have explained the study to the extent compatible with the subject's understanding, and the subject has agreed to be in the study.

OR

☐ The subject is not able to assent due to lack of mental capacity.

_____ _____
Signature of Person Conducting Assent Discussion Date/Time

13.17.5 FDA Guidance for Industry for Computerized Systems Used in Clinical Trials (April 1999)

The requirements for the software developed for this study is based of the FDA Guidance for Industry for Computerized Systems Used in Clinical Trials (April 1999). In response to the FDA Guidance, this document follows the outline of the FDA Guidance but affirms/responds to how the system will address each issue.

I. Introduction
This system is designed to create, modify, maintain, archive, retrieve, and transmit clinical data that is attributable, original, accurate, contemporaneous, legible, and auditable. Technically, the system is a web-based system with a centrally stored application server and database server. The application will be designed using the Microsoft .Net framework. The database server will utilize Microsoft SQL Server 2000.

The design of this system reflects the FDA Guidance or Industry for Computerized Systems Used in Clinical Trials (April 1999) as well as the Electronic Records/Electronic Signatures rule (21 CFR part 11). Data is entered into the system by authorized users. Automatic data entry techniques (machine-to-machine) are not employed by the system.

II. DEFINITIONS

Audit Trail - A secure, computer generated, time-stamped electronic record that allows reconstruction of the course of events relating to the creation, modification, and deletion of an electronic record.

Certified Copy - A copy of original information that has been verified, as indicated by dated signature, as an exact copy having all of the same attributes and information as the original.

Commit - A saving action, which creates or modifies, or an action which deletes, an electronic record or portion of an electronic record. An example is pressing the key of a keyboard that causes information to be saved to durable medium.

Computerized System - Computer hardware, software, and associated documents (e.g., user manual) that create, modify, maintain, archive, retrieve, or transmit in digital form information related to the conduct of a clinical trial.

Direct Entry - Recording data where an electronic record is the original capture of the data. Examples are the keying by an individual of original observations into the system,

or automatic recording by the system of the output of a balance that measures subject's body weight.

Electronic Case Report Form (e-CRF) - An auditable electronic record designed to record information required by the clinical trial protocol to be reported to the sponsor on each trial subject.

Electronic Record - Any combination of text, graphics, data, audio, pictorial, or any other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

Electronic Signature – A computer data compilation of any symbol or series of symbols, executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

Software Validation - Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through the software can be consistently fulfilled. For the purposes of this document, design level validation is that portion of the software validation that takes place in parts of the software life cycle before the software is delivered to the end user.

Source Documents - Original documents and records including, but not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Transmit - To transfer data within or among clinical study sites, contract research organizations, data management centers, or sponsors.

III. GENERAL PRINCIPLES

A. The study protocol identifies at which steps this system will be used to create, modify, maintain, archive, retrieve, or transmit data.

B. Documentation will identify what software and hardware is to be used in computerized systems that create, modify, maintain, archive, retrieve, or transmit data. This documentation will be retained as part of study records.

C. Source documents are to be retained to enable a reconstruction and evaluation of the trial.

D. When original observations are entered directly into the system, the electronic record is the source document.

E. The system will ensure that all applicable regulatory requirements for recordkeeping and record retention in clinical trials are met with the same degree of confidence as is provided with paper systems.

F. Clinical investigators will retain either the original or a certified copy of all source documents sent to a sponsor or contract research organization. Query resolution correspondence will be maintained and tracked by the system.

G. Any change to a record required to be maintained will not obscure the original information. The record will clearly indicate that a change was made and clearly provides a means to locate and read the prior information though the audit trail.

H. Changes to data will have an audit trail, in accordance with 21 CFR 11.10(e). Documentation includes who made the changes, when, and why they were made.

I. The FDA may inspect all records maintained by this system.

J. Data will be retrievable in such a fashion that all information regarding each individual subject in a study is attributable to that subject.

K. The system is designed: (1) So that all requirements of the study protocol are satisfied; and, (2) to preclude errors in data creation, modification, maintenance, archiving, retrieval, or transmission.

L. Security measures will prevent unauthorized access to the data and to the system.

IV. STANDARD OPERATING PROCEDURES

Standard Operating Procedures (SOPs) pertinent to the use of the system will be available at each site in the study.

SOPs will be established for:

- System Setup/Installation
- Data Collection and Handling
- System Maintenance

- Data Backup, Recovery, and Contingency Plans
- Security
- Change Control

DATA ENTRY

A. Electronic Signatures

1. To ensure that individuals have the authority to proceed with data entry, the system is designed so that individuals need to enter an electronic signature (user ID and password) at the start of a data entry session.

2. The data entry system ensures attributability. Each entry to an electronic record, including any change, will be made under the electronic signature of the individual making that entry. A separate electronic signature is not required for each entry or change. A single electronic signature can cover multiple entries or changes.

a. The printed name of the individual who enters data will be displayed on each data entry screen throughout the data entry session. This is intended to preclude the possibility of a different individual inadvertently entering data under someone else's name.

If the name displayed by the screen during a data entry session is not that of the person entering the data, then that individual must log on under his or her own name before continuing.

3. Individuals can only work under their own user ID/password and cannot share these with others. Individuals can not log on to the system in order to provide another person access to the system.

4. Passwords will be changed on a monthly basis. Passwords will not be distributed electronically.

5. When someone leaves a workstation, the person must log off the system. The system will automatic log off the user after 10 minutes of inactivity. For periods of 3-10 minutes of inactivity, an automatic screen saver that prevents data entry until a password is entered will be employed.

B. Audit Trails

1. Section 21 CFR 11.10(e) requires persons who use electronic record systems to maintain an audit trail as one of the procedures to protect the authenticity, integrity, and, when appropriate, the confidentiality of electronic records.

a. A computer-generated, time-stamped audit trail will independently record the date and time of operator entries and actions that create, modify, or delete records. A record is created when it is saved to the data server, as described under "commit" in Section II, Definitions.

b. Audit trails will be retained for a period at least as long as that required for the subject electronic records (e.g., the study data and records to which they pertain) and will be available for agency review and copying.

2. Personnel who create, modify, or delete electronic records will not be able to modify the audit trails.

3. The Data Monitoring Center will retain the audit trails.

4. FDA personnel will be able to read audit trails both at the study site and at any other location where associated electronic study records are maintained.

5. Audit trails will created incrementally, in chronological order, and in a manner that does not allow new audit trail information to overwrite existing data in violation of §11.10(e).

C. Date/Time Stamps

Controls will in place to ensure that the system's date and time are correct.

The ability to change the date or time is limited to authorized personnel at the Data Monitoring Center. The Data Monitoring Center will be notified if a system date or time discrepancy is detected. Changes to date or time will be documented.

Dates and times are local to the activity being documented and will include the year, month, day, hour, and minute. The date and time of the database server, where all data is stored, will be synchronized to the National Institute of Standard and Technology via the NIST Internet Time Service.

VI. SYSTEM FEATURES

A. The system includes the following features that facilitate the collection of quality data.

Prompts, lookup values, cross-field validations, flags, and on-line help will be used to encourage consistent use of clinical terminology and to alert the user to data that are out of acceptable range. The automatic entry of data into a field when that field is bypassed is not used.

The system will allow for users to make annotations. Annotations add to data quality by allowing ad hoc information to be captured. This information may be valuable in the event of an adverse reaction or unexpected result. The system clearly indicate who recorded the annotations and when (date and time).

B. To facilitate the inspection and review of data tags (different colored font or background) are used to indicate which data have been changed or deleted, as documented in the audit trail.

C. Retrieval of Data

Any data retrieval software, script, or query logic used for the purpose of manipulating, querying, or extracting data for report generating purposes is documented and maintained for the life of the report. The transcription process is validated by the Data Monitoring Center.

D. Reconstruction of Study

To assist the FDA in reconstructing this study, all versions of application software, operating systems, and software development tools involved in processing of data or records will be available as long as data or records associated with these versions are required to be retained. The Data Monitoring Center will contract with the software vendor to retain the ability to run the software. Although FDA expects sponsors or vendors to retain the ability to run older versions of software, the agency acknowledges that, in some cases, it will be difficult for sponsors and vendors to run older computerized systems.

VII. SECURITY

A. Physical Security

External safeguards are in place to ensure that access to the computerized system and to the data is restricted to authorized personnel. Servers are stored in a physically secured, guarded data center. Staff will be aware of system security measures and the importance of limiting access to authorized personnel. SOPs will be in place for handling and storing the system to prevent unauthorized access.

B. Logical Security

Access to the data at the clinical site will be restricted and monitored by the system through required log-on, security procedures, and audit trail. The data will not altered,

browsed, queried, or reported via external software applications that do not enter through the protective system software.

To further ensure restricted access to only authorized users and systems, log-on procedures will be supplemented with 128-bit data encryption on the transport layer level. All data will be protected by a firewall.

There will be a cumulative record that indicates, for any point in time, the names of authorized personnel, their titles, and a description of their access privileges. The record will be in the study documentation that is accessible at the site.

Computerized system at each site of the clinical study may be used as part of a system normally used for other purposes. As the system is web-based, all data and applications, used for the study are logically and physically isolated as to preclude unintended interaction with non-study software. Remote sites do not have the ability to change the logical security of the system.

Virus scanners will be used on all systems that collect and store data as to prevent, detect, and mitigate effects of computer viruses on study data and software.

SYSTEM DEPENDABILITY

Effort is made to ensure and document that the system conform to the study's requirements for completeness, accuracy, reliability, and consistent intended performance.

A. Systems documentation will be readily available at the site where clinical trials are conducted. Such documentation provides an overall description of the system and the relationship of hardware, software, and physical environment.

B. FDA may inspect documentation that demonstrates validation of software.

1. The Data Monitoring Center will perform functional testing, by use of test data sets, to determine and mitigate any software problems or defects.

2. Documentation to demonstrate software validation includes:

Written design specification that describes what the software is intended to do and how it is intended to do it;

A written test plan based on the design specification, including both structural and functional analysis; and,

Test results and an evaluation of how these results demonstrate that the predetermined design specification has been met.

C. Change Control

Written procedures will be in place to ensure that changes to the computerized system such as software upgrades, equipment or component replacement, or new instrumentation will maintain the integrity of the data or the integrity of protocols.

The impact of any change to the system will be evaluated and a decision made regarding the need to revalidate. Revalidation will be performed for changes that exceed operational limits or design specifications.

All changes to the system will be documented.

IX. SYSTEM CONTROLS

A. Software Version Control

Measures are in place to ensure that versions of software used to generate, collect, maintain, and transmit data are the versions that are stated in the systems documentation.

B. Contingency Plans

Written procedures will describe contingency plans for continuing the study by alternate means in the event of hardware or facilities failures with alternate hardware or at an alternate site.

C. Backup and Recovery of Electronic Records

Backup and recovery procedures will be clearly outlined in the SOPs to protect against data loss. Records will be backed up daily, to prevent a catastrophic loss from compromising the quality and integrity of the data.

Backups will be stored at a secure location specified in the SOPs. Redundant backup storage will be stored in separate buildings. Backups will be stored onsite, at the facility housing the servers, and offsite, at the Data Monitoring Center.

Backup and recovery logs will be maintained to facilitate an assessment of the nature and scope of data loss resulting from a system failure.

X. TRAINING OF PERSONNEL

A. Qualifications

Each person who enters or processes data will have the education, training, and experience to perform the assigned functions necessary to successfully operate the system.

Individuals responsible for monitoring the trial have the education, training, and experience in the use of the computerized system necessary to adequately monitor the trial.

B. Training

Training will be provided to individuals in the specific operations that they are to perform.

Training will be conducted by qualified individuals from the Data Monitoring Center on a continuing basis, as needed, to ensure familiarity with the computerized system and with any changes to the system during the course of the study.

C. Documentation

Employee education, training, and experience will be documented.

XI. RECORDS INSPECTION

A. FDA may inspect all records. The system will be able to generate accurate and complete copies of records in both human readable and electronic form via ASCII files.

B. Hardware and software necessary will be available for FDA personnel to inspect the electronic documents and audit trail at the site where an FDA inspection is taking place.

XII. CERTIFICATION OF ELECTRONIC SIGNATURES

As required by 21 CFR 11.100(c), will certify to the FDA that the electronic signatures in the system is intended to be the legally binding equivalent of traditional handwritten signatures.

As set forth in 21 CFR 11.100(c), the certification shall be submitted in paper form signed with a traditional handwritten signature to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville Maryland 20857. The certification will be submitted prior to the time electronic signatures are used.

XIII. REFERENCES

FDA, Guidance for Industry COMPUTERIZED SYSTEMS USED IN CLINICAL TRIALS, April 1999.