POSITIVE: PerfusiOn imaging Selection of Ischemic STroke PatIents for EndoVascular ThErapy

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POSITIVE: PerfusiOn imaging Selection of Ischemic STroke PatIents for EndoVascular ThErapy

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Study Center: _____

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

_____ _____

Investigator Date

_____

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Study Synopsis:

Title: **POSITIVE**: PerfusiOn imaging Selection of Ischemic STroke PatIents for EndoVascular ThErapy

Objective: The primary objective of this randomized trial is to determine the safety and efficacy of intra-arterial reperfusion in Acute Ischemic Stroke (AIS) patients ineligible for or refractory to treatment with IV-tPA as selected by physiologic imaging criteria for mechanical thrombectomy within 6-12 hours of symptom onset or time last seen normal.

Study Design: This study will be a prospective, randomized, multi-centered international trial that will enroll up to 200 patients at up to 35 centers.

Patient Population: AIS patients, ineligible for or refractory to treatment with IV-tPA, (patients seen within 6 hours of symptom onset will be immediately considered for endovascular therapy according to the site's standard of care. Likewise, patients presenting beyond 12 hours will be treated according to the site's standard of care),who are found by physiologic imaging to have significant viable tissue to warrant endovascular recanalization and are able to undergo mechanical thrombectomy within 6-12 hours of symptom onset or time last seen normal. Patients will be randomized to treatment by endovascular mechanical thrombectomy or best medical therapy (MT).

Indication: The use of mechanical thrombectomy devices has been shown to be safe and effective for the revascularization of occluded cerebral vessels. However, study results to date have only evaluated the treatment of patients within the first eight hours from symptom onset. Pilot data have shown that patients selected with physiologic imaging can be treated with endovascular thrombectomy without time restrictions.

Inclusion Criteria:

1. Age 18 and older (i.e., candidates must have had their 18th birthday)
2. NIHSS ≥8 at the time of neuroimaging
3. Presenting or persistent symptoms within 6-12 hours of when groin puncture can be obtained
4. Neuroimaging demonstrates large vessel proximal occlusion (distal ICA through MCA M1 bifurcation)
5. The operator feels that the stroke can be appropriately treated with traditional endovascular techniques (endovascular mechanical thrombectomy without adjunctive devices such as stents)
6. Pts are within 6-12 hours of symptom onset, that have received IV-tPA without improvement in symptoms are eligible for this study. Patients presenting earlier than 6 hours should be treated according to local standard of care.
7. Pre-event Modified Rankin Scale score 0-1
8. Consenting requirements met according to local IRB

Exclusion Criteria:

1. Patient is less than 6-hours from symptom onset
2. Rapidly improving neurologic examination
3. Absence of large vessel occlusion on non-invasive imaging
4. Known or suspected pre-existing (chronic) large vessel occlusion in the symptomatic territory
5. Absence of an associated large penumbra as defined by physiologic imaging according to standard of practice at the participating institution
6. Any intracranial hemorrhage in the last 90 days
7. Known irreversible bleeding disorder
8. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR > 2.5 or institutionally equivalent prothrombin time of 2.5 times normal
9. Platelet count < 100 x 10^3 cells/mm^3 or known platelet dysfunction
10. Inability to tolerate, clinically documented evidence in medical history of adverse reaction to, or contraindication to medications used in treatment of the stroke
11. Contraindication to CT and MRI (i.e., iodine contrast allergy or other condition that prohibits imaging from either CT or MRI)
12. Known allergy to contrast used in angiography that cannot be medically controlled
13. Relative contraindication to angiography (e.g., serum creatinine > 2.5 mg/dL)
14. Women who are currently pregnant or breast-feeding (Women of child-bearing potential must have a negative pregnancy test prior to the study procedure (either serum or urine)
15. Evidence of active infection (indicated by fever at or over 99.9 °F and/or open draining wound) at the time of randomization
16. Current use of cocaine or other vasoactive substance
17. Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments through 90 days
18. Patients who lack the necessary mental capacity to participate or are unwilling or unable to comply with the protocol's follow up appointment schedule (based on the investigator's judgment)

Head CT or MRI Scan Exclusion Criteria

- Presence of blood on imaging (subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), etc.)
- High density lesion consistent with hemorrhage of any degree
- Significant mass effect with midline shift
- Large (more than 1/3 of the middle cerebral artery) regions of clear hypodensity on the baseline CT scan or ASPECTS of < 7; Sulcal effacement and/or loss of grey-white differentiation alone are not contraindications for treatment.

*Primary Endpoint**:***

The primary objective is to show that AIS patients, ineligible for or refractory to treatment with IV-tPA, with appropriate image selection, treated with mechanical thrombectomy within 6-12 hours of symptom onset have less stroke related disability and improved good functional outcomes as compared to those treated with best MT with respect to endpoint defined as:

- 90-day global disability assessed via the modified Rankin score (mRS), analyzed using raw mRS scores. Statistical details can be found in section 7.2.

*Secondary Endpoints**:***

- 90-day global disability in the 6-12 hr cohort assessed via the overall distribution of mRS
- Proportion of patients with good functional recovery for the 6-12 hr cohort as defined by mRS 0-2 at 90 days
- Mortality at 30 and 90 days
- Intracranial hemorrhage with neurological deterioration (NIHSS worsening >4) within 24 hours of randomization
- Procedure related serious adverse events (SAE's)
- Arterial revascularization measured by TICI 2b or 3 following device use

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1. Introduction

Acute ischemic stroke remains a potentially devastating condition and is a leading cause of morbidity and mortality affecting estimated 800,000 people per year in the United States alone and costing an estimated $41 billion in 2007 [1]. The most devastating strokes are generally those caused by proximal occlusions in the cervical and cerebral vasculature. The natural history of untreated or unrevascularized large vessel occlusions in acute stroke patients results in mortality rates approaching 30% and only 25% of patients achieving good neurologic outcomes at 90 days.[2 3] Intravenous (IV) tissue plasminogen activator (tPA) administration is approved for use within 3 hours of symptom onset, with newer evidence suggesting potential benefit out to 4.5 hours. [1 4-6] However, IV tPA does a poor job of effectively revascularizing large vessel occlusions [7]. Among patients presenting within the approved time window, close to half are ineligible to receive IV tPA due to exclusionary criteria. Moreover, a recent meta-analysis of 502 patients with a perfusion mismatch treated with IV tPA beyond the approved time window failed to show evidence of benefit. [8]

Beyond 4.5 hours patients that present to hospitals that do not offer intra-arterial therapy (IAT) are subject to medical therapy (MT). International Stroke Trial (IST) and Chinese Acute Stroke Trial (CAST) evaluated the effect of early aspirin administration in patients with acute stroke.[9 10] This data shows that aspirin results in fewer deaths (nine per 1,000) and more patients with a good functional outcome (seven per 1,000) at 30 days after ischemic stroke [11] Best medical therapy also consists of aggressively managing blood sugar levels, blood pressure, and hemodynamic status according to the standard of practice at each institution. The medication regimen is primarily centered on anti-aggregation approach such as aspirin therapy and institution of statins. Managing these patients, especially those with large strokes at presentation, in a stroke unit with available neurocritical care has also been shown to improve outcomes.

The randomized PROACT II trial demonstrated that stroke patients with MCA occlusions undergoing IA fibrinolysis had higher rates of recanalization, 66% with IA thrombolysis vs. 18% with placebo ($p=0.001$), and were more likely to have a 90 day mRS ≤ 2, 40% compared with only 25% in the nonrecanalization group ($p=0.04$). [12] This was further supported with subgroup analysis from the multi-center Merci trial where 49% of revascularized patients achieved mRS ≤ 2 as compared to 10% of non-revascularized patients ($p<0.001$). That study also showed a significant increase in 90-day mortality in patients that were not revascularized compared to those that were 52% versus 25% ($p<0.001$). [13] Similarly, the Penumbra POST Trial found that 45% of patients who were revascularized achieved a mRS ≤ 2 compared to 13% of patients who were not successfully recanalized.[14] The more recent randomized SWIFT and TREVO studies utilized the latest stent retrievers for mechanical thrombectomy to build on the safety and efficacy that the Penumbra and MERCI studies have shown. SWIFT showed that Solitaire device was able to recanalize 68% of occluded vessels with resultant 36% patients with good neurologic outcomes at 90 days. Similarly, TREVO was able to achieve 68% recanalization rates with 40% good clinical outcomes at 90 days.[15 16]

Despite the compelling data from device trials, many stroke practitioners do not consider

IAT standard of care for patients that are not candidates for IV-tPA or where IV-tPA does not work. The American College of Chest Physicians recently convened the Antithrombotic Therapy and Prevention of Thrombosis Panel to develop evidence based medicine recommendations for any disease process requiring antithrombotics. In regards to patients with acute ischemic stroke, they recommended *against* the use of mechanical thrombectomy devices based on current literature, except in select patients who "value the uncertain benefit of mechanical thrombectomy higher than the associated risks of intervention". [17] A recent analysis of the National Inpatient Sample found that 4000 patients over 2 years that underwent endovascular thrombectomy had a 25% mortality rate while hospitalized and 50% were discharged to long-term care facilities. [18] Another recent publication also concluded that thrombectomy devices were an intriguing option but there was little evidence to support their use in routine practice without further appropriately designed clinical trials. [19]

Current randomized trials such as the mechanical retrieval and recanalization of stroke clots using embolectomy Trial (MR RESCUE), Penumbra THERAPY Trial and the efficacy and safety study of desmoteplase to treat acute ischemic stroke Trial (DIAS-3) are evaluating the utility of perfusion imaging to select acute stroke patients for treatment. The results of these trials are pending.[20 21] More importantly, these trials did not utilize the latest generation of endovascular mechanical thrombectomy devices in which early results suggest promising results with much faster recanalization times and high rates of good neurologic outcome. [22 23] At the time of this protocol's initial composition there are also two active clinical trials that use perfusion studies as guidance in treating patients presenting with stroke symptoms with no clear time of onset. The first is the MR WITNESS study which is taking place in NIH stroke center and Massachusetts General Hospital (MGH). Secondly, the DAWN trial is being performed by MGH and the University of Pittsburgh.[24 25] Our study is unique in that it will utilize perfusion imaging to select patients who are not eligible for or refractory to treatment with IV-tPA and randomize those patients between best medical therapy and the latest generation (FDA approved) mechanical thrombectomy devices.

However, these trials are focusing on patients within the 8-hour time period. Several recent reports have suggested that with image based selection patients may be effectively treated beyond these strict time boundaries with good outcomes. [26-29] A five year pilot study from our institution utilizing a perfusion imaging based paradigm to select AIS patients, irrespective of time, for IAT with mechanical thrombectomy indicates that we can treat patients safely (90 day mortality rate 26%, symptomatic bleed rate 7%) and effectively (90 day mRS 0-2, 38%) outside of the traditional time windows. In this series, our average time to treat from the last time the patient was seen normal was 11.3 hours. Furthermore, the patient outcomes and complications in those treated after 8 hours were no different than those treated before 8 hours.[30 31] We have further combined our data with those from 2 other centers and found that in 247 patients there were no differences in patient outcomes in those treated beyond 8 hours as opposed to those treated less than 8 hours when selected by physiologic imaging.[32]

Intra-arterial (IA) thrombolysis within 6 hours and mechanical thrombectomy within 8 hours have been shown to be feasible methods by which to achieve revascularization and there are data which suggest that revascularization improves patient outcomes.[7 12 33-36]

Until now, there has not been a single trial showing efficacy of intra-arterial thrombectomy (IAT) over medical therapy. The POSITIVE trial was originally designed and approved by the FDA to evaluate mechanical thrombectomy to treat acute ischemic stroke (AIS) related to a large blood vessel occlusion (LVO). Since the trial began, there have recently been data released from four trials that all show overwhelming positive outcomes of IAT over medical therapy of patients presenting within 6 hours of AIS onset.[37-41]

Due to this recent data, the POSITIVE trial halted enrollment of patients presenting within 8 hours of AIS on 11/08/2014, until the published data was available from these multiple trials. The final data from these trials was finally fully available on 2/11/15. The POSITIVE steering and executive committees, in discussion with the study investigators, decided to permanently halt patients presenting within 6 hours of AIS and to change the late time group from 8-12 to 6-12. The reason to halt enrollment in the early time group was due to the overwhelming data across multiple trials. The MR CLEAN trial demonstrated an absolute difference of 13.5% in rate of functional independence in favor of IAT over medical therapy (32.6% vs 19.1%). MR CLEAN was notable in that it randomized 500 patients in the Netherlands to IV-tPA vs IV tPA and IAT presenting within 6 hours of stroke onset.[38] More robustly, the ESCAPE trial favored IAT over medical therapy by an odds ratio of 2.6 with a significant reduction in mortality (10.4% vs 19.0%). The ESCAPE trial was halted after enrolling 316 patients at 22 centers around the world presenting within 12 hours of stroke onset. The trial required advanced imaging to select patients with LVO and ability to rapidly transition from diagnosis to IAT within 30 minutes.[39] Similarly, the EXTEND IA trial based in Australia, was halted after 70 patients were enrolled due to positive results in the MR CLEAN trial. Interim analysis found a marked improvement in ability to achieve functional outcome with IAT (71%) over medical therapy (40%).[41] This overwhelming data has created an environment where equipoise has been lost in patients presenting within 6 hours of AIS onset.

The ESCAPE trial, while overwhelmingly positive and treating patients out to 12 hours, unfortunately did not show a significant difference in patients treated between 6-12 hours. There was a signal in the direction of intervention (odds ratio 1.7), but this was not significant.[39] It should be noted that only 49 of the 316 patients were in this 6-12 hour time frame. This perhaps highlights the obvious absence of Level 1 data available in treating patients presenting with AIS beyond 6 hours. The POSITIVE trial is notable in that it will continue to evaluate patients out to 12 hours, requiring documentation with advanced imaging of LVO and emphasize selecting patients with small or no infarctions present at time of triage.

All of the recent trials reported data randomizing IAT with or without IV-TPA against IV-tPA alone. Given the overwhelming benefit in patients receiving IAT, it is now reasonable to include patients that fail IV-tPA, which also significantly increases the potential to enroll POSITIVE Trial candidates. Many stroke center networks operate where small community hospitals or satellite hospitals are enabled to give IV-tPA through stroke neurology telemedicine systems. These hospitals then usually ship the patients to larger tertiary hospitals where endovascular interventions can be performed,as was frequently done in the MR-CLEAN and ESCAPE trials. This can often create situations where the patient receives IV-tPA at the outside hospital, but by the time they arrive at the tertiary hospital they are beyond the recognized 6 hour time window. Those patients within the 6 and 12 hour time from symptom onset would be eligible for this trial. Patients seen within 6 hours of symptom onset will be immediately considered for endovascular therapy according to the site's standard of care. Likewise, patients presenting beyond 12 hours will be treated according to the site's standard of care. Similarly, the ESCAPE trial showed that patients over 80 years old significantly benefitted from IA therapy just as much as patients younger than 80 years.[39] To better reflect this new clinical reality, there will not be any upper age limitations in the exclusion criteria of POSITIVE.

1.1 Rationale for study

Intravenous (IV) tissue plasminogen activator (tPA) administration has been shown to be safe and effective for treatment of AIS within 3 hours of symptom onset, and newer evidence has shown potential benefit out to 4.5 hours. Mechanical thrombectomy for AIS patients has been shown in clinical trials to be safe up to 8 hours after symptom onset. The rapid progression of thrombectomy devices over the last several years has resulted in faster recanalization times while maintaining a high degree of safety. This has resulted in improved patient outcomes, similar to prior randomized trial data showing improved outcomes over medical therapy or earlier devices. Data from the MERCI trial suggests that patients > 85 as well as those with a baseline NIHSS score > 30 are unlikely to benefit from thrombectomy. Patients with rapidly improving neurologic deficits likely will have an excellent recovery with conventional care, precluding the ability to detect a beneficial treatment effect of thrombectomy.

Pilot data incorporating physiologic imaging has shown that appropriate patients can be selected for thrombectomy. This selection methodology has shown the ability to maintain the same level of safety and efficacy as those patients treated in the highly selective environment of a clinical trial, despite presenting far beyond accepted time based standards. Vertebrobasilar occlusion patients are excluded to maintain a homogenous study population, particularly since no data currently is available addressing the comparability of imaging penumbral patterns in the anterior vs. posterior circulation. This has also been shown to be reproducible at multiple centers and with different imaging modalities. However, all prospective interventional stroke studies performed to date have been restricted by the 8-hour time window.

2. Purpose and Hypothesis

The primary aim of acute ischemic stroke treatment is to restore a patient who is severely neurologically impaired due to a blockage of a major brain blood vessel back to their previous functional status. Identification and selection of appropriate patients is always paramount to good clinical outcomes. Evidence supports the safety of thrombectomy for patients presenting with AIS within 8 hours of symptom onset. Pilot data support thrombectomy in some patients after 8 hours based on selection using physiological perfusion imaging.

The purpose of this randomized trial is to demonstrate the safety and efficacy of mechanical thrombectomy over best medical therapy for treating acute ischemic stroke patients ineligible for or refractory to treatment with IV-tPA with persistent symptoms within a 6-12 hour time window from symptom onset as selected by physiologic perfusion imaging criteria, (patients seen within 6 hours of symptom onset will be immediately considered for endovascular therapy according to the site's standard of care. Likewise, patients presenting beyond 12 hours will be treated according to the site's standard of care).

2.1 Risk Analysis

The primary risks to subjects in this study are associated with evolution of large brain infarctions or bleeding within the brain, which can cause symptomatic deterioration of the subject. Large brain infarctions are much more common when blood vessels are not recanalized and recanalization rates are much higher with endovascular therapy.[12 13 14] Excessive bleeding from the site of the femoral artery puncture, from other puncture sites, or from other body systems is not likely as this trial is evaluating patients ineligible for or refractory to treatment with IV-tPA. The use of Aspirin, as will be standard in the medical arm, does not appear to increase the risk of brain bleeding.[9 10 11] For patients undergoing mechanical thrombectomy, the risk of symptomatic bleeding in prior device trials has been reported 7-9% of cases.

Additional risks, approximately 3%, associated with angiography include the risks of contrast allergic reactions, kidney dysfunction, vessel perforation and ischemic infarction. The CT scans, CT angiography, and cerebral angiography involve exposure to a small amount of radiation in addition to the usual x-ray studies done in stroke patients. On average, for a complete 2-hour thrombectomy procedure a subject would receive an average total dose of 50-100 rads, approximately 9.2 rads for a CTA, and 2.8 rads for a head CT scan. There is a small chance of skin or hair damage, but this has yet to happen in reported studies for stroke treatments.

Best medical therapy (MT) consists of aggressively managing blood sugar levels, blood pressure, and hemodynamic status according to the standard of practice at each institution. The medication regimen is primarily centered on anti-aggregation approach such as aspirin therapy and institution of statins. International Stroke Trial (IST) and Chinese Acute Stroke Trial (CAST) evaluated the effect of early aspirin administration in patients with acute stroke.[9 10] This data shows that aspirin results in fewer deaths (nine per 1,000) and more patients with a good functional outcome (seven per 1,000) at 30 days

after ischemic stroke. [11] Data from device trials using the devices planned for this trial suggest a superior functional outcome in patients undergoing mechanical thrombectomy ranging from 36-40%. [14 15 16] Thus, the POSITIVE Investigators feel that subjects will likely receive an effective treatment. It has also been shown that the recanalization rates associated with mechanical thrombectomy are higher than what has been reported for best medical therapy alone. Thus, there is a real possibility that mechanical thrombectomy may be more effective than best medical therapy alone.

We do not feel that extending the time parameters beyond the accepted 8-hour indication poses a significant risk in appropriately selected patients. For this reason, we have required imaging selection to ensure that we are only including patients with large vessel occlusions and also exclude those with a significant underlying infarction and little viable/salvageable tissue. The MUSC experience with this approach over the last five years has undergone peer review and been published. To briefly summarize, the MUSC experience with 140 patients treated with perfusion imaging selection, irrespective of time from symptom onset, has shown similar rates of good neurologic outcome in those treated earlier than the median time (from last normal) of 7 hours as those treated after 7 hours (30.2% vs 45.5, p=0.1, respectively) with no significant change in mortality (30.2% vs 21.2%, p=0.4). This was similarly shown in a multicenter study where 247 patients were treated with a median time of 8 hours and similarly showed near identical rates of good neurologic outcome (42.8% vs 41.9%, p=1.0) and similar mortality rates (24.9 vs 20.3%, p=0.5). We believe this data shows that extending the time window does not pose any increased risk to the patient.

All information concerning subjects will be kept confidential so as to reduce the risk of a breach of privacy. Subjects will be assigned study ID #. No personal identifying information will be used in presentation or publication of data from this study.

3. Objectives

3.1 Primary Objective

The primary objective is to show that AIS patients, ineligible for or refractory to treatment with IV-tPA, (patients seen within 6 hours of symptom onset will be immediately considered for endovascular therapy according to the site's standard of care. Likewise, patients presenting beyond 12 hours will be treated according to the site's standard of care), with appropriate image selection, treated with mechanical thrombectomy within 6-12 hours of symptom onset have less stroke related disability and improved good functional outcomes as compared to those treated with best MT with respect to endpoint defined as:

- 90-day global disability assessed via the modified Rankin score (mRS), analyzed using raw mRS scores. Statistical details can be found in section 7.2.

3.2 Secondary Endpoints

- 90-day global disability in the 6-12 hr cohort assessed via the overall distribution of mRS

- Proportion of patients with good functional recovery for the 6-12 hr cohort as defined by mRS 0-2 at 90 days
- Mortality at 30 and 90 days
- Intracranial hemorrhage with neurological deterioration (NIHSS worsening >4) within 24 hours of randomization
- Procedure related serious adverse events (SAE's)
- Arterial revascularization measured by TICI 2b or 3 following device use

4. Trial design

This is a prospective, randomized trial comparing mechanical thrombectomy and best MT in AIS patients ineligible for or refractory to treatment with IV-tPA selected with perfusion imaging and presenting within 6-12 hours of symptom onset, (patients seen within 6 hours of symptom onset will be immediately considered for endovascular therapy according to the site's standard of care. Likewise, patients presenting beyond 12 hours will be treated according to the site's standard of care). Any cleared mechanical thrombectomy device that is in common use in the operators region of practice is approved for use in the mechanical thrombectomy arm. Best MT will be determined by practice standards utilized in the operators region of practice. Patients will be enrolled who meet the inclusion and exclusion criteria and consent to participate will be randomly assigned by a central web-based system in a 1:1 manner to treatment with either mechanical thrombectomy or MT. Data on each patient will be collected at the time of enrollment and treatment, and at subsequent follow-up visits.

4.1 Inclusion criteria

1. Age 18 and older (i.e., candidates must have had their 18th birthday) NIHSS ≥8 at the time of neuroimaging
2. Presenting or persistent symptoms within 6-12 hours of when groin puncture can be obtained
3. Neuroimaging demonstrates large vessel proximal occlusion (distal ICA through MCA M1 bifurcation)
4. The operator feels that the stroke can be appropriately treated with traditional endovascular techniques (endovascular mechanical thrombectomy without adjunctive devices such as stents)
5. Pre-event Modified Rankin Scale score 0-1
6. Patients are within 6-12 hours of symptom onset, that have received IV-tPA without improvement in symptoms are eligible for this study. Patients presenting outside of this window should be treated according to local standard of care.
7. Consenting requirements met according to local IRB

4.2 Exclusion criteria

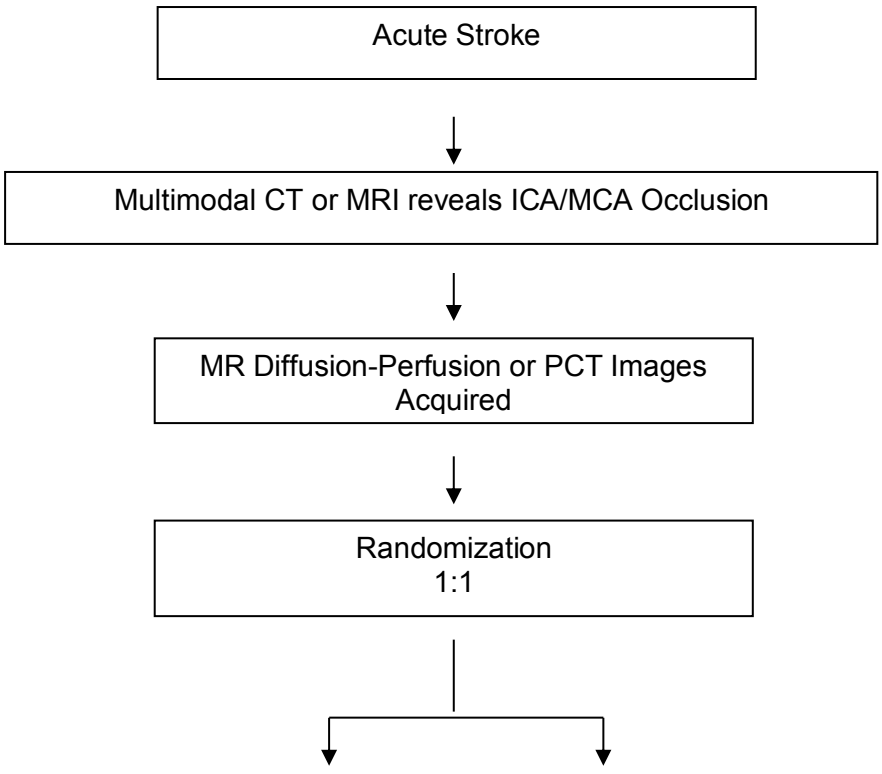
1. Patient is less than 6-hours from symptom onset
2. Rapidly improving neurologic examination
3. Absence of large vessel occlusion on non-invasive imaging
4. Known or suspected pre-existing (chronic) large vessel occlusion in the symptomatic territory

5. Absence of an associated large penumbra as defined by physiologic imaging according to standard of practice at the participating institution
6. Any intracranial hemorrhage in the last 90 days
7. Known irreversible bleeding disorder
8. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR > 2.5 or institutionally equivalent prothrombin time of 2.5 times normal
9. Platelet count < 100 x 10^3 cells/mm^3 or known platelet dysfunction
10. Inability to tolerate, clinically documented evidence in medical history of adverse reaction to, or contraindication to medications used in treatment of the stroke
11. Contraindication to CT and MRI (i.e., iodine contrast allergy or other condition that prohibits imaging from either CT or MRI)
12. Known allergy to contrast used in angiography that cannot be medically controlled
13. Relative contraindication to angiography (e.g., serum creatinine > 2.5 mg/dL)
14. Women who are currently pregnant or breast-feeding (Women of child-bearing potential must have a negative pregnancy test prior to the study procedure (either serum or urine)
15. Evidence of active infection (indicated by fever at or over 99.9 °F and/or open draining wound) at the time of randomization
16. Current use of cocaine or other vasoactive substance
17. Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments through 90 days
18. Patients who lack the necessary mental capacity to participate or are unwilling or unable to comply with the protocol's follow up appointment schedule (based on the investigator's judgment)

4.2.1 Head CT or MRI Scan Exclusion Criteria

- Presence of blood on imaging (subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), etc.)
- High density lesion consistent with hemorrhage of any degree
- Significant mass effect with midline shift
- Large (more than 1/3 of the middle cerebral artery) regions of clear hypodensity on the baseline CT scan or ASPECTS of < 7; Sulcal effacement and/or loss of grey-white differentiation alone are not contraindications for treatment.

4.3 Overview of Study Flow



All sites will keep a screen failure log of all acute stroke patients presenting within 24 hours of symptom onset but who are not randomized into the study. Reason(s) for exclusion will be recorded. Logs will be data entered by the clinical sites on a monthly basis. Recruitment rates will be tracked over time for each hospital. The actual recruitment rates as well as potential recruitment rates will be useful for planning further clinical trials and determining the widespread impact of the therapy.

4.4 Study Visits

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

- Baseline
- Randomization
- 24 hours (+/-12 hours) Post-Randomization
- 7 Days Post-Randomization or Discharge (whichever comes first)
- 30 Days (+/- 14 days) Post-Randomization Follow-up
- 90 Days (+/- 14 days) Post-Randomization Follow-up

4.5 Recruitment

The target population for the POSITIVE trial is patients greater than 18 years of age who have a clinical diagnosis of acute ischemic stroke from a large cerebral vessel occlusion, ineligible for or refractory to treatment with IV-tPA, and an identified significant penumbral region within 6-12 hours of symptom onset. Patients seen within 6 hours of symptom onset will be immediately considered for endovascular therapy according to the site's standard of care. Likewise, patients presenting beyond 12 hours will be treated according to the site's standard of care.

Potential study participants and/or their authorized surrogate will be identified by the study team at each site to obtain consent and determine eligibility. Up to 20 sites will be included in this study to enroll approximately 200 patients.

4.6 Screening

Consent is obtained, medical history screened, available clinical/neurologic exams obtained, and lab work and imaging information per institution standard of care is evaluated to determine patient eligibility. Imaging must be performed to confirm evidence of a large vessel occlusion. A patient will be considered enrolled upon randomization. Randomization will be 1:1 to best MT or a combined best MT and mechanical thrombectomy.

4.7 Informed Consent

A member of the research team will explain the study's objectives to potential participants, including a description of standard treatment with the study devices, the

requirements of the clinical investigation, and risks and benefits of participating. All informed consent documents used under this study protocol will be consistent with applicable elements of ISO14155, Good Clinical Practice Guidelines and 21 CFR Part 50, and will be approved by the site's reviewing IRB/EC prior to study initiation.

4.8 Baseline Evaluation

Inclusion and exclusion criteria will be confirmed. Once the patient meets all eligibility criteria, and the patient or surrogate has provided written informed consent, he/she will undergo standard non-study surgical preoperative workup including but not limited to: demographic confirmation, medical history, and focused physical examination (see Table 1 for complete assessment schedule). Baseline imaging may either be CT/CTA/CTP or MRI/MRA/MRP prior to the pre-procedure DSA. The baseline neurologic examination will be performed by a health care provider or study team member, certified to administer the exam and able to give an unbiased neurological and functional assessment (pre-stroke mRS and presentation NIHSS). A pregnancy test will be conducted for applicable subjects (females <50 years old and of child bearing potential). Concomitant medications will be collected at baseline, 24 hours post-randomization, at discharge, and at follow up visits (30 days and 90 days post-randomization).

Table 1: Schedule of Events

Activity	**Baseline**	**Randomization/Procedure**	**24hrs Post-Randomization**	**7days Post-Randomization or Discharge**	**30d Post-Randomization**	**90d Post-Randomization**	**Neurological Deterioration**	**Any Add' l FU (if needed)**	**Study Closure**
Evaluation of Criteria									
Eligibility Labs[1]	X								
Informed Consent	X								
Randomization		X							
Past Medical History	X								
Clinical Evaluation	X		X	X	X	X	X	X	
Modified Rankin Scale	X[4]		X[5]	X[5]	X[5]	X[5]		X	
NIH Stroke Scale	X[4]		X[5]	X[5]	X[5]	X[5]	X	X	
Glasgow Outcome Scale			X[5]	X[5]	X[5]	X[5]		X	
Stroke Impact Scale						X			
CT/CTA or MRI/MRA[2]	X		X				X		
Angiogram, TIMI/TICI scores[3]		X							
Mechanical Thrombectomy Procedure[3]		X							
Concomitant Medications	X	X	X	X	X	X			
Adverse Event assessment	X	X	X	X	X	X	X	X	X

[1]Eligibility Labs are those required to be within a certain range as part of the inclusion/exclusion criteria list, including: pregnancy test (if applicable), INR, platelets, and creatinine.

[2]CT/CTA or MRI/MRA are required at baseline and 24hrs post-randomization, and any time there is a neurological deterioration (a change in NIHSS of 4 points or more) or hemorrhage.
[3]Only applicable to those patients randomized to receive mechanical thrombectomy.
[4]Must be completed by an unbiased healthcare provider.
[5]Must be completed by a BLINDED stroke study team member.

4.9 Randomization

A stratified randomization will take place centrally within REDCap (Research Electronic Data Capture™), the database system that will be used for this study. Randomization occurs in a 1:1 ratio to either the mechanical thrombectomy procedure or the best MT treatment group. The treatment assignment will be based on stratification by NIHSS (<20 vs. ≥20) within each center. The randomization table will be prepared by the study statistician, which will be uploaded to REDCap before the study begins. Once a patient is determined to meet all study eligibility criteria, immediately prior to the procedure, the Investigator (or authorized team member) will log on to REDCap to randomize the subject. The Investigator will not be blinded to treatment assignment. Once a patient is randomized, the patient is considered enrolled in the study and must be followed through the end of study.

5. Study Screening and Treatment Procedure

The screening and treatment procedures are described briefly below. The study procedure will take place after clinical baseline assessment and immediately following randomization to the thrombectomy arm in order to minimize time between initial evaluation and stroke treatment. Groin puncture must occur within one (1) hour of randomization.

5.1 Imaging Assessment for Eligibility for Trial Participation

The subject should be clinically evaluated in the same manner as any routine acute ischemic stroke patient. Clinical assessment documenting NIHSS and significant past medical history should be obtained. Imaging with CT or MR per the institution standard of care is required to exclude acute intracranial hemorrhage. Additional anatomic and physiologic imaging with CT or MR perfusion imaging per the institution standard of care should then be performed on patients that do not have evidence of significant ischemia on initial scans. Anatomic imaging can utilize CT angiography (CTA) with contrast bolus imaging to visualize the vessels of the head as well as presence of collateral circulation. Similar anatomic cerebral imaging can be performed with MR angiography (MRA). The studies must demonstrate an acute major vessel intracranial anterior circulation occlusion (ICA or MCA).

All MRIs will be performed on MR scanners equipped with echo-planar imaging capability to allow rapid acquisition of diffusion and perfusion scans. Patients with contraindications to MRI (metal implants such as pacemakers, claustrophobia, etc.) are not eligible for inclusion in the trial using MRI but may be eligible for inclusion using CT. The following sequences will be obtained: DWI, FLAIR (optional but recommended for baseline study), PWI, T2* GRE, and intracranial time-of-flight MRA (total 15 minute acquisition time), and contrast-enhanced neck MRA. For the baseline study, the sequences must be performed in the following order: DWI, GRE, intracranial MRA,

contrast enhanced neck MRA, PWI, FLAIR. All MRIs will be performed on 1.5-3.0 T scanners equipped with echo-planar imaging capability. The GRE sequence will be used to rule out hemorrhage and a pretreatment head CT scan will not be required in order to minimize any delay to therapy. A standard DWI sequence (b=0, 1000 s/mm^2 applied in each of three principal gradient directions, with ADC map calculation) will be used. MRI perfusion measurements will be made using sequential T2*-weighted (gradient echo) EPI time sequence scanning. Early in the time series, a bolus (0.1 mmol/kg) of MRI contrast material will be rapidly infused (5 ml/sec through an 18 or larger gauge angiocatheter) using a power injector. Alternative approaches to contrast dosing will be discussed as needed on a site by site basis.

Physiologic imaging should also be performed utilizing contrast bolus tracking technique with either MR or CT technologies. Post processing will be as per the institution routine perfusion evaluation, with deconvolution algorithms preferred. Patient selection will be based on the presence of a significant mismatch between the region of infarction depicted on the routine brain imaging scan (extent of CT low attenuation or DWI hyperintensity) and/or low CBV on perfusion maps as per institution standard of care. The viable ischemic penumbra will be determined as the region of tissue at risk as determined on the CBF and MTT (or Tmax) maps minus the region of infarction previously identified. Site-specific perfusion thresholds are to be chosen to include only significant prolongation in transit times or reduction in blood flow, such that minor perfusion changes reflecting benign oligemia are not included in 'at risk' tissue estimates. The qualitative presence of at least 2 color change difference from the normal is considered significant on the color rainbow scale perfusion maps or if quantitative measures are used then an absolute CBV <2 ml/100g reflected the infarct core and relative MTT >145% (or absolute value of >6 seconds) of the contralateral hemisphere most accurately reflected the penumbra. There must be at least 50% volume tissue at risk or an identified eloquent region at risk. The presence of greater than 1/3 territory MCA infarction, ASPECTS <7 or acute infarction greater than 35 cc (from recent data from MR RESCUE trial) volume is considered a boundary for exclusion. Acute volumes will be estimated at the site using AxBxC/2 calculations.

5.2 Preparation for Treatment

Patients randomized to the control group will receive best conventional MT for acute stroke as determined by the attending stroke physician. All attending stroke physicians will follow current AHA guidelines for the treatment of acute ischemic stroke. Patients randomized to thrombectomy will receive ASA 325 mg x1 during the first 24 hours following the procedure. Other anti-thrombotic regimens may be initiated or resumed after 24 hours. Clopidogrel may be employed in patients intolerant of aspirin. Endovascular intervention can be performed under either general anesthesia or conscious sedation based on best practices as determined by treating physician. Attempt should be made to expedite the transition from imaging to treatment in as rapid a fashion as possible. The subject should be prepared for the planned interventional procedure according to standard hospital procedures. Mechanical trombectomy should be performed with the operator's standard thrombectomy technique using aspiration or a stent retriever, separately or in combination.

5.3 Medication during Treatment

Subjects will undergo the index study treatment procedure as per the standard anesthetic protocol at the individual clinical site. Concomitant medications and therapies will be administered using standard hospital practice. The use of IA Verapamil will be allowed as per clinical standard for the treatment or prophylaxis of vasospasm encountered in the access to the intracranial vessels. IA or IV abciximab will be allowed to treat fresh platelet aggregation on deployed devices. Low dose IV heparin will be allowed per clinical practice to prevent acute thrombus formation. Administration and dosage of these medications will be captured in the study CRF.

Table 2: Recommended Medical Therapy Prior to and After Procedure

During procedure:	IA verapamil or nitroglycerine IA or IV abciximab IV heparin
After procedure:	Aspirin IV heparin

5.4 Pre-Procedure Angiography

If the patient is randomized to mechanical thrombectomy, the groin puncture to initiate the procedure should occur within 1 hour. An introducer sheath will be placed in the femoral artery. Diagnostic angiography is initially performed via the transfemoral approach with catheterization of the carotid artery appropriate to the patient's presenting symptoms. Once thrombus in the appropriate vessel is identified, the thrombectomy procedure will be initiated. If at the time of diagnostic angiography, the vascular lesion is deemed to not be an appropriate candidate for treatment with a clot retriever device or if no clot is visualized in the appropriate vessels, endovascular thrombectomy will not be pursued. Vascular lesions that are not appropriate candidates for clot retrieval are: the presence of dissection that precludes safe passage of the microcatheter or significant (>67%) proximal cervical common or internal carotid artery atherosclerotic stenosis that will obstruct retrograde extraction of a distal thrombus. Please note: angioplasty of the proximal cervical common or internal carotid artery to achieve < 67% stenosis for enrollment in the trial is prohibited.

Per local standard of care and prior to the thrombectomy, a Digital Subtraction Angiography (DSA) will be performed to define the angio-architecture of the occluded vascular segment. When possible, an assessment of collateral blood flow by DSA should be done per institutional standard of care, particularly in cases of terminal internal carotid artery occlusion. Prior to mechanical thrombectomy by the thrombectomy device, baseline Thrombolysis in Myocardial Infarction/Thrombolysis in Cerebral Infarction (TIMI/mTICI) scores by DSA (see Tables 3 and 4) will be obtained. CTA or MRA is not an acceptable substitute for this assessment. The investigator shall make an initial assessment of TIMI/mTICI flow in the target vessel territory.

Immediate post-treatment angiograms in the AP, lateral, and working positions will be obtained, and de-identified DICOM images will be submitted to the Independent Core Lab (ICL). The site Investigator will take necessary steps to ensure that pre- and post-

placement angiograms are performed using similar views, magnifications, and contrast amount so as to ensure valid "before-after" comparisons. TIMI/mTICI scores are to be assessed after completion of the procedure. Note should be made of any complicating factors such as vessel dissection or perforation. Pre-procedure and post-procedure angiograms shall be sent to an independent Core Laboratory to make a final determination on TIMI/mTICI flow.

Table 3: Thrombolysis in Myocardial Infarction (TIMI) Flow Classification

TIMI Score	**Classification of Blood Flow**
TIMI 0	No Perfusion
TIMI 1	Penetration without perfusion. Penetration past the initial occlusion, but no distal branch filling
TIMI 2	Partial perfusion of the artery with incomplete or slow distal branch filling
TIMI 3	Complete perfusion of the artery

* From *Chesebro et al. Circulation 1987;76:142-154 and Khatri et al. Stroke 2005;36:2400-2403*

Table 4: Modified Thrombolysis in Cerebral Infarction (mTICI) Perfusion Categories

Grade 0:	**No Perfusion**. No antegrade flow beyond the point of occlusion.
Grade 1:	**Penetration With Minimal Perfusion**. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.
Grade 2:	**Partial Perfusion**. The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, e.g, the opposite cerebral artery or the arterial bed proximal to the obstruction.
Grade 2a:	**Partial filling** with <50% of the entire vascular territory is visualized.
Grade 2b:	**Partial filling** with ≥50% of the entire vascular territory is visualized. If complete filling of all of the expected vascular territory is visualized, the filling is slower than normal.
Grade 3:	**Complete Perfusion**. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction *and* clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.

** From *Higashida et al. Stroke2003;34:e109-37*and *Tomsick et al. AJNR 2008;29:582-587*

5.5 Devices and Equipment

In addition to the thrombectomy device, devices that may be required for the study procedure include, but are not limited to, those shown in Table 5. All devices required to

perform the procedure are to be provided by the site and are available commercially for the indications for which they are proposed in this study.

Table 5: Devices that may be used during the Thrombectomy Procedure

Access devices:	Guiding catheter and sheath
Thrombectomy devices:	All FDA cleared cerebral mechanical aspiration and stent retriever thrombectomy devices are allowed. Note: The Merci retrieval device will NOT be allowed in the trial.
Non-ionic contrast:	Institutional standard of care
Guidewires:	Investigator preference from FDA approved devices and standard of care
Additional:	Any other adjunctive, approved/cleared device for IA stroke treatment

Device Instructions:

All thrombectomy devices are to be used in accordance with directions for use in the package insert approved by the FDA with the exception of the 8-hour from symptom onset use limit.

First generation thrombectomy devices such as Merci retrieval device will NOT be allowed in the trial.

It is recommended that all medical therapy decisions are made in accordance with guidelines from the AHA/ASA or critical care guidelines.

5.6 Post-Procedure Care

Patients randomized to the medical therapy group will receive best conventional MT for acute ischemic stroke as determined by the attending stroke physician. Standardization of medical management in both arms will occur according to the following:

- General medical management according to AHA/ASA guidelines
- Admission to monitored or intensive care unit for at least 24 hours
- Aggressive hypertensive-hypervolemic therapy should be used only in the case of symptomatic blood pressure fluctuations or if blood pressure drops below the normal range for the patient
- Antithrombotics: ASA 325 mg PO qd X 7 days (clopidogrel may be used as adjunctive therapy if indicated for cardiac disease) then per discretion of treating physician
- Close monitoring of BP and glucose with treatment according to AHA/ASA guidelines
- Follow-up imaging study required in any patient with neurologic deterioration

Neurological and functional exams will be conducted (NIHSS and mRS at a minimum) within 24 (+/-12) hours of randomization by a dedicated, pre-specified Blinded Study Stroke team member with NIHSS certification and expertise with a back up person named for cases in which the blinded team member was involved. Follow-up imaging (i.e., non-contrast CT scan) will be performed at 24 (+/-12) hours after randomization, and will be reviewed to assess hemorrhagic transformation based on ECASS definitions:

HI 1:	Small petechiae along the margins of the infarcted area without space-occupying effect
HI 2:	More confluent petechiae within the infarcted area but without space-occupying effect

PH 1:	Hematoma in <30% of the infarcted area with some slight space occupying effect
PH 2:	Hematoma in >30% of infarcted area with substantial space occupying effect

Based on previous work, only PH 2 will be defined as a clinically significant hemorrhage.

In addition, any neurological deterioration should be evaluated by urgent CT scan and other evaluations as indicated according to investigator/hospital best practice. A symptomatic intracranial hemorrhage will be defined as 24 hour CT evidence of an ECASS defined intracerebral and a 4-point or more worsening of the NIHSS score.

5.7 Recovery and Discharge

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

At 7 Days Post-Randomization or Discharge the following will be completed by a dedicated, pre-specified Blinded Study Stroke team member not involved in the patient's treatment: neurological exams (including NIHSS, mRS, and GOS), a review of any adverse events, and a review of current medications.

5.8 Hospital Costs

For each subject, device costs (the market price for each device) will be collected for the hospitalization during which the index procedure took place. These costs will include device costs, materials used to treat the occlusion, and number of days spent in the hospital (ICU and non-ICU length of stay).

5.9 Follow-Up Examination

5.9.1 Clinical

Several clinical outcome measures were selected for this study. These were chosen on the basis of their reliability, familiarity to the neurologic community, adaptability for use in

patients who have had a stroke, and comparability to end points used in other trials of thrombolytic therapy. The modified Rankin Scale (mRS) is an overall assessment of global handicap. In the original Rankin Scale, a score of zero indicates the absence of symptoms and a score of 5, severe disability. The modified Rankin Scale adds a score of 6 for fatal outcomes. The Glasgow Outcome Scale (GOS) is a global assessment of function.[42] A score of zero on the GOS indicates a good recovery; a score of 2 moderate disability; a score of 3 severe disability; a score of 4 survival but in a vegetative state; and a score of 5, death. It has been used in previous trials assessing outcome in hemorrhagic and ischemic stroke patients. [43][43] [43] [43] [43] [43] [43] [42] [42] [38] [36][36, 35] The National Institutes of Health Stroke Scale (NIHSS) is a 42 point scale that quantifies neurologic deficits in 11 categories. Normal function without neurologic deficit is given a score of zero.

Additionally a quality of life scale outcome measure will be utilized in this study. Quality of life scales are designed to be sensitive to changes in outcome from mild and moderate stroke undetected by other outcome measures. Important parameters not fully interrogated by conventional outcome scales can be assessed by quality of life scales, including emotion, communication, cognition, and social role function. Standard measures, such as the mRS, primarily evaluate physical aspects of stroke outcome, not addressing more relevant quality of life measures. The Stroke Impact Scale (SIS) is a validated assessment of quality of life specifically in patients with stroke. [44] [39] [37][37, 36]

All 24hr Post-Randomization (mRS, GOS, NIHSS), Day 7/Discharge (mRS, GOS, NIHSS), Day 30 (mRS, GOS, NIHSS), and Day 90 (mRS, GOS, NIHSS, SIS) clinical outcome measures will be assessed by a dedicated, pre-specified Blinded Study Stroke team member with NIHSS certification and expertise with a back up person named for cases in which the blinded team member was involved in the case during the acute hospitalization. Nursing staff, patients, and their family members will be instructed not to unblind the investigators performing these assessments.

5.9.2 Angiographic

All angiograms will be assessed by a central core lab neuroradiologist who is blinded to treatment assignment and clinical status. The extent of angiographic reperfusion after treatment will be classified in the primary analysis according to Thrombolysis in Myocardial Infarction (TIMI) grades.[37,38,40, 44,45] Recanalization is graded according to the TIMI scale shown in Table 3 above. A TIMI Score will be recorded for all affected vessel segments. Additionally, mTICI classification will also be documented.

5.9.2.1 Neuroimaging Outcome Measures

- **Ischemic Core Lesion Volumes**
  The initial ischemic core lesion volume will be defined using the model equations noted above respectively for MRI and CT. Final infarct volume will be defined as hyperintense regions on the day 7 FLAIR sequence (or hypodense region on day 7

CT). Lesion volumes will be quantified employing an interactive semi-automated program. For each patient, "percent lesion change" will be defined as:

$$\frac{\text{(Day 7 Final Infarct Volume – Pretreatment Core Lesion Volume)}}{\text{Day 7 Final Infarct Volume}} \times 100$$

- **Perfusion Lesion Volume**
  Regions of abnormal perfusion will be identified by visual inspection and outlined by hand using an interactive semi-automated image analysis program.

- **Percent Salvaged Penumbral Tissue**
  The percent salvaged tissue will be defined as:

  Number of Penumbral Voxels on Pretreatment Imaging Not Designated as Final Infarct Abnormality on D7 X 100

- **Hemorrhagic Transformation**
  Hypointense regions consistent with acute hemorrhage will be identified by visual inspection on the noncontrast CT or GRE sequences and outlined by hand to provide lesion volumes. Regions of hemorrhagic transformation will be categorized as petechial hemorrhage or hematoma according to the Berger classification scheme:

HI (hemorrhagic infarction)	
Type 1:	Small petechiae along the margins of the infarct
Type 2:	More confluent petechiae within the infarcted area, but without space-occupying effect

PH (parenchymal hemorrhage)	
Type 1:	Hematoma < 30% of the infarcted area with some slight space-occupying effect
Type 2:	Dense hematoma >30% of the infarcted area with substantial space-occupying effect, or as any hemorrhagic lesion outside of the infarcted area

- **Vessel Stenosis or Occlusions**
  For the pretreatment studies, the intracranial vessels will be evaluated for the presence of flow voids or signal loss suggestive of vessel occlusions or stenoses. The lesion location and severity of narrowing will be recorded for each abnormality. CTA or MRA will be considered positive for stenosis of a major vessel (ICA, MCA, ACA, PCA, basilar, vertebral) if the measured percent stenosis is ≥ 67% or if a flow gap is present. Percent stenosis will be measured using WASID trial criteria adapted for the intracranial circulation from the NASCET method:

$$\% \text{ stenosis} = \left(1 - \frac{D_{stenosis}}{D_{normal}} \right) X\ 100$$

(Selecting D_{normal}: distal for ICA; proximal for intracranial vessels)

5.9.3 Serious Adverse Events

All serious adverse events (SAE's) occurring during the 90 days of study participation will be recorded. Adverse events and serious adverse events are critical endpoints and will be assessed as they occur and at the scheduled clinic visits. A serious adverse event is one that is fatal or life-threatening, is permanently or substantially disabling, requires or prolongs hospitalization, or any event that the treating clinician judges to be a significant hazard, contraindication, side effect, or precaution. For each recorded adverse event, the patient's attending physician will be asked to classify the causal relationship of the event to the study treatment as definitely related, probably related, possibly related, unlikely related, or not related. Especially detailed form and narrative reports of the following specific adverse events will be obtained:

- Neurologic Deterioration: Increase of 4 or more points in the NIHSS
- Symptomatic Hemorrhagic Event: an ECASS defined ICH visualized on follow-up imaging study and associated with a 4 or more point worsening on the NIHSS score*
- Angiographic or thrombectomy procedural complications: Groin hematoma requiring transfusion or surgery, vessel dissection, vessel perforation, presence of emboli in a previously uninvolved territory, or other unanticipated procedure-related event, device fracture
- Malignant cerebral edema: Edema associated with neurologic impairment or requiring medical or surgical intervention
- Subarachnoid Hemorrhage (SAH): Both symptomatic and asymptomatic SAH visualized on follow-up imaging study.

*Asymptomatic hemorrhage events are not considered serious adverse events

An unblinded Safety Monitor will review all serious adverse events individually on a continuous basis as they occur and aggregate unblinded data on adverse events quarterly. This individual will report independently to the appointed DSMB at regularly scheduled DSMB meetings. This individual also has the authority to alert the DSMB at any time if a potential safety issue arises. If at any point, these reviews raise any safety concerns, the DSMB will be empowered to suggest that the trial be placed on hold and request additional analyses of the trial dataset.

6. Study Primary Endpoints

The primary objective is to show that AIS patients, ineligible for or refractory to treatment with IV-tPA, Patients seen within 6 hours of symptom onset will be immediately considered for endovascular therapy according to the site's standard of care. Likewise, patients presenting beyond 12 hours will be treated according to the site's standard of care. with appropriate image selection, treated within 6-12 hours with mechanical thrombectomy have superior rates of good functional outcomes as compared to those treated with best MT with respect to endpoint defined as:

- 90-day global disability assessed via the modified Rankin score (mRS), analyzed using raw mRS scores. Statistical details can be found in section 7.2.

6.1 Analysis of Primary Endpoint

6.1.1 Definition of Analysis Samples

- Target Population
  The target population for the POSITIVE trial is patients who are at least 18 who have a clinical diagnosis of Acute Ischemic Stroke who are ineligible for or refractory to treatment with IV-tPA and able to begin the thrombectomy procedure within a 6-12 hour time window of symptom onset or time last seen normal and as selected by physiologic imaging criteria.

- Intent to Treat Sample
  As the primary analysis, all efficacy and safety outcome measures will be analyzed under the intent-to-treat (ITT) principle. Under this principle, the evaluable sample includes all subjects who are randomized. Each subject will be analyzed according to the treatment group to which they were assigned at randomization.

- Per Protocol Sample
  In addition to the defined ITT analysis sample, a per-protocol sample is defined as a subset of the ITT sample. This sample will be used for secondary sensitivity analyses of the primary and secondary outcomes. The per-protocol sample will include all randomized subjects that do not have the following protocol violations or deviations:
    a. Eligibility violation
    b. Treatment crossover
    c. Missing 90 day primary outcome (not including missing due to death prior to the 90 days)

7. General Statistical Considerations

The **POSITIVE** Trial is a multicenter, randomized, Phase III clinical trial investigating the safety and efficacy of endovascular mechanical thrombectomy administration in acute ischemic stroke patients ineligible for or refractory to treatment with IV-tPA presenting within a 6-12 hour time window as selected by physiologic imaging criteria compared to best MT. The primary hypothesis to be tested is that treatment with endovascular mechanical thrombectomy will improve outcomes at 90 days as compared to the best MT group. Each eligible subject will be randomized in a 1:1 ratio to either the endovascular mechanical thrombectomy or the best MT treatment group with a stratified randomization by NIHSS (<20 vs. ≥ 20) within each center to balance randomization. This variable was chosen because of the known association with outcome. Randomization will take place centrally through the web-based REDCap database system. The centrally controlled randomization will help ensure the treatment balance at any interim analysis as well as in the final analysis.

7.1 Sample Size Estimation for the Primary Outcome

For this study design, power and sample size are computed by assuming that the true proportions of subjects with various mRS outcomes at the 90-day follow-up visit are consistent with the observed OR across all three recently published positive mechanical thrombectomy trials (EXTEND IA = 2.0, ESCAPE = 2.6, MR CLEAN = 1.67), which yields an average OR across all three of 2.1[37-39]These data were used for the sample size calculation under the proportional odds ordinal logistic model. With the hypothesized OR of 2.1, a total sample size of 180 was estimated to achieve at least 80% power to detect the difference in mRS scores between the control and treatment groups. After accounting a loss of follow-up rate of 10%, the revised POSITIVE trial with a total of 200 patients would provide adequate power with moderate effect size.

7.2 Statistical Evaluation of Primary Endpoint

90-day global disability assessed via the modified Rankin score (mRS), analyzed using raw mRS scores.

Statistical analysis of the primary endpoint will be conducted with a proportional odds ordinal logistic model using raw Rankin scores 0 to 6 (with 5 and 6 collapsed). The stratification variables used in the randomization (NIHSS and center) along with pre-specified potential confounding (prognostic) variables will be adjusted in the analyses. The potential confounding (prognostic) variables include race, age, previous stroke, smoking history, DM, hypertension, and hypercholesterolemia. As a sensitivity analysis, unadjusted analyses will be also performed.

7.3 Missing Data and Imputation Methods

Under the ITT principle, all patients who are randomized are included in the analysis. Therefore, missing data, especially in the outcome measures, can be problematic. Every effort is to be made to keep all missing data, particularly the Day 90 outcomes, to a minimum. Despite the clinical sites' best efforts, some missing data may be inevitable mainly due to lost-to-follow-up (LTFU). The number and proportion of subjects eligible for and compliant with each follow-up examination will be presented. Subjects who withdraw from the study will be tabulated with reasons for withdrawal. Since the primary endpoint is defined using mRS, subjects deceased during study follow-up will be scored as mRS 6. Other subjects not completing the 90-day follow-up visit will be categorized for the primary endpoint using the mRS as of the last available follow-up visit or discharge (whichever is later). As a sensitivity analysis, we will also perform analysis after excluding subjects without 90-day follow-up evaluations. Additional details will be provided in the Statistical Analysis Plan (SAP).

7.4 Secondary Statistical Analysis

7.4.1 Secondary Outcomes

- 90-day global disability in the 6-12 hr cohort assessed via the proportion of patients achieving a mRS of 0-2
- Proportion of patients with good functional recovery for the 6-12 hr cohort as defined by mRS 0-2 at 90 days

- Mortality at 30 and 90 days
- Intracranial hemorrhage with neurological deterioration (NIHSS worsening >4) within 24 hours of randomization
- Procedure related serious adverse events (SAE's)
- Arterial revascularization measured by TICI 2b or 3 following device use

Secondary outcome endpoints will be compared between randomized groups in an ITT fashion; with overall Type I error controlled using hierarchical testing. That is, if statistical significance is observed on the primary effectiveness endpoint, the secondary clinical efficacy endpoints will then be tested in sequential fashion each at a two-sided alpha level of 0.05, with testing ceasing once a null hypothesis cannot be rejected. The statistical tests will be performed in the order specified above.

7.4.2 Subgroup Analysis

7.4.2.1 Clinical Efficacy

- Maximum documented change in NIHSS
- Percentage of patients achieving NIHSS ≥10 point improvement or NISSS ≤4
- NIHSS at Discharge/Day 7 post-randomization of thromectomy versus MT arms
- Functional independence (mRS 0-2) according to MR vs CT based selection methodology
- Functional independence (mRS 0-2) according to involved hemisphere
- Functional independence (mRS 0-2) correlated with location of vascular occlusion, vascular collateral score, NIHSS, and age
- Time at which functional independence (mRS 0-2) was achieved (Discharge/7 day, 30 day, and 90 day)
- Percentage of patients receiving hemicraniectomy

7.4.2.2 Technical Efficacy:

- Volume of cerebral infarction as measured by a CT or MRI scan at 24(+/-12)hrs post randomization
- Correlation of core infarct volume predicted by initial CT Perfusion imaging with 24(+/-12)hrs post randomization stroke infarction in subjects who achieved TICI 2b-3 reperfusion
- Correlation of at risk penumbral volume predicted by initial CT Perfusion imaging with 24(+/-12)hrs post randomization stroke infarction in subjects who were randomized to MT
- mRS (at 90 days) of patients successfully revascularized (TICI 2b and 3 versus TICI 1 and 2a; TICI 1 and 2a/b versus TICI 3)

Subgroup analysis will be compared between randomized groups in an ITT fashion, with adjustment for multiple comparisons such that each will be evaluated at a two-sided alpha level of 0.01. Subgroup analyses are prospectively defined ancillary endpoints and will be presented descriptively. Additional details for these subgroup analyses will be provided in the Statistical Analysis Plan (SAP).

This is a multi-device clinical study where various devices may be used to treat vessel occlusion. The study is conducted with standardization of subject enrollment, data entry and adverse event reporting. All investigational sites will follow the requirements of a common protocol, data collection procedures and forms, and will utilize approved mechanical thrombectomy devices in accordance with product labeling.

7.5 Safety Analysis

7.5.1 Safety Outcomes

Several specific adverse events will be monitored throughout the study. However the primary safety outcomes to be assessed at completion of the trial are:

- Symptomatic intracranial hemorrhage at 24 hours post-randomization
- Asymptomatic intracranial hemorrhage at 24 hours post-randomization
- Intracranial hemorrhage within 90 days of hospital discharge
- Clinically significant complications (pneumonia, sepsis, UTI, etc.) at time of discharge or 7 days post randomization, whichever comes first.
- Mortality rates at 30 days post-hospital discharge
- Mortality rates at 90 days post-hospital discharge
- Treatment-related SAEs up to 48 hours post-randomization

7.5.2 Interim Safety Monitoring

7.5.2.1 Stopping the Trial Based on Interim Safety Data

The DSMB will receive periodic safety reports of all AEs and SAEs. In addition, the treatment-related SAE's occurring within 48 hours of randomization will be monitored as a safety outcome along with the following:

- Symptomatic intracranial hemorrhage within 24 hours of randomization
- Asymptomatic intracranial hemorrhage within 24 hours of randomization
- Mortality rates at 30 days post-hospital discharge
- Mortality rates at 90 days post-hospital discharge
- Treatment-related SAEs during the study
- All SAE's during the study
- Major non- intracranial hemorrhage bleeding complications during hospitalization
- Recurrent stroke within 90 days of hospital discharge

Additional details of the monitoring plan will be included in the study SAP and Monitoring Plan.

7.6 Blinding

This study is not blinded. Blinding is difficult, if not impossible, from a clinical perspective. It is not possible to blind the Investigator who treats the patient, nor is it possible to blind the internal review committee (IRC) members. Additionally, physicians treating subjects who experience an adverse event after must know how the stroke was treated in order to effectively report the adverse event and plan further treatment. Blinding the study is not required for interpretation of study outcomes. However to avoid bias in study results, the person performing the primary outcome assessment at 90 days

must be blinded to the subject's treatment assignment and have not been associated with the care of the subject during the acute treatment phase.

8. Study Withdrawal

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

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

8.1 Unattended Visits

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

9. Data Safety Monitoring Board (DSMB)

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

10. Trial Operating Committee

This study will have a trial operating committee (TOC) whose goal is to oversee trial operations. The TOC will consist of the study PI, statistical PI, project managers, data managers, and others deemed necessary in overseeing the day to day operations of the trial. The TOC will review study progress, study conduct at individual clinical sites, other clinical site performance measures, and blinded DSMB reports.

11. Scientific Advisory Committee (SAC)

This committee will be comprised of prominent investigators who are not part of this study. The SAC will function as an independent group that is charged with critically reviewing all aspects of the trial and advising the TOC on new scientific developments that may affect the design or conduct of this trial. Removed from the day-to-day operation of the trial, this committee is charged with providing a frank appraisal of the overall success of the TOC in achieving its operational objectives related to recruitment, data quality, and safety. This committee will be available to the Principal Investigators and TOC to consult on any problems that occur during the trial.

Unlike the Data Safety Monitoring Board, however, the SAC will not review data on overall rates of outcome or interim effectiveness data. The SAC does not have authority

to change the research protocol; it may recommend changes, but these would have to be approved by the Data Safety Monitoring Board before implementation.

The SAC will meet once prior to the start of enrollment to review the final protocol and procedure manual. Thereafter, it will meet as often as it deems necessary. At least one week before each meeting, the Principal Investigator will provide a progress report to the SAC to include all information requested by its Chair. It is anticipated that this report will require contributions from the respective centers in this study.

12. Steering Committee (SC)

The Steering Committee will be comprised of the trial PI's, principal investigators from the 5 top enrolling centers, statistician, and a representative from each corporate sponsor. The SC will be responsible for overall supervision and execution of the trial including adherence to protocol, progress of enrollment, patient safety, and consideration of new information. While daily trial management is the responsibility of the TOC, the TOC will provide key input to the SC for study planning, execution and data presentation.

12.1. Study Management

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

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

13. Investigator Responsibilities

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

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

Responsibilities of the Investigator include, but are not limited to:

- Ensuring that IRB approval is obtained prior to undertaking the trial at a clinical site
- Ensuring that participation of a subject in a clinical trial includes obtaining written informed consent prior to randomization and/or other non-standard of care study-related assessments
- Providing the study sponsor with accurate and complete financial information per 21 CFR Part 54
- Ensuring that all personnel assisting with the clinical trial are adequately informed and understand their trial-related duties and functions

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

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

14. Required Documents from the Investigator

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

- Signed Investigator Agreement
- Written and dated IRB/EC approval
- Written and dated IRB/EC approval for ICF document
- IRB/EC approval for any other written documents to be provided to the study subject (e.g., advertising)
- HIPAA documentation (if applicable)
- Investigator and Co-Investigators' current Curriculum Vitae*
- Current medical licenses
- Any other relevant documents requested by the study sponsor or the reviewing IRB/EC or other regulatory authorities,
- FDA Form 3454 or 3455 (or equivalent) regarding financial interests
- Fully executed contract
- Ongoing IRB approval documents
- Source Documents for data verification
- Site Delegation of Authority Log

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

15. Investigator Records

The Investigator must ensure that all study subject records are stored for at least 6 years after the end of the clinical study. To avoid error, the study site should contact Aquilla Turk, DO prior to the destruction of study records to ensure that they no longer need to be retained. In addition, Aquilla Turk, DO should be contacted if the Investigator plans to leave the investigational site so that arrangements can be made for the handling or transferring of study records.

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

- Clinic progress notes recording subject's medical history and medications
- Medical charts with operative reports and subject condition upon discharge
- Medical records regarding AE's/SAE's, including treatment and clinical outcome
- Results of diagnostic examinations, imaging (such as x-rays, MRIs), as well as the report of the radiologist's reading/interpretation of diagnostic imaging
- Signed notes of phone calls and/or correspondence indicating investigational site's attempts to follow study subjects at the required follow-up visits until subject's participation in the study is complete or terminated
- Records relating to patient death (e.g., death certificate, autopsy report, if available, or terminal medical records)

15.1 Data Collection

15.1.1 Data Management Overview

Data management will be handled by the VUMC Cerebrovascular Clinical Research group, which is housed in the Department of Neurological Surgery at the Vanderbilt University Medical Center (VUMC). All activities will be conducted in coordination with the study PI, the sites, and the TOC. The data validation procedure will be implemented on two levels: first, automated checks will display warnings for invalid data, and second, the Project Manager will verify individual data fields and query discrepancies. More information can be found in the Monitoring Plan.

15.1.2 Data Acquisition and Central Study Database

The entire study will be conducted using an electronic data acquisition method where all clinical data on enrolled subjects will be data entered (single-keyed) by the site personnel into a web-based data management system entitled Research Electronic Data Capture (REDCap) system that provides a user-friendly and easy-to-navigate interface, The latest version of each eCRF and source document worksheets will be available as a PDF file on the REDCap website for use by study personnel.

15.2 Randomization Module

The web-based Randomization Module will be used by authorized site personnel for the purpose of randomizing eligible patients. The Study Coordinator (or other appropriate study team member) will log onto the REDCap system using a unique username and confidential password. When a subject is deemed eligible, a unique subject ID and record

will be generated in REDCap. Once the Study Coordinator has entered the required subject information and clicked "Randomize", the computer program will display the treatment assignment for the subject. The subject is considered randomized and enrolled at the time the REDCap system generates the treatment assignment.

15.3 Security, Privacy, and Confidentiality

VUMC employs several layers of data protection to ensure data security. The first part of security is physical protection of the hardware systems, access to which is limited to authorized personnel. By limiting access, ensuring only authorized personnel have access, and tracking all entry, we can ensure this risk is minimal. Additionally, REDCap has a built-in audit trail that tracks all user activity and changes made to the data entry fields with a date-time stampe.

16. Adverse Events

Adverse events (AE's) may occur at any time after randomization. Pre-existing conditions (existing prior to randomization) will be documented in the subject's medical record as part of prior medical history but will not count as an AE unless it worsens during the study. Adverse events (serious and non-serious) will be documented on an Adverse Event form. Non-serious adverse events will be recorded from randomization through hospital discharge or 7 days post-randomization (whichever is earlier). Serious adverse events will be recorded from randomization through the end of study (i.e., 90 day post-randomization follow-up).

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

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

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

16.1 Serious Adverse Events

An adverse event is considered serious if it:

- Resulted in death
- Resulted in permanent impairment or damage
- Required inpatient hospitalization or prolongation of existing hospitalization
- Required medical or surgical intervention to prevent any of the above outcomes

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

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

16.2 Reporting and Review of Adverse Events

To provide for consistent reporting of adverse events, serious and non-serious adverse events will be recorded on the Adverse Event form in the database. Non-serious adverse events will be recorded from randomization through Day 7 or hospital discharge (whichever occurs first). Serious adverse events will be recorded from randomization through the end of study (i.e., 90 day final follow-up visit, death, or withdrawal of consent).

In order to ensure prompt reporting of adverse events, we require that all adverse events (as well as all related study data) be entered into the REDCap database within five working days of the study team becoming aware of the event for the following timepoints: Procedure and 7 Days Post-Randomization/Discharge (whichever occurs first). For all serious adverse events (SAEs), we require that they be reported in the REDCap within 24 hours of the study site staff first being made aware of the occurrence of the SAE. The 24 hour reporting requirement for SAEs applies to all study timepoints.

Reports of serious or life-threatening adverse events will be provided to appropriate members of the TOC and the Medical Safety Monitor (MSM). The MSM will conduct an independent review of each SAE. If the MSM believes the adverse event is serious, unexpected and either definitely, probably, or possibly related to the investigational

device(s) and/or study procedures, the TOC staff forward a Safety Report (pre-filled with as much data as possible) to the clinical site Investigator to be completed with any additional information that may be relevant to the SAE. The Safety Reports will be included in the reports prepared for the DSMB. The principal investigator at each clinical site will be responsible for reporting to his/her own IRB/EC according to individual IRB/EC policies. After the submission of the initial Safety Report, the principal investigator at the corresponding clinical site will be responsible for obtaining follow-up information about the event and reporting it to the TOC.

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

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

17. Ethical Considerations

The rights, safety, and well-being of clinical investigation subjects shall be protected consistent with the ethical principles laid down in the Declaration of Helsinki. This shall be understood, observed and applied at every step in this clinical investigation.
It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The Sponsor and the Investigator(s) shall avoid improper influence or inducement of the subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

18. Protection of Patient Confidentiality

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

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

19. Ethics Committee/Institutional Review Board Approval

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

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

20. Informed consent

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

The written informed consent document (and any other written information to be provided to the study subject) should be updated whenever new information becomes available that may require significant revisions to the informed consent document

previously signed by a subject. Any such revision or update must be approved by the reviewing IRB/EC before being provided to the study subject. Previously consented subjects will be made aware of the changes and depending on the extent and/or severity of the new information a subject may be asked to "re-consent" to continued participation in the trial.

21. Quality Assurance

To ensure monitoring responsibilities are performed to the fullest extent possible on a real-time basis through REDCap, the VUMC Cerebrovascular Clinical Research group will perform on-site and centralized monitoring for the trial. In addition to on-site monitoring, centralized monitoring (per the FDA's most recent monitoring guidance developed in August 2011) reflects a modern, risk-based approach and will include uploading of all non-de-identified source documents to the REDCap system. Centralized monitoring focuses on critical study parameters and relies on a combination of monitoring activities. In this recent guidance, the FDA has encouraged the implementation of centralized monitoring due to its ability to ensure quality and integrity of data. Centralized monitoring is also very effective at identifying data fraud, data fabrication, and data errors.

For the first subject enrolled at any site, 100% of the data will be verified against source documents. For subsequent subjects, a checklist of key outcome and safety data variables requiring source document verification (SDV) has been developed based on the trial's safety and efficacy endpoints. Sites will be evaluated in an ongoing manner to determine if there is a need to monitor more frequently or more thoroughly or via on-site evaluation. All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the subject's privacy as far as reasonably practicable. Only users with password-protected REDCap access will have the ability to view study data within the secure REDCap database. The Primary Investigator, Sponsor and representatives of regulatory authorities are permitted to inspect the study documents as needed. All attempts will be made to preserve subject confidentiality.

22. Protocol Deviations

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

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

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

23. Final Report

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

24. Information Confidentiality

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

25. Trial Registration

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

26. Risk Analysis

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

27. Publication Policy

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

29. References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation 2011;**123**(4):e18-e209 doi: 10.1161/CIR.0b013e3182009701[published Online First: Epub Date]|.
2. Higashida RT. Recent advances in the interventional treatment of acute ischemic stroke. Cerebrovascular diseases 2005;**20 Suppl 2**:140-7 doi: 10.1159/000089368[published Online First: Epub Date]|.
3. Vallabh Janardhan1 RMG, Sherman H, Chen1, Parita Bhuva1, Mark M. Murray1, Patricia Santos,1 Anita Guthmann,1 Madhu B. Vijayappa1, Paul A. Hansen1, Vivek Misra1, Raymond Cheung2, Thomas Leung3, Iris Grunwald4, Heather Hernandez5, Leticia Barraza5, Hope Buell5, Sophia Kuo5, Arani Bose5, Siu Po Sit5 Preliminary Results from the FIRST Trial: Natural History of Acute Stroke from Large Vessel Occlusion. In: (ISC) ISC, ed. International Stroke Conference (ISC). Hawaii: International Stroke Conference (ISC), 2013.

4. Adams HP, Jr., del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke; a journal of cerebral circulation 2007;**38**(5):1655-711 doi: 10.1161/STROKEAHA.107.181486[published Online First: Epub Date]|.
5. Shi ZS, Loh Y, Walker G, Duckwiler GR. Clinical outcomes in middle cerebral artery trunk occlusions versus secondary division occlusions after mechanical thrombectomy: pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI trials. Stroke 2010;**41**(5):953-60 doi: 10.1161/STROKEAHA.109.571943[published Online First: Epub Date]|.
6. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. Stroke; a journal of cerebral circulation 2008;**39**(4):1205-12 doi: 10.1161/STROKEAHA.107.497115[published Online First: Epub Date]|.
7. Nogueira RG, Smith WS. Emergency treatment of acute ischemic stroke: expanding the time window. Curr Treat Options Neurol 2009;**11**(6):433-43
8. Mishra NK, Albers GW, Davis SM, et al. Mismatch-based delayed thrombolysis: a meta-analysis. Stroke 2010;**41**(1):e25-33 doi: 10.1161/STROKEAHA.109.566869[published Online First: Epub Date]|.
9. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet 1997;**349**(9065):1569-81
10. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet 1997;**349**(9066):1641-9
11. Sandercock PA, Counsell C, Gubitz GJ, Tseng MC. Antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev 2008(3):CD000029 doi: 10.1002/14651858.CD000029.pub2[published Online First: Epub Date]|.
12. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). Jama 1995;**274**(13):1017-25
13. Schellinger PD, Thomalla G, Fiehler J, et al. MRI-based and CT-based thrombolytic therapy in acute stroke within and beyond established time windows: an analysis of 1210 patients. Stroke; a journal of cerebral circulation 2007;**38**(10):2640-5 doi: 10.1161/STROKEAHA.107.483255[published Online First: Epub Date]|.
14. Tarr R, Hsu D, Kulcsar Z, et al. The POST trial: initial post-market experience of the Penumbra system: revascularization of large vessel occlusion in acute ischemic stroke in the United States and Europe. Journal of neurointerventional surgery 2010;**2**(4):341-4 doi: 10.1136/jnis.2010.002600[published Online First: Epub Date]|.
15. Saver JL, Jahan R, Levy EI, et al. SOLITAIRE with the intention for thrombectomy (SWIFT) trial: design of a randomized, controlled, multicenter study comparing

the SOLITAIRE Flow Restoration device and the MERCI Retriever in acute ischaemic stroke. International journal of stroke : official journal of the International Stroke Society 2012 doi: 10.1111/j.1747-4949.2012.00856.x[published Online First: Epub Date]|.

16. Nogueira RG, Lutsep HL, Gupta R, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet 2012;**380**(9849):1231-40 doi: 10.1016/S0140-6736(12)61299-9[published Online First: Epub Date]|.
17. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;**141**(2 Suppl):e601S-36S doi: 10.1378/chest.11-2302[published Online First: Epub Date]|.
18. Brinjikji W, Kallmes DF, Rabinstein AA, Lanzino G, Cloft HJ. Hospitalization costs for patients with acute ischemic stroke treated with endovascular embolectomy in the United States. Stroke; a journal of cerebral circulation 2011;**42**(11):3271-3 doi: 10.1161/STROKEAHA.111.618405[published Online First: Epub Date]|.
19. Baker WL, Colby JA, Tongbram V, et al. Neurothrombectomy devices for the treatment of acute ischemic stroke: state of the evidence. Ann Intern Med 2011;**154**(4):243-52 doi: 10.1059/0003-4819-154-4-201102150-00306[published Online First: Epub Date]|.
20. Kidwell CS, Jahan R, Alger JR, et al. Design and rationale of the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) Trial. International journal of stroke : official journal of the International Stroke Society 2012 doi: 10.1111/j.1747-4949.2012.00894.x[published Online First: Epub Date]|.
21. Paciaroni M, Medeiros E, Bogousslavsky J. Desmoteplase. Expert opinion on biological therapy 2009;**9**(6):773-8 doi: 10.1517/14712590902991497[published Online First: Epub Date]|.
22. Nogueira RG, Smith WS, Sung G, et al. Effect of time to reperfusion on clinical outcome of anterior circulation strokes treated with thrombectomy: pooled analysis of the MERCI and Multi MERCI trials. Stroke; a journal of cerebral circulation 2011;**42**(11):3144-9 doi: 10.1161/STROKEAHA.111.624163[published Online First: Epub Date]|.
23. Saver JL, Warach S, Janis S, et al. Standardizing the structure of stroke clinical and epidemiologic research data: the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Common Data Element (CDE) project. Stroke; a journal of cerebral circulation 2012;**43**(4):967-73 doi: 10.1161/STROKEAHA.111.634352[published Online First: Epub Date]|.
24. International Stroke Conference Poster Presentations. International Stroke Conference Poster Presentations.: Rev Neurol Dis. 2009 Spring;6(2):E72-4., 2010.
25. International Stroke Conference Poster Presentations. International Stroke Conference Poster Presentations., 2009.
26. The Interventional Management of Stroke (IMS) II Study. Stroke; a journal of cerebral circulation 2007;**38**(7):2127-35 doi: 10.1161/STROKEAHA.107.483131[published Online First: Epub Date]|.

27. Ezzeddine MA, Lev MH, McDonald CT, et al. CT angiography with whole brain perfused blood volume imaging: added clinical value in the assessment of acute stroke. Stroke 2002;**33**(4):959-66
28. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. Jama 1999;**282**(21):2003-11
29. Lin R, Vora N, Zaidi S, et al. Mechanical approaches combined with intra-arterial pharmacological therapy are associated with higher recanalization rates than either intervention alone in revascularization of acute carotid terminus occlusion. Stroke 2009;**40**(6):2092-7 doi: 10.1161/STROKEAHA.108.544783[published Online First: Epub Date]|.
30. Turk A, Magarik JA, Chaudry I, et al. CT perfusion-guided patient selection for endovascular treatment of acute ischemic stroke is safe and effective. J Neurointerv Surg 2011 doi: 10.1136/neurintsurg-2011-010067[published Online First: Epub Date]|.
31. Turk AS, Nyberg EM, Chaudry MI, et al. Utilization of CT perfusion patient selection for mechanical thrombectomy irrespective of time: a comparison of functional outcomes and complications. J Neurointerv Surg 2012 doi: 10.1136/neurintsurg-2012-010452[published Online First: Epub Date]|.
32. Turk AS, Magarick JA, Frei D, et al. CT perfusion-guided patient selection for endovascular recanalization in acute ischemic stroke: a multicenter study. J Neurointerv Surg 2012 doi: 10.1136/neurintsurg-2012-010491[published Online First: Epub Date]|.
33. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. The New England journal of medicine 1995;**333**(24):1581-7 doi: 10.1056/NEJM199512143332401[published Online First: Epub Date]|.
34. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. The New England journal of medicine 2008;**359**(13):1317-29 doi: 10.1056/NEJMoa0804656[published Online First: Epub Date]|.
35. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;**352**(9136):1245-51
36. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. Stroke 2005;**36**(7):1432-8 doi: 10.1161/01.STR.0000171066.25248.1d[published Online First: Epub Date]|.
37. Campbell BC, Mitchell PJ, Yan B, et al. A multicenter, randomized, controlled study to investigate EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy (EXTEND-IA). Int J Stroke 2014;**9**(1):126-32 doi: 10.1111/ijs.12206[published Online First: Epub Date]|.
38. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;**372**(1):11-20 doi: 10.1056/NEJMoa1411587[published Online First: Epub Date]|.

39. Goyal M, Demchuk AM, Menon BK, et al. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. N Engl J Med 2015 doi: 10.1056/NEJMoa1414905[published Online First: Epub Date]|.
40. Sheth SA, Jahan R, Levy EI, et al. Rapid learning curve for Solitaire FR stent retriever therapy: evidence from roll-in and randomised patients in the SWIFT trial. Journal of neurointerventional surgery 2015 doi: 10.1136/neurintsurg-2014-011627[published Online First: Epub Date]|.
41. Solitaire With the Intention For Thrombectomy as PRIMary Endovascular Treatment (SWIFT PRIME) Trial. International Stroke Conference; 2015; Nashville, TN.
42. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;**2**(7872):81-4
43. Haley EC, Jr., Brott TG, Sheppard GL, et al. Pilot randomized trial of tissue plasminogen activator in acute ischemic stroke. The TPA Bridging Study Group. Stroke 1993;**24**(7):1000-4
44. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Laster LJ. The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. Stroke 1999;**30**(10):2131-40
45. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. New England Journal of Medicine 1985;**312**(14):932-6