UTHealth The University of Texas Health Science Center at Houston | McGovern Medical School

SEGA - SEdation versus General Anesthesia for Endovascular Therapy in Acute Ischemic Stroke – a Randomized Comparative Effectiveness Trial.

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SEGA CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER	**HSC-MS-17-0436**	
PROTOCOL TITLE	**SEGA - SE**dation versus **G**eneral **A**nesthesia for Endovascular Therapy in Acute Ischemic Stroke – a Randomized Comparative Effectiveness Trial.	
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PROTOCOL SYNOPSIS

Title	**SEGA**: Sedation versus General Anesthesia for Endovascular Therapy in Acute Ischemic Stroke – a Randomized Comparative Effectiveness Trial.
Study Purpose	**Background:** Endovascular therapy (EVT) with stent retrievers improve functional outcome in acute stroke patients. Although both are routinely performed as usual care during EVT, controversy remains regarding the optimal type of anesthesia during EVT – general anesthesia (GA) vs. sedation (CS). Retrospective case-control studies found an association between better clinical outcomes with the latter. However, one small, single-center randomized trial suggested no significant differences in early outcomes. **Primary Objective**: To estimate overall treatment benefit (improvement in disability) among acute ischemic stroke patients that are randomized to GA compared with CS during endovascular therapy. **Secondary Objectives:** Assess safety (as measured by incidence of symptomatic intracranial hemorrhage); rates of EVT procedural complications, reperfusion; and quality of life.
Design	Multicenter, randomized, comparative effectiveness trial with un-blinded caregivers but blinded assessors (PROBE – Prospective Randomized Outcome Blinded Endpoint).
Study Population Overview	**260** total acute ischemic stroke patients with proximal intracranial arterial occlusions treated with endovascular therapy within 16 hours of symptom onset. Patients must not require intubation for any clinical indication. Arterial occlusion must be demonstrated by either CT-angiogram (CTA) or MR-angiogram (MRA).
Intervention	Time of randomization is study time=0. Patients will be randomized 1:1 to receive during endovascular therapy either: 1) **General anesthesia** (balanced for equal randomization into intravenous vs. inhalational) or **2) Sedation** Both GA and CS delivered and managed by anesthesiologist.
Primary Outcome	Independent functional outcome as measured by the modified ordinal Rankin Scale (mRS) at 90 days assessed by study personnel blinded to treatment.
Secondary Outcomes	1) Dichotomized mRS at 90 days (0-2 vs 3-6) 2) Safety as measured by rates of symptomatic intracerebral hemorrhage within 24-36 hours after endovascular therapy. 3) Angiographic reperfusion defined as modified TICI score ≥ 2b. 4) Peri-procedural complications. 5) Difference in 24-36-hour NIHSS scale. 6) Proportion of independent functional outcome at 90 days in GA patients treated with inhalational vs. intravenous medications. 7) Difference in quality of life at 90-days.

Study Duration	Total trial duration: 24 ± 4 months a. Enrollment – approximately 18 months with 6 months of data-monitoring and statistical analysis b. Patient participation - 90 days
Statistics	• Planned number of sites (US + international): 10-15. • Sample size: 260 patients randomized 1:1 (130 per group). • Final analysis uses a Bayesian approach to obtain odds ratio (OR) of good functional outcome at 90-days. Bayesian prior assumes treatment equipoise and uses a neutral, informative prior (OR=1.0; 95% credible intervals of 0.3-3.0). • Trial success is defined as a >80% posterior probability that GA is superior (OR >1.0 of 90-day mRS) to CS.
Assessments	• **Baseline:** History & physical exam; vital signs; laboratory tests; non-contrast CT head, arterial vessel imaging – CTA or MRA, NIHSS, pre-stroke mRS, home medications. • **Endovascular Procedure:** Continuous vital signs (Blood pressure, pulse, oxygen saturation, $PETCO_2$ in general anesthesia [GA] patients);anesthesia medications; monitor for device-specific malfunction and serious adverse events; cross-over (e.g., CS to GA). • **24-36 hours post EVT:** Non-contrast head CT or MRI brain as per local usual care; NIHSS • **7-days or discharge** (whichever occurs first): Vital signs, physical examination, mRS, NIHSS, Blinded assessment of mRS and NIHSS; Stroke etiology. • **90 ± 15 days:** Blinded assessment of mRS and Quality of Life; Stroke etiology.
Significance	Data generated will inform the optimal anesthesia management of EVT-treated ischemic stroke patients and would be expected to result in significant change of medical practice.

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List of Abbreviations

A1	1st segment of anterior cerebral artery
A2	2nd segment of anterior cerebral artery
ACA	Anterior Cerebral Artery
AE	Adverse event
AHA	American Heart Association
A-line or Aline	Arterial Line
ASA	American Stroke Association
aICH	Asymptomatic intracerebral hemorrhage
aPTT	Activated partial thromboplastin time
aOR	Adjusted Odds Ratio
aRR	Adjusted Relative Risk
ASPECTS	Alberta Stroke Program Early CT Score
BA	Basilar Artery
BP	Blood Pressure
CABG	Coronary artery bypass graft
CAS	Carotid Artery Stenting
CBC	Complete blood count
CEA	Carotid Endarterectomy
CFR	Code of Federal Regulations
CI	Confidence interval
CK	Creatine kinase
CrCl	Creatinine clearance
CrI	Credible Interval
CO_2	Carbon dioxide
CRF	Case Report Form
CS	Conscious Sedation
CT	Computed tomography
CTA	Computed tomography-Angiogram
CTP	Computed tomography-Perfusion
CVA	Cerebrovascular accident
DBP	Diastolic blood pressure
DTN	Door to needle
DTG	Door to groin
ECG	Electrocardiogram
EDH	Epidural Hematoma
eGFR	Estimated Glomerular Filtration Rate
ESCAPE	Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke
EQ-5D	European Quality of Life-5 Dimensions
EVT or ET	Endovascular Therapy
EXTEND-IA	Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial
GA	General Anesthesia
GI	Gastrointestinal
H, h or hr, hrs	Hour(s)
$_{\beta}$HCG	beta-human chorionic gonadotropin
HERMES	Highly EffectiveReperfusion evaluated in Multiple Endovascular Stroke
HT1 or HT-1	Hemorrhagic Transformation Type-1
HT2 or HT-2	Hemorrhagic Transformation Type-2
ICA	Internal carotid artery

ICH	Intracranial hemorrhage
IRB	Institutional Review Board
IV	Intravenous
IV-tPA	Intravenous recombinant tissue plasminogen activator
IVH	Intraventricular Hemorrhage
kg	Kilogram
LFT	Liver function test
LMWH	Low molecular weight heparin
LOS	Length of stay
M1	1st segment of middle cerebral artery
M2	2nd segment of middle cerebral artery
M3	3rd segment of middle cerebral artery
mmHg	Millimeters of mercury
MAP	Mean arterial pressure
MCA	Middle cerebral artery
MR CLEAN	Multicenter Randomized Clinical trial of Endovascular Treatment in the Netherlands
mRS	Modified Rankin Scale
mTICI	Modified Thrombolysis In Cerebral Ischemia
NA	Not available or Not applicable
ND	Not done
NIHSS	National Institute of Health Stroke Scale
NNH	Number needed to harm
NNT	Number needed to treat
OR	Odds Ratio
pH	Hydrogen ion concentration
PH1 or PH-1	Parenchymal Hematoma Type-1
PH2 or PH-2	Parenchymal Hematoma Type-2
Q or q	Every
rt-PA or tPA	Recombinant tissue plasminogen activator
RCT	Randomized Clinical Trial
REVASCAT	Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours
SAE	Serious adverse event
SAH	Subarachnoid hemorrhage
SBP	Systolic blood pressure
SD	Standard deviation
SDH	Subdural Hematoma
sICH	Symptomatic Intracerebral Hemorrhage
SIESTA	Sedation vs. intubation for endovascular stroke treatment
SWIFT-PRIME	Solitaire with the intention for thrombectomy as primary endovascular treatment trial
tICA or TICA	Terminal Internal Carotid Artery
TICI	Thrombolysis In Cerebral Ischemia
TNKase	Tenecteplase
VA	Vertebral artery

1.0 BACKGROUND AND RATIONALE

Stroke is the fourth leading cause of death in developed nations. Each year in the US, approximately 795,000 people experience a new or recurrent stroke. On average, every 40 seconds, someone in the United States has a stroke.[1] Representing approximately 30-40% of all ischemic strokes, proximal intracranial arterial occlusions result in the most disabling types of ischemic strokes, and are closely associated with poor neurological outcomes at hospital discharge.[2] Recent randomized clinical trials conclusively demonstrated that early endovascular therapy (EVT) with stent-retrievers (i.e., embolectomy) significantly improves functional outcomes in patients with acute ischemic stroke up to 6 hours after onset and are recommended by the American Heart Association/Stroke Association (AHA/ASA).[3-6] However, controversy remains regarding the optimal type of anesthesia that should be used during in EVT.[7-10] The AHA/ASA guidelines do not support a recommended choice of anesthesia as the selection should be individualized to the patient (Class IIb; Level of Evidence C).[11] Further, the guidelines state that randomized trials are needed.

1.1 Retrospective Studies of Anesthesia during Endovascular Therapy

Many retrospective case-control studies, propensity score analyses and post-hoc analyses of EVT trials have suggested, compared to CS, an association between GA and worse stroke outcomes including mortality – see table 1.[12-19] In these studies, GA compared to conscious sedation (CS) in EVT reduced the odds of 90-day good functional outcome (mRS ≤ 2).

Following 1:1 matching using propensity score analysis, 507 general anesthesia and 507 CS patients, the outcome of thrombectomy patients receiving CS had decreased in-hospital mortality, pneumonia, and lower hospital costs and lengths of stay when compared with patients who received general anesthesia.[12] This study suffered significant selection bias, which compromised its conclusion. A post-hoc analysis of the thrombectomy patients in MR CLEAN (Multicenter Randomized Clinical trial of Endovascular Treatment in the Netherlands) showed better functional 90-day outcome in the absence of general anesthesia, but again, patients were not randomized to the type of anesthesia.[17]

1.2 Randomized Trials of conscious sedation vs. general anesthesia during Endovascular Therapy

Until the recent publication of the first randomized trial testing general anesthesia vs. CS, [20] none of these studies randomized patients to a particular anesthesia approach – see table 1. The SIESTA trial randomized 150 (1:1) EVT treated stroke patients to either GA or CS at a single institution in Germany. The primary outcome, improvements in 24-hour mean NIHSS scores were nearly identical (3.2 vs. 3.6 points in GA vs. CS, respectively). The mean difference between the two groups was 0.4 and not statistically significant, P=0.82. Both arms demonstrated similar rates of successful angiographic reperfusion (TICI 2b or 3): 89%-GA vs. 81%-CS. More GA patients had prolonged intubation, incidence of pneumonia and hypothermia. Despite the increased incidence of adverse events and lack of clinical improvement at 24 hours, GA patients were more likely to be functionally independent (mRS ≤2) at 90 days: 37% GA vs. 18% CS, P=0.01 (see table 1). Both in-hospital and 90-day mortality were nearly identical in the two study arms. Authors concluded SIESTA results did not support superiority of CS over GA and they recommended a larger, multicenter RCT powered to address longer-term outcomes.

Table 1. Summary of clinical studies of ET and anesthesia. Shaded row indicates the lone RCT of EVT patients randomized to GA versus CS.

REF	Design	Anesthesia Preferred	Benefit	Harm	Comments
12	Retrospective Propensity Analysis	Sedation	• Sedation associated with: ↓hospital mortality; ↓pneumonia; ↓hospital costs/LOS	GA associated with: ↑ in-hospital mortality (25% v 12%) OR=2.4, 95%CI 1.7-3.4, p<0.001. ↑pneumonia 17% v 9% OR=2, 95%CI 1.4-2.96, p<0.001. • ICH/SAH rates similar: 11% v 12%, p=0.62.	- 1:1 propensity score matching 507 GA & 507 CS patients - Usage rate of GA decreased from 83.8% in 2006 to 74% in 2013.
13	Post-Hoc analysis of Multicenter RCT (IMS-3)	Sedation	No significant difference in: - Adjusted risk of SAH (P=0.32) or sICH P=0.37	• GA associated with: ↑ in-hospital mortality - aRR 2.8; 95%CI, 1.7-4.9,P<0.001 • ↓ 90d mRS ≤2, RR 0.68; 95%CI 0.5-0.9; P=0.006	Sedation – 269 (62%) GA – 147 (33.9%) Undetermined – 18 (4%)
14	Retrospective analysis (n=126)	Sedation	• Intra-procedural complications lower in patients who received Sedation 6% v GA 15% P=0.13 • Sedation assoc with good outcome (OR 3.06, P=0.04)	GA associated with ↑ICU LOS: 6.5 days v 3.2 days, P<0.00)	Sedation – 73 (58%); GA – 53 (42%)
15	Retrospective analysis (n=109)	Sedation	Duration of procedure & time to revascularization was significantly lower in Sedation	GA 18% greater mortality rate compared with the CS group (*P*=0.045)	- CS – 74; GA - 35 - GA & post procedure glucose significant predictors of mortality
16	Retrospective pre-trial Cohort of MR-CLEAN (n=348)	Sedation	• Sedation better clinical outcomes - (OR 2.1, 95% CI, 1.02–4.31) • After adjusting for pre-specified prognostic factors, statistical significance was lost (OR1.9, 95% CI, 0.89–4.24).	No difference in sICH or Asymptomatic ICH Mortality - GA group (21%) vs. Sedation (17%) No difference in device dissection or device-related complications	CS - 278 GA – 70
17	Post-Hoc analysis of RCT (MR-CLEAN)	Sedation	mRS in favor of non-GA compared to control group (adjusted common OR 2.2, 95%CI 1.5-3.2.	GA associated with significant (p = 0.011) effect modification, resulting in estimated ↓of 51% (95%CI 31%-86%) in EVT effect compared to CS.	Treatment without GA was associated with a significant treatment benefit in MR CLEAN.
18	Retrospective Case-Control	Sedation	• No difference in hemorrhage	GA associated with ↑mRS >2 at 90 days (OR 2.33) and also ↑mortality (OR 1.7)	Older study (2005 – 2009); n=980
19	Post-Hoc Meta-Analysis of 9 studies	Sedation	• No difference in treatment times between the two groups	GA associated with: ↑mortality OR 2.6, ↑respiratory complications OR 2.1 ↓good clinical outcomes (OR = 0.43)	- GA patients with higher NIHSS presenting scores. - n=1956
20	**RCT Monocentric**	**GA** - no support for CS advantage	• No significant difference (P=0.82) in primary outcome (24 hour NIHSS) between groups. • ↑ mRS ≤2 at 90d 37%-GA v. 18% CS without mortality diff.	GA had more: - hypothermia (32%, P<0.001) - delayed extubation (49.3%, P<0.001) - pneumonia (13.7%, P=0.03)	**Only RCT that randomized EVT patients to either GA or CS.** Sedation – 77; GA - 73
Campbell (ISC 2017)	Post-Hoc Meta-Analysis 5 RCTs	Sedation	• Both CS & GA superior compared to usual care • Equivalent procedure complications	↑good outcomes in non-GA group (OR 1.6). ↑ pneumonia in GA group (16% v 9%), - Randomization to treatment time prolonged in GA	HERMES collaboration; n=1287; NIHSS, age, onset to random. times comparable CS v. GA

A recent retrospective study of a multi-hospital administrative database between 2006-2013, found 80% of 2515 EVT patients received GA, whereas 20%, received CS.[21] These findings suggest the majority of neuro-interventionists preferred GA. Since that time, multiple retrospective studies have been published (detailed in table 1) that suggest CS may be preferable to GA. We recently sent a questionnaire to vascular neurologists and both neurology and neurosurgery trained neuro-interventionalists. The aim was to determine the state of anesthesia equipoise among physicians who perform or direct care for EVT stroke patients. Notably, the questionnaire was sent 4 months after publication of the SIESTA trial. EVT specialists were asked if a randomized trial was still needed – Figure 1. Out of 97 respondents, the responses were similar.

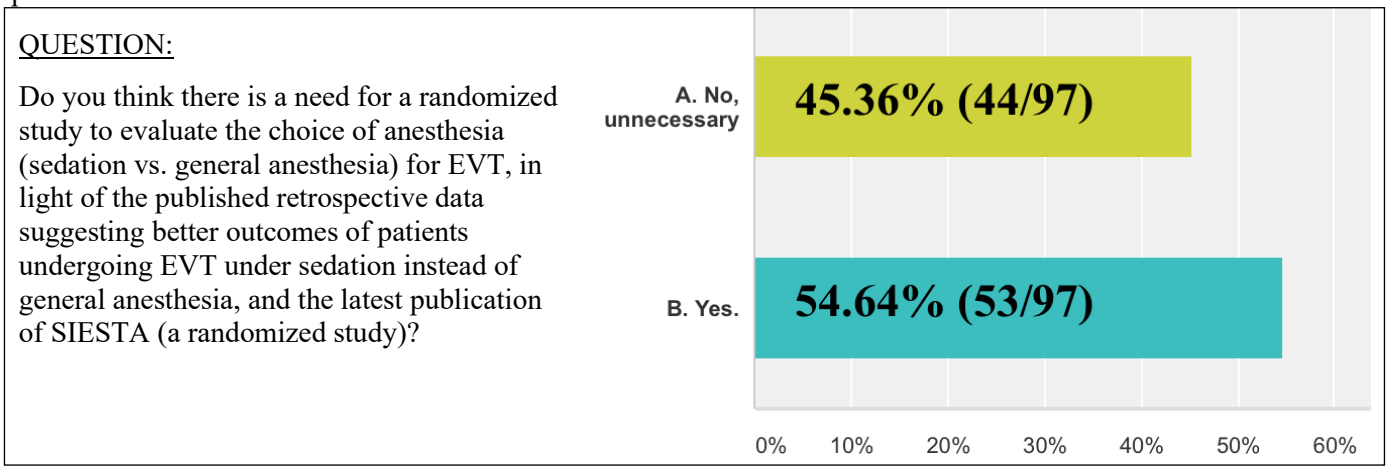

Figure 1. Results of questionnaire from comprehensive stroke center's opinion for a current randomized trial of anesthesia in EVT.

For thrombectomy following acute stroke, any delay will likely result further brain infarction. Relative to CS, general anesthesia may result in more delays to recanalization time.[7] On the other hand, patients who receive CS are more likely to suffer agitation and move while on the treatment table, potentially delaying recanalization as well, and increasing procedural risk. Iatrogenic arterial rupture and inability to catheterize the occluded vessel are key concerns. There has also been speculation of potential anesthetic-related worsening ischemic volume due to a vasodilatory "steal phenomenon".[7] The cumulative dose of norepinephrine during general anesthesia was considered a predictor of an unfavorable outcome.[22]

GA for EVT can be administered using intravenous anesthetics, inhaled anesthetics, or a combination. There is no clear standard of care as to the type of GA for this procedure: the various retrospective and prospective studies investigating this issue have used both. Lacking evidence of the superiority of one type of anesthetic over the other in EVT, the decision of which type to administer is based on anesthesiologist preference and/or common local practice. Different anesthetic techniques have differential effects on cerebral blood flow, which may affect flow to the penumbra either directly, or by increasing flow to unaffected regions ("steal phenomenon"). One retrospective study found that outcomes were better in patients administered an inhaled general anesthetic compared to intravenous or combination techniques.[9]

As expected secondary to study design, previous retrospective studies comparing the utilization of the CS vs. GA are severely limited by probable selection bias. The "sicker" patients with cardiovascular instability or respiratory distress, agitation, aphasia from dominant hemispheric stroke location, and the inability to protect their airway were typically treated under general anesthesia. These patients remained intubated for the same reasons after the procedure as well; whereas patients who were otherwise conscious and cooperative at baseline, without airway issues, with stable cardiovascular and pulmonary status were selected for EVT under CS. Intuitively, patients within the former group had longer ICU and hospital stay, higher hospital mortality, and worse neurological and functional outcomes.
The soundest mechanism for reducing selection bias remains randomization with allocation concealment. Most importantly, randomization balances all the known and unknown patient characteristics. Therefore, a randomized study comparing CS and GA during EVT is needed to evaluate the objective outcomes to help determine the future treatment paradigm.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the hypothesis that GA during EVT for acute ischemic stroke improves functional outcomes at 90 days compared to sedation.

2.2 Secondary Objectives

Evaluate safety, reperfusion, early neurological improvement, effect modification by type of GA, and quality of life in EVT patients randomized to GA versus sedation.

3.0 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is a comparison of independent clinical outcome, defined as a modified ordinal Rankin Scale (mRS) at 90 days (scores 5 and 6 combined) among patients randomized to GA versus sedation. Primary analysis will be intention to treat (ITT) and adjusted for stratification variables.

3.2 Secondary Clinical Endpoints

1) As treated analysis of primary outcome adjusted for stratification variables
    a. Patients will be analyzed according to the type of anesthesia received (e.g., a patient randomized to Sedation that crosses-over to GA will be analyzed in the GA group).
2) Dichotomized mRS at 90-days (0-2 vs 3-6) adjusted for stratification variables.
3) Angiographic reperfusion defined as modified TICI score ≥ 2b.
4) Early clinical improvement measured by difference in 24-36 hour NIHSS scale.
5) Proportion of independent functional outcome at 90 days in GA patients treated with inhalational vs. intravenous medications.
6) Difference in quality of life at 90-days.

3.3 Secondary Safety Endpoints

1) Symptomatic intracerebral hemorrhage within 18-36 hours.
    1. Defined as the SITS-MOST definition: Increase in NIHSS of ≥4 points and PH-2/rPH-2.[23]
2) All-cause mortality.
3) Rates and types of peri-procedural or device-related complications.

3.4 Exploratory Analyses

1) Ordinal ITT and as-treated analysis of primary outcome comparing three groups (CS, GA IV, GA inhalational) adjusting for stratification variables.
2) Multivariable adjusted analysis (including stratification variables) for both primary (mRS 0-2) and ordinal analysis of 90-day mRS outcomes, to include (but not limited to) baseline variables known to be clinically associated with stroke outcomes:
    a. Age
    b. NIHSS
    c. Time from stroke onset-to-EVT groin puncture
    d. IV-tPA treatment before EVT
    e. Atrial Fibrillation
3) Duration of time during EVT spent below a systolic blood pressure of 140mmHg.
4) Total ICU and ventilator days.
5) Subgroup analyses to test for heterogeneity in patient benefit and Provider Skill:
    a. Proximal vs. Distal occlusion location (ICA+M1-MCA vs. others)
    b. High-volume vs. low-volume centers
6) Costs from a health system perspective

4.0 STUDY DESIGN

4.1 Overview

This trial is a multicenter, randomized, parallel-group, open-label treatment with blinded end point adjudication (PROBE). Patients with acute stroke who meet endovascular therapy criteria for large arterial vessel occlusion will be randomized 1:1 to Sedation or GA. Patients randomly assigned to GA will then be randomized to either inhalational or IV anesthesia using a 1:1 ratio.

The total estimated duration for trial completion is 2 years (18 months for enrollment, 6 months for data collection, data cleaning and statistical analysis); subject participation is expected for 90 days from onset of acute stroke event

4.2 Enrollment and Randomization

Enrollment in this study is defined as the moment when the randomization process is completed and the subject is assigned to a study arm. After randomization, no crossover is permitted unless either the neurovascular interventionalist or anesthesiologist determines the patient meets criteria as described in section 5.0
Randomization will occur via a secure, password-protected, web-based system. Subjects will be randomized 1:1 to GA or Sedation using permuted blocks and stratified by center, terminal ICA occlusion (yes/no), and time of stroke symptom onset (≤ 6 hours or 6-16 hours). Patients randomized to GA will subsequently be randomly assigned in a 1:1 ratio to either inhalational or IV anesthesia.

Stroke management and endovascular therapy procedures will occur as per local site usual care. Only FDA-approved thrombectomy devices should be used with first line use of stent retriever. Both general anesthesia and Sedation should be delivered and managed by an anesthesiologist.

5.0 STUDY POPULATION

5.1 Inclusion Criteria

1. Acute ischemic stroke due to large intracranial vessel occlusion demonstrated on CT-angiography in the following anterior circulation locations that will be treated by endovascular therapy (EVT):
    a. Internal Carotid Artery (terminal "T" or "L-type"- occlusion)
    b. Middle Cerebral Artery (MCA) M1 or proximal M2
    c. Anterior Cerebral Artery (ACA) A1 or proximal A2
    - Patients who receive IV-tPA thrombolysis are eligible provided the drug was delivered within 4.5 hours of stroke onset or last seen normal and in accordance with local hospital standard of care.
    - Patients who receive TNKase are also eligible, given that drug was delivered in accordance with the local hospital standard of care.
2. Ages 18-90.
3. National Institute of Health Stroke Scale (NIHSS) score 6-30
4. Time of stroke symptom onset of last seen normal to start of EVT (defined as groin puncture) ≤ 16 hours.
5. Limited infarct core, as defined below and adapted from the 2018 American Heart Association guidelines [28]
    a. For patients presenting ≤ 6 hours from time of symptom onset or last seen normal, Alberta Stroke Program Early Computed Tomography Score (ASPECTS) ≥ 6
    b. For patients presenting > 6 hours and ≤ 16 hours from time of symptom onset or last seen normal, they must satisfy EITHER ONE of the two following criteria:
        i. Ischemic core by CT Perfusion or MRI/MR Perfusion < 70 mL, a ratio of volume of penumbral tissue to infarct core of ≥ 1.8, and and absolute volume of penumbral tissue of ≥ 15 mL [29]

        OR

        ii. For patients with NIHSS ≥ 10, infarct core of < 31 mL by CT Perfusion or MRI; For patients with NIHSS ≥ 20, infarct core < 51 mL.[30]
6. Subject willing/able to return for protocol required follow up visits.
7. No significant pre-stroke disability (modified Rankin Score must be ≤ 2).
8. Females of childbearing potential must have a negative serum or urine pregnancy test.
9. Patient or patient's legally authorized representative has given Informed Consent according to Good Clinical Practices (GCP) and/or local IRB policies.

5.2 Exclusion Criteria

1. Coma on admission (Glasgow Coma Scale <8), need for intubation upon ED arrival, or transferred patients who present previously intubated.
2. Severe agitation or seizures on admission that preclude safe vascular access.
3. Loss of airway protective reflexes and/or vomiting on admission.
4. Predicted or known difficult airway.
5. Pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, e.g. dementia.
6. Presumed septic embolus, or suspicion of bacterial endocarditis
7. Currently participating or has participated in any investigational drug or device study within 30 days.
8. Inability to follow-up for 90-day assessment.
9. Known history of allergy to anesthesia drugs.
10. Known history or family history of malignant hyperthermia

5.3 Crossover Criteria

1. Severe agitation or seizures.
2. Loss of airway protective reflexes, vomiting, or aspiration.
3. Inability to maintain airway.
4. Loss of consciousness.
5. Hemodynamic instability.
6. Determination by anesthesiologist and/or neurointerventionalist that randomized method of anesthesia is contraindicated for some other reason (see section 5.4)

5.4 NPO Status

Lack of confirmation of duration of fasting status (*nil per os; NPO*) shall, in and of itself, not be considered a contraindication to moderate sedation for the purposes of this study. Patients should not be excluded from the study or crossed-over from sedation to GA solely due to NPO status.

Rationale:
NPO status is often unknown in patients presenting with acute ischemic stroke. Despite this, the recommendation by the AHA/ASA is that moderate sedation is preferred over general anesthesia for EVT [31] and this is routinely practiced at stroke centers across the country. The determination of a potential subject's eligibility for sedation should be based on the overall clinical picture, other risk factors for pulmonary aspiration, and consideration of the target depth of sedation for this procedure (moderate sedation).

EVT for acute ischemic stroke is an emergency procedure. The American Society of Anesthesiologists' guidelines for pre-procedural fasting are intended for elective procedures[32], and the guidelines for procedural sedation state that "the literature does not provide sufficient evidence that pre-procedure fasting results in a decreased incidence of adverse outcomes in patients undergoing either moderate or deep sedation," leading the task force to conclude that "in urgent, emergent, or other situations in which gastric emptying is impaired, the potential for pulmonary aspiration of gastric contents must be considered in determining (1) the target level of sedation, (2) whether the procedure should be delayed, or (3) whether the trachea should be protected by intubation." [33] The American College of Emergency Physicians has developed specific guidelines that support the use of extended-duration moderate sedation for standard-risk patients undergoing urgent procedures, and for high-risk patients undergoing emergency procedures.[34] See Appendix III.

6.0 STUDY PROCEDURES

All subjects who are enrolled into the trial will be followed for 90 days (± 10) unless they withdraw early from the trial, expire before the 90 day follow up window is reached, or are lost to follow up. The study event schedule is illustrated in Table 2.

6.1 Informed Consent

Written informed consent or electronic consent will be obtained for all subjects who are screened and meet the trial inclusion/exclusion criteria. If sites choose to utilize electronic consent, the method of electronic consent used will be based on each individual institution's choice, as approved by the site's IRB. In the event that IRBs of participating centers determine the trial meets criteria for exception from informed consent (EFIC), sites will have the option to pursue local procedures to include community consultation, etc. Below, we provide explanations that justify the use of delayed or exception from informed consent in this particular population.

The trial compares two anesthesia approaches for EVT delivered as usual care. We have demonstrated clinical equipoise in participating stroke centers of excellence. Therefore, the trial meets criteria for comparative effectiveness research. Participation in SEGA should never delay the time-sensitive nature of providing emergent reperfusion therapy in acute ischemic stroke. In addition, a significant proportion of these severe stroke patients are air-transported to the comprehensive stroke centers (CSC) and family members must drive from the outlying hospital to the CSC. Due to the expected stroke severity routinely encountered with proximal intracranial occlusions, the majority of patients will be suffering from either aphasia (language disturbance of either comprehension or expression) or severe neglect (inability to understand or acknowledge they are suffering a stroke). Hence, the majority of patients will be unable to provide informed consent due to lack of capacity. Unfortunately, the majority of legal next of kin fail to arrive before the commencement of EVT procedures; including the transfer from the emergency department to the angio suite for EVT.

As a result, traditional written approach to informed consent in this patient population is rarely feasible and will impact study recruitment, results and generalizability. First, the trial would recruit at a very slow pace and enrollments will be predominantly a less-severe subpopulation of strokes. Second, it is well established across clinical research that the patients who benefit the most from effective interventions are usually those most severely affected. Thus, our estimations of treatment differences would result in decreased probability of observing a difference between the study arms. Critically, traditional written emergent consent will inherently delay EVT procedures and possibly result in worse clinical outcomes. Pooled analyses from EVT RCTs have demonstrated that minor delays to arterial reperfusion of 20 minutes are associated with worse clinical outcomes. Third, participation in a clinical trial could directly benefit the patient and ultimately society if a new treatment is discovered. The inability to participate in promising research for the most severely affected patients is sometimes interpreted as a breach of the ethical principle of justice. The basic concept of distributive justice, as it relates to clinical research, should not categorically exclude certain subgroups with clinically relevant characteristics such as disease severity, sex, age, etc. This discrimination is unjust and results in skewed generalizable knowledge that guides health care practices.
We recognize that emergency research such as this trial or any research that requires study-related research outcomes will require subsequent written consent from the patient of legal next of kin. Therefore, each site must make a reasonable attempt to reach family members that are available in the hospital or will be arriving within 15 minutes. For patients enrolled via EFIC, explicit written consent must be obtained during the study period of 90-days. Usually, this should occur within 5 days of enrollment during the hospitalization. Ultimately, each participating center must follow their local IRB's decision regarding consent in this trial

Table 2. Schedule of events.

ASSESSMENTS	VISITS				
	Baseline	<16 hours from stroke onset/LSN	18-36 hours	Day 7 or discharge, whichever occurs first	90 ± 15 days
Demographics	Y		Y		
Medical History	Y				
Stroke History	Y		Y		
mRS	Y			Y*	Y
EQ-5D					Y*
NIHSS	Y		Y	Y	
EVT Procedure Variables		Y			
Imaging assessment Parenchymal - CT or MRI Arterial – CTA or MRA	 Y Y		Y		
Assess for adverse events		Y	Y	Y	
Note: Except those notated by *, all procedures and assessments are collected a usual care for acute ischemic stroke patients.					

6.2 Treatment Period

6.2.1 Endovascular Procedure and Time Metrics

As recommended by the AHA/ASA, the first line therapeutic embolectomy device should be a stent retriever. The use of a proximal balloon guide catheter or a large-bore distal-access catheter, rather than a cervical guide catheter alone, in conjunction with stent retrievers may be beneficial. Future studies should examine which systems provide the highest recanalization rates with the lowest risk for nontarget embolization

Additional EVT therapies including, but not limited to, intra- or extracranial angioplasty ± stenting; antithrombotics (oral, IV or IA antiplatelets or anticoagulants) intra-arterial thrombolytics; are left to the decision of the local treatment team. Conversely, in general, off-label use or therapies not supported by scientific evidence are discouraged. Importantly, the use of these therapies will not be considered a protocol deviation.

Time to reperfusion in EVT trials is correlated with improved outcomes and societies have published position statements on timing metrics. The current protocol provides guidance for centers derived from these recommendations (see table 3).[26]

Table 3. SEGA recommended guidelines for timing metrics

Acute Stroke Time Metric	Maximal Target Time
Door to Imaging (parenchymal imaging – non-contrast CT, MRI)	15 minutes
Door to IV-tPA bolus/ TNKase	60 minutes
Door to Groin Puncture	90 minutes
Angiosuite arrival to Groin Puncture	20 minutes
Door to Reperfusion	150 minutes

The following intra-procedure (thrombectomy) variables will be collected (see CRFs for further details):

- Door to puncture time
- Decision of intervention to puncture time
- Time from puncture to first recanalization attempt
- Time to Revascularization: defined as arterial puncture to TICI ≥ 2b revascularization or end of procedure.
- Revascularization assessment at the end of the procedure (using Thrombolysis in Cerebral) Infarction (TICI) score.
- Number of recanalization attempts (i.e. thrombectomy attempts or stent-retriever passes)
- Name of the mechanical retrieval device used
- Utilization of aspiration technique
- Failure to reach clot

6.2.2 Angiographic measures of arterial perfusion and collaterals

Using angiography, the modified TICI (mTICI) score is defined according to the level of blood flow through an occlusion site and consists of 5 discrete categories (table 4a).

Table 4a. Angiographic scoring of large vessel occlusions and reperfusion.

mTICI score	Definition
0	**No Perfusion** - No antegrade flow beyond the point of occlusion
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.
2	**Partial Perfusion** - 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. • **2a** Only partial filling (< 50%) of the entire vascular territory is visualized. • **2b** Filling of > 50% all of the expected vascular territory is visualized, but the filling is slower than normal.
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.

Cerebral collaterals play a key role in determining outcome in endovascular treatments for acute ischemic stroke. In addition, given the hypothesized effect of general anesthesia on blood pressure and cerebral perfusion, collateral grade may be a particularly relevant determinant of outcome in this cohort. Collaterals will be graded from the angiograms by society guidelines, as shown in Table 4b [25]

Table 4b. Angiographic scoring of cerebral collaterals

Collateral score	Definition
0	No collaterals visible to the ischemic site.
1	Slow collaterals to the periphery of the ischemic site with persistence of some of the defect.
2	Rapid collaterals to the periphery of the ischemic site with persistence of some of the defect and to only a portion of the ischemic territory.
3	Collaterals with slow but complete angiographic blood flow to the ischemic bed by the late venous phase.
4	Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion.

6.3 90-day (± 15 days) Follow-up

The study participation will be considered completed after the 90 day follow up visit has been completed. If for any reason the patient cannot visit the clinic/hospital for the follow up, the Investigator or research staff should ask permission from the patient and family if an in-person visit could take place at the current dwelling facility to assess patient's neurological condition. In the event that in-person assessment is not possible, research team-members should conduct a phone interview. In the event that the patient cannot be reached or is unable to answer assessment questions, their caregiver or family member can be questioned.

The patient's quality of life will be assessed using the EQ-5D provide a numerical measure of the patient's health utility. In the event the patient is unable to communicate or understand the questions, his/her next of kin (proxy) who knows the most about their current health state will be asked to fill out these questionnaires on behalf of the patient. Importantly, the proxy will be instructed to fill answer the quality of life questionnaires from the patient's perspective – knowing everything they know about the patient, how would they answer if they capable.

7.0 ANESTHESIA GUIDANCE

7.1 Sedation

Sedation will be provided under the supervision of an anesthesiologist using a combination of fentanyl, midazolam, dexmedetomidine infusion (with or without loading dose), remifentanil infusion, and/or low-dose propofol by intermittent bolus or infusion, with a target Richmond Agitation Sedation Scale (RASS) score of -1 to -3 (light to moderate sedation – responds to verbal stimulation; see Appendix II).

Sedation patients who do not tolerate sedation (e.g., patient agitation, airway difficulty, loss of consciousness, aspiration, cardiovascular instability) should be converted to Inhalational GA and the corresponding protocol followed.

7.2 General Anesthesia

Induction of anesthesia will be achieved with propofol and/or etomidate; muscle paralysis with succinylcholine or non-depolarizing paralytic (rocuronium or vecuronium); and adjuvant lidocaine and fentanyl as deemed appropriate by the anesthesiologist. Hyperventilation should be avoided during induction.

Intravenous: Maintenance of anesthesia will be achieved by propofol infusion at 50 to 150 mcg/kg/min with redosing of non-depolarizing paralytic and fentanyl (and/or remifentanil infusion) as needed.

Inhalational: Maintenance of anesthesia will be achieved with sevoflurane 1% to 2% or desflurane 3% to 6% end-tidal concentration with redosing of non-depolarizing paralytic and fentanyl (and/or remifentanil infusion) as needed.

7.3 Blood Pressure Management

Systolic blood pressure (SBP) should be maintained at 140 to 180 mmHg with pressors (e.g., phenylephrine, norepinephrine) or antihypertensives (e.g., nicardipine, labetalol) as needed. Diastolic blood pressure should be maintained <105 mmHg.

In patients who are reperfused after EVT (defined as achieving TICI 2b or TICI 3), SBP should be maintained at 140 mmHg in the first 24 hours to minimize the risk of reperfusion-related brain hemorrhage. Blood pressure of patients who fail to achieve recanalization will be left to the discretion of the individual stroke centers' usual care.

7.4 Anesthesia Monitoring

Invasive hemodynamic monitoring should be attempted prior to induction of GA to allow for tight hemodynamic control. To limit any delay in time to revascularization, attempts to establish peripheral invasive arterial access should be limited to 5 minutes; after that time, continuously-cycled non-invasive blood pressure measurements should be performed until invasive hemodynamic monitoring can be achieved through the femoral sheath. SBP should be maintained at 140 to 180 mmHg throughout with phenylephrine and/or norepinephrine as needed. Patients who are converted from sedation who already have invasive hemodynamic monitoring through the femoral sheath do not need additional arterial access.

End-tidal CO_2 concentration ($PETCO_2$) in patients receiving GA should be maintained at 35 to 40 mmHg (corresponding to a $PaCO_2$ ~40-45 mmHg).

All patients who are deemed medically appropriate for extubation should be awakened and extubation attempted at the conclusion of the procedure. Muscle paralysis should be reversed at the conclusion of the procedure using neostigmine or sugammadex; those patients with deep neuromuscular blockade that precludes reversal with neostigmine should be reversed with an adequate dose of sugammadex to avoid unnecessary prolonged intubation.

7.5 Anesthetic Data Collection

The following intra-procedural anesthesia variables will be collected:

- Anesthetic agents used for GA or sedation
- $PETCO_2$ q5 min in GA group.
- RASS score q15 min in sedation group.
- Oxygen saturation q15 min
- Continuous BP measurements from an electronic anesthetic record for determination of time spent with SBP <140 mmHg.
- Utilization of norepinephrine, phenylephrine, or other vasopressors as well as total dose administered.
- Documentation of post-procedure extubation or the reason for remaining intubated.
- Reason of crossover of anesthesia modality (sedation to GA) – patient agitation, airway difficulty, loss of consciousness, aspiration, cardiovascular instability

8.0 SAFETY

8.1 Adverse Events

An adverse event could include any of the following events, which develop or increase in severity during the course of the study:

- Any signs or symptoms whether thought to be related or unrelated to the condition under study;
- Any clinically significant laboratory abnormality;
- Any abnormality detected during physical examination.

These data will be recorded on the appropriate CRFs, regardless of whether they are thought to be associated with the study arm treatment. Signs or symptoms will be graded by the Investigator as mild, moderate or severe according to the following definitions:

Grade:	Definition
Mild:	Causing no limitation of usual activities
Moderate:	Causing some limitations of usual activities
Severe:	Causing inability to carry out usual activities.

8.2 Serious Adverse Events (SAEs)

A serious adverse event is defined as any event that suggests a significant hazard, contraindication, side effect or precaution. A serious adverse event includes any event that:

- Results in death;
- Is life threatening;
- Results in prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Important or significant medical events that require medical or surgical intervention, based upon appropriate clinical judgment.

The Investigator must assess the relationship of the adverse event to the study device using the following criteria categories and definitions:

- Unrelated - The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the type of anesthesia utilized.
- Possible - The adverse event is determined to be potentially related to the treatments received for anesthesia and an alternative etiology is equally or less likely compared to the potential relationship to the type of anesthesia provided.
- Probable - There is a strong relationship to the type of anesthesia, or recurs on re-challenge, and another etiology is unlikely.
- Highly Probable - There is no other reasonable medical explanation for the event.

8.2.1 Reporting of Serious Adverse Events

Each clinical site will follow their internal policies for reporting SAEs to their IRB. In addition, sites will alert the UT-Houston data-core within 24-hours of becoming aware of the SAE. This alert will be relayed to the study PIs for review. If an SAE is confirmed, the coordinating site will be responsible for reporting to the DSMB as outlined in the DSMB charter. DSMB reports will be forwarded to all participating clinical sites for local IRB submission.

The study sponsor is responsible for the coding and reporting any adverse event required by regulatory authorities. The study sponsor will code AEs using MedDRA (Medical Dictionary for Regulatory Affairs). Unanticipated serious adverse events that meet criteria for FDA submission per 21 CFR part 803 will be submitted by the study sponsor.

8.3 Follow-Up of Adverse Events

All adverse events will be collected from the time of randomization and monitored until day 7 or hospital discharge, whichever occurs first. AEs that do not meet criteria for resolution will be categorized as on-going after day 7 or discharge.

9.0 STATISTICAL METHODS

The study will be conducted under a common umbrella protocol developed by UTHealth with the itention of combining data from all satellite centers for analysis. Each participating site will give utmost importance to follow the study protocol to maintain consistency in study execution at all centers. Detailed analysis plan for all pre-specified outcome measures are located in separate statistical analysis plan.

9.1 Sample Size Justification

A maximum of 260 patients, 130 per arm will be randomized. Assuming a neutral prior probability (centered at OR of 1.0, 95% prior interval: 0.3–3.0) for the intervention effect, the sample size provides 80% power that General Anesthesia improves outcome (lower ordinal mRS) compared to Sedation if the true OR is >1.50. Monte Carlo simulations were performed using R to estimate the Bayesian power of the study for the primary outcome measure. We assumed a threshold of 80% posterior probability of the OR >1.0 to declare effectiveness. See Appendix II for summary of simulation results.

9.2 Statistical Analyses

Intent-to-treat analyses will be performed. To summarize the data, descriptive statistics will be used. Demographics, vital signs, laboratory variables, stroke type and duration from onset of symptoms will be summarized for each treatment arm. Vital signs taken during the treatment period will be displayed graphically. In addition to ICH, other medical events will be tabulated by body system and severity.

Primary analyses will focus on comparing GA (combining inhalational and IV anesthesia) to sedation. All analyses will be conducted under a Bayesian paradigm to obtain estimates of odds ratio (OR) for primary outcome (ordinal mRS), relative risk (RR) for binary outcomes, and probability of treatment benefit or harm (quantities that cannot be obtained from frequentist analyses). For the treatment effect, we will use a neutral prior centered at OR of 1.0 with 95% prior interval of 0.3-3.0. This prior assumes a priori equipoise and excludes large treatment effects. Weakly informative priors will be used for all other parameters to exclude large treatment effects.[24]

Generalized linear mixed models will be used to analyze all outcomes and will include treatment group, terminal ICA occlusion and time from onset of symptoms (stratification variables) as covariates and center (stratification variable) as a random effect to account for center variability. For the primary outcome of ordinal mRS at 3 months (scores 5 and 6 combined), we will use an ordinal logistic model. For binary outcomes we will use log binomial (or logistic in case of non-convergence) models to directly estimate relative risks (or odds ratios) and 95% CIs. The prior for the treatment effect will be a Normal (0, sd=0.57) in the log OR/RR scale. The prior for the intercept will be Normal (0, sd=10) and Normal (0,1) for other covariates in the model. A half-Normal(0,1) prior will be used for the standard deviation of the center random effect. For non-binary outcomes, we will select the best fitting models and use neutral, weakly informative priors that exclude large treatment effects. We will examine residuals from each model to ensure reasonable adherence to the assumptions of the models.

If, despite randomization with stratification for center, tICA, and time from onset of symptoms, any important differences between intervention groups occur in baseline variables related to outcome, secondary analyses will be performed controlling for these factors.

For the primary outcome of ordinal mRS at 3 months, a secondary analysis will be conducted comparing CS to inhalational anesthesia and to IV anesthesia adjusting for the stratifying variables. Models and priors will be the same as for the primary analysis.

9.3 Missing Data

If patients are lost to follow-up at the 90-day end of study evaluation, the worst-case scenario will be entered into the database (i.e., mRS = 6). In the event that the percent of patients lost to follow-up exceeds 5%, we will use multiple imputation methods. This technique quantifies the uncertainty due to the missing data.

9.4 Safety Monitoring

Formal interim analyses of safety will occur when 100 and 200 patients are enrolled. Safety endpoints will consist of intracerebral hemorrhage within 18-36 hours and death. Bayesian interim monitoring will be used to assess whether systematic differences are evident among the treatment groups for the occurrence of the interim safety analysis endpoint. The posterior probability that either treatment group has a higher incidence of the interim safety analysis endpoint will be determined. These posterior probabilities for safety will be assessed using the log-binomial regression model with covariates, described more completely in section 9.2. Either treatment will be considered harmful (i.e., the DSMB may consider termination of the trial) if the posterior probability of treatment harm in one treatment arm compared to the other exceeds 97.5%. In addition to reporting the above posterior probability, the 95% credible interval for the RR, and the entire posterior distribution of RR will be presented graphically to the DSMB in order to assure a full appreciation of the range of possible values of each RR.

9.5 Interim Efficacy Analysis

One interim analysis is planned after the first n=132 patients (50% of data accrual) have been randomized and have completed the 3-month primary outcome assessment. Ordinal mRS outcome will be compared between GA and CS groups using a Bayesian logistic model detailed in section 9.2. The same neutral priors will be used to calculate posterior probabilities of benefit for either treatment group. Posterior median OR and 95% intervals will also be calculated.

During the interim analyses of efficacy, the DSMB may consider termination if the posterior probability of benefit (improving independent clinical outcome) of either treatment arm compared to the other is greater than 95%. Given that this is a comparative effectiveness trial, no interim futility analyses will be conducted since they are not appropriate for evaluating therapies already in use.[27]

10.0 DATA MANAGEMENT

10.1 Data Collection

Detailed clinical data collection will be performed using an established standard method approved by each site's IRB. Data will be de-identified and recorded initially on paper CRFs and then transferred to the study's secure web-based application.

Every reasonable effort should be made to complete data entry within one week of data collection. Data discrepancies may be queried during ongoing review of data by the trial's data coordinating center (DCC) or may be identified and queried during remote or in-person monitoring visits. Data monitoring will be performed to verify data accuracy and ensure queries are resolved. The Principal Investigator or Sub-investigator must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate CRFs.

Each participating center will provide appropriate source documentation for data monitoring. Data monitoring can take place either remotely (review of eCRFs compared with uploaded, deidentified s ments) or in-person by a

designee of the trial PI. Remote data monitoring will require the site to scan the appropriate source documents. After scanning, local sites will be required to redact all patient identifiers. Finally, the redacted file will be saved and uploaded to the trial website's secure repository. The DCC will be responsible for comparing the eCRF data and the uploaded source documents.

11.0 STUDY COMMITTEES AND CORE LABS

11.1 Steering Committee

The steering committee will be responsible for oversight of the overall conduct of the study. These duties include protocol development and amendments, study progress, and overall data quality and integrity. The Steering Committee will oversee dissemination of study results through appropriate scientific meetings and publications. The Steering Committee may select additional investigators, based on enrollment, to participate on a Publication Committee. The Publication Committee will participate in the review and approval of all requests for data analysis, abstract and manuscript preparation and journal submission.

11.2 Data Safety Monitoring Committee

The Data Safety Monitoring Committee (DSMB) will include specialists in stroke neurology, neuro-intervention and biostatistics, none of whom are participating in the trial or have affiliation with the trial sponsor, UTHealth. The DSMB is responsible for monitoring subject safety through pre-defined, periodic review of the clinical study safety data. Details regarding DSMB responsibilities, qualifications, membership, meeting frequencies, and procedures are outlined in the DSMB charter.

The trial's un-blinded biostatistician will assist the data-core in preparing blinded DSMB reports. Data will be supplied to, and reviewed by, the DSMB as tables and/or figures. The DSMB can request more data. At each review the DSMB will evaluate whether the study should continue unchanged, require modification/amendment or be closed to enrollment and will inform the trial Co-PIs.

The principal investigator (study sponsor), DSMB or the Institutional Review Board (IRB) have the authority to terminate, suspend, or require trial modifications.

11.3 Imaging Core Labs

An independent imaging core lab will blindly review baseline parenchymal and vascular imaging that is performed as each site's routine care of acute ischemic stroke patients who may be eligible for EVT. The image-core interpretations of all neuroimaging will serve as the data source for analyses such as ASPECTS score, hemorrhage and hemorrhage classification (see table 5) and angiographic measures of occlusion, reperfusion and collateral grade (see table 4). Baseline imaging will usually include a non-contrast CT of the head, CT-angiogram of the head +/- neck and to a lesser degree, a CT-perfusion of the head. According to local practice, baseline MRI and MRA are also accepted.

Follow-up neuroimaging (CT or MRI) that is routinely collected between 18-36 hours post thrombolysis or EVT will be used to determine the presence of infarction and hemorrhage. Conventional cerebral angiograms will be assessed for pre-intervention (e.g., diagnostic [first intracranial run] angiogram) clot location and TICI score. Reperfusion, graded using the modified TICI reperfusion score, will be recorded by the imaging core lab post EVT. Additional angiographic scales will be assessed including but not limited to collateral flow grade. All neuroimaging will be de-identified at the local site

and submitted to the sponsor DCC either digitally in DICOM format via a secure FTP portal or saved to a CD-ROM disc and mailed directly to the DCC.

Table 5. Definition and description of intracranial hemorrhage.

Intracranial Hemorrhage	Definition
HT-1	Hemorrhagic Transformation Type 1. Small, scattered petechiae within ischemic field without mass effect.
HT-2	Hemorrhagic Transformation Type 2. Confluent petechiae within ischemic field without mass effect
PH-1	Hematoma within ischemic field with some mild space-occupying effect but involving ≤ 30% of the infarcted area
PH-2	Hematoma within ischemic field with space-occupying effect involving > 30% of the infarcted area
RIH	Any intraparenchymal hemorrhage remote from the ischemic field
rPH-2	PH-2 remote from the ischemic field
IVH	Intraventricular hemorrhage
SDH	Subdural Hematoma. Blood between the dura mater and the arachnoid mater
EDH	Epidural Hematoma - Blood between the dura mater and the skull
SAH	Subarachnoid hemorrhage

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13.0 APPENDICES

Appendix I. Richmond Agitation Sedation Scale (RASS)

Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s), aggressive	
+2	Agitated	Frequent nonpurposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressively vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert but has sustained awakening (eye opening/eye contact) to *voice* (≥10 seconds)	Verbal Stimulation
-2	Light sedation	Briefly awakens to *voice* with eye contact (<10 seconds)	
-3	Moderate sedation	Movement or eye opening to *voice* (but no eye contact)	
-4	Deep sedation	No response to voice but movement or eye opening to *physical* stimulation	Physical Stimulation
-5	Unarousable	No response to *voice* or *physical* stimulation	

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Appendix II. Monte Carlo simulation results of Bayesian power

1. Primary outcome of ordinal mRS at 90 days

Based on data from 3 previous trials, we assumed rates of 10%, 14%, 11%, 19%, 18%, and 28% for mRS outcome categories of (0, 1, 2, 3, 4, 5+6) for Conscious Sedation group. Data from ANSTROKE trial was downweighted 50%. We assumed a treatment effect size corresponding to an OR=1.53 (GA group having better outcomes). We simulated 10,000 trials for two total sample sizes, N=265 and N=250 and assuming rates of follow-up of 100%, 98%, 97%, 95%, and 90%. We calculated power (Table 1) to declare benefit based on range of thresholds to declare effectiveness (i.e., Pr(OR>1)>threshold). For analyses, we used a neutral prior centered at OR of 1.0 (95% CI: 0.3–3.0) for the treatment effect and ordinal logistic analysis detailed in Section 9.2. Assumed cross-over rate of CS group to GA group is 10%. Type I error rates are given in Table 2.

Table 1: Power under a neutral prior and cross-over rate of 10%.

Pr(OR>1)>	N=265	N=260	N=257	**N=250**	N=245	N=242	N=238	N=225
0.95	0.50	0.49	0.49	0.48	0.47	0.47	0.46	0.44
0.90	0.66	0.64	0.64	0.64	0.63	0.62	0.62	0.60
0.85	0.74	0.73	0.73	0.73	0.72	0.72	0.71	0.70
0.80	0.81	0.80	0.80	**0.80**	0.79	0.79	0.78	0.77
0.75	0.85	0.85	0.84	0.85	0.84	0.83	0.83	0.82

Table 2: Type I error rates under a neutral prior and cross-over rate of 10%.

Pr(OR>1)>	N=265	N=260	N=257	**N=250**	N=245	N=242	N=238	N=225
0.95	0.04	0.04	0.04	0.03	0.04	0.04	0.04	0.04
0.90	0.08	0.08	0.08	0.08	0.08	0.08	0.09	0.08
0.85	0.13	0.13	0.13	0.13	0.13	0.13	0.14	0.13
0.80	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
0.75	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.24

2. Secondary outcome of dichotomized mRS at 90 days

We assumed good outcome (mRS of 0-2) rates of 45% for General Anesthesia group and 35% for Conscious Sedation group. We simulated 10,000 trials for each of the sample sizes in Table 3 and calculated power to declare benefit based on range of thresholds to declare benefit (i.e., Pr(RR>1)>threshold). For analyses, we used a neutral prior centered at RR of 1.0 (95% CI: 0.3–3.0) for the treatment effect and a log binomial model detailed in section 9.2.

Table 3: Power under a neutral prior and cross-over rate of 10%.

Pr(RR>1)>	N=265	N=260	N=250	N=242	N=225
0.95	0.42	0.43	0.42	0.37	0.41
0.90	0.58	0.57	0.56	0.54	0.56
0.85	0.67	0.67	0.66	0.62	0.64
0.80	0.73	0.74	0.73	0.71	0.72
0.75	0.79	0.79	0.77	0.76	0.77

To compute type I error, we assumed equal rates of good outcomes of 35% for both groups. We used the same neutral prior (RR of 1.0, 95% CI, 0.3–3.0) and log binomial model for analysis. Type I error rates are given in Table 4.

Table 4: Type I error rates under a neutral prior and cross-over rate of 10%.

Pr(RR>1)>	N=265	N=260	N=250	N=242	N=225
0.95	0.05	0.04	0.04	0.05	0.04
0.90	0.09	0.09	0.08	0.09	0.08
0.85	0.14	0.14	0.14	0.15	0.12
0.80	0.19	0.21	0.19	0.19	0.17
0.75	0.24	0.25	0.23	0.24	0.24

We also computed the power under a skeptical prior expressing prior belief that Conscious Sedation will have higher rates of good outcome. Using a skeptical prior centered at RR of 0.82 (95% CI: 0.27–2.5) for the analyses gives power shown in Table 5. Here, there will be >50% power to convince a skeptic of benefit of General Anesthesia (RR>1) using a posterior probability threshold of 90% or lower.

Table 5: Power under a skeptical prior and cross-over rate of 10%.

Pr(RR>1)>	N=265	N=260	N=250	N=242	N=225
0.95	0.37	0.40	0.37	0.40	0.34
0.90	0.52	0.56	0.53	0.53	0.50
0.85	0.62	0.65	0.61	0.63	0.58
0.80	0.70	0.73	0.70	0.71	0.65
0.75	0.76	0.78	0.75	0.77	0.71

Appendix III. Prudent limits of targeted depth and length of ED procedural sedation and analgesia according to presedation assessment of aspiration risk

Standard-risk patient[a]

Oral intake in the prior 3 hours	Procedural Urgency[b]			
	Emergent Procedure	*Urgent Procedure*	*Semi-Urgent*	*Non-Urgent*
Nothing	All levels of sedation	All levels of sedation	All levels of sedation	All levels of sedation
Clear liquids only	All levels of sedation	All levels of sedation	Up to and including brief deep sedation	Up to and including extended moderate sedation
Light snack	All levels of sedation	Up to and including brief deep sedation	Up to and including dissociative sedation; non-extended moderate sedation	Minimal sedation only
Heavier snack or meal	All levels of sedation	Up to and including extended moderate sedation	Minimal sedation only	Minimal sedation only

Higher-risk patient[a]

Oral intake in the prior 3 hours	Procedural Urgency[b]			
	Emergent Procedure	*Urgent Procedure*	*Semi-Urgent*	*Non-Urgent*
Nothing	All levels of sedation	All levels of sedation	All levels of sedation	All levels of sedation
Clear liquids only	All levels of sedation	Up to and including brief deep sedation	Up to and including extended moderate sedation	Minimal sedation only
Light snack	All levels of sedation	Up to and including dissociative sedation; non-extended moderate sedation	Minimal sedation only	Minimal sedation only
Heavier snack or meal	All levels of sedation	Up to and including dissociative sedation; non-extended moderate sedation	Minimal sedation only	Minimal sedation only

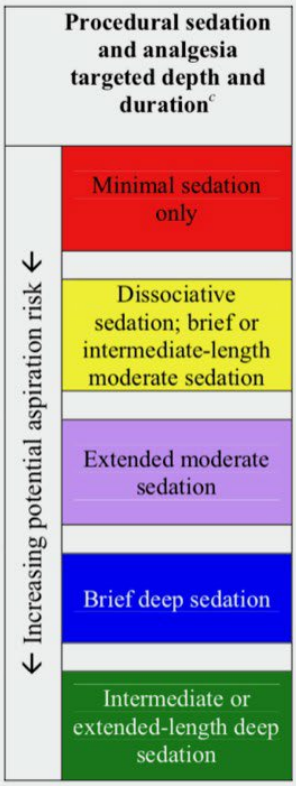

Figure. Prudent limits of targeted depth and length of ED procedural sedation and analgesia according to presedation assessment of aspiration risk