PROTOCOL TITLE

SELECT 2:
A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke

NCT03876457

Protocol Version Date:

4 August, 2021

Global Principal Investigator:
Amrou Sarraj, MD
Department of Neurology, Stroke Division
6431 Fannin Street, MSB 7.116
McGovern Mecical School at UTHealth
Houston, Texas 77030

Funded by: McGovern Medical School at UTHealth at Houston through an unrestricted grant from Stryker Neurovascular

SELECT 2

AGREEMENT ON THE PROTOCOL

By signing below I confirm that:

1) I have read this protocol and it contains all necessary details for conducting this study

AND

2) I agree to conduct the trial in compliance with this protocol and to adhere to all regulations that govern the conduct of the study.

_____ _____

Principal Investigator's Signature **Date**

_____

Principal Investigator's Name

_____

Site Name

SELECT 2 Steering Committee

Dr. Gregory Albers, Professor, Stanford University, Palo Alto, CA

Dr. Ameer Hassan, Associate Professor, The University of Texas Health Science Center – San Antonio, Harlingen, TX

Dr. M. Shazam Hussain, Director, Stroke Program, Cleveland Clinic, Cleveland, OH

Dr. Michael Chen, Associate Professor, Rush University, Chicago, IL

Dr. Michael Abraham, Associate Professor, Kansas University Medical Center, Kansas City, MO

Dr. Maarten Lansberg, Associate Professor, Stanford University, Palo Alto, CA

Dr. Marc Ribo, Assistant Professor, Hospital Vall d'Hebron, Barcelona, Spain

Dr. Vitor Pereira, Associate Professor, Toronto General Hospital & University Network, Toronto, Canada

Dr. Santiago Ortega-Gutierrez, Assistant Professor, The University of Iowa, Iowa City, IA

Dr. Bruce Campbell, Professor, The University of Melbourne, Melbourne, Australia

SELECT 2 Neurointerventional Committee

Dr. Ameer Hassan, Associate Professor, The University of Texas Health Science Center – San Antonio, Harlingen, TX

Dr. Michael Chen, Associate Professor, Rush University, Chicago, IL

Dr. Michael Abraham, Associate Professor, Kansas University Medical Center, Kansas City, MO

Dr. Vitor Pereira, Associate Professor, Toronto General Hospital, Toronto, Canada

Dr. Marc Ribo, Associate Professor, Hospital Vall d'Hebron, Barcelona, Spain

Dr. Peng R. Chen, Associate Professor, McGovern Medical School at UTHealth, Houston, TX

Dr. Santiago Ortega-Gutierrez, Assistant Professor, The University of Iowa, Iowa City, IA

SELECT 2 Imaging Core Lab

Dr. Clark Sitton, Associate Professor, McGovern Medical School at UTHealth, Houston, TX

Dr. Roy Riascos, Professor, McGovern Medical School at UTHealth, Houston, TX

SELECT 2 Statistical Committee

Dr. Phillip Lavori, Professor (Emeritus), Biomedical Data Science, Stanford University, Palo Alto, CA

Dr. Chunyan Cai, Assistant Professor, Clinical and Translational Sciences, McGovern Medical School at UTHealth, Houston, TX

SELECT 2 Data Safety Monitoring Board

Chair: Dr. Lawrence R. Wechsler, Professor & Chair, The University of Pittsburgh School of medicine, Pittsburgh, PA

Co-chair: Dr. Stephen Davis, The University of Melbourne, Melbourne, Australia

Statistician: Dr. Scott Hamilton, Associate Professor, Stanford University School of Medicine, Palo Alto, CA

Voting Member: Dr. Thanh Nguyen, Associate Professor, Boston University School of Medicine, Boston, MA

Voting Member: Dr. Johanna Fifi, Associate Professor, Mount Sinai Health System, New York City, NY

Table of Contents

SELECT 2 Steering Committee 3
SELECT 2 Neurointerventional Committee 3
SELECT 2 Imaging Core Lab 3
SELECT 2 Statistical Committee 4
SELECT 2 Data Safety Monitoring Board 4
Protocol Synopsis 7
1. Scientific Background 11
1.1. Thrombectomy in Patients with Unfavorable Imaging Profiles (i.e. Large Core) 12
1.2. Rationale for randomization in patients with favorable CT profile (ASPECTS 6-10) and unfavorable perfusion imaging profile (CTP: rCBF <30% volume or MRP: ADC <620 ≥50cc) 15
1.3. Rationale for including patients with very large core on advanced perfusion (CTP: rCBF (<30%) volume or MRP: ADC < 620 >100cc) 17
1.4. Rationale for excluding patients with very large core on CT (ASPECTS 0-2) 18
1.5. Imaging selection for thrombectomy 19
1.6. Thrombectomy efficacy and safety in patients with favorable CT but unfavorable perfusion imaging profile 23
1.7. Rationale and use of iSchemaView RAPID and iSchemaView RAPID ASPECTS 23
1.8. Rationale for including patients with exctracranial ICA occlusion: 24
2. Study Question, Aim, and Hypothesis 25
3. Methods 26
3.1. Study Design 26
3.2. Enrollment Inclusion and Exclusion Criteria 28
Table 1. The SELECT 2 study inclusion and exclusion criteria 28
3.2.1.1. Specific Neuroimaging Inclusion Criteria 29
3.2.1.2. Specific Neuroimaging Exclusion Criteria 29
3.3. Enrollment and Randomization 30
3.4. Remote consent procedure: 30
3.5. Endovascular Thrombectomy 35
3.6. Medical Management 36
3.7. Outcome Measures 37
3.7.1.1. Primary Outcome 37
3.7.1.2. Secondary Outcomes 37

3.7.1.3. Imaging Outcomes 38
3.8. Clinical and Imaging Evaluations 38
3.9. Table 2. Schedule of Events 40
3.10. Assessment and Follow-up Visits 41
4. Sources of Materials 42
5. Site Approval and Monitoring Plan 43
6. Sample Size Calculation and Statistical Analysis Plan 44
6.1. Sample Size justification, Adaptive Enrichment Design, and Statistical Analysis Plan 44
6.2. Statistical plan for the second aim 51
6.3. Poolability analysis across centers 51
6.4. Feasibility of enrollment 52
6.5. Missing Data/Lost to Follow-up (LTFU) 52
7. SELECT 2 Timetable 53
8. Risk Analysis 53
9. Methods to mitigate risks to subjects in the trial 55
10. Stopping rules or safety triggers for the study 56
11. Imaging Core Lab 64
12. National Data Management Center 65
13. Data Management Plan 65
14. Compliant Handling Plan 66
15. Data Safety and Monitoring Board 66
16. Independent Medical Safety Monitor 67
17. Adverse Event Reporting 68
18. Reporting Procedures for All Adverse Events 69
19. Study Design 71
References 72
Appendix A: Minimization Randomization Algorithm 76
Appendix B. Efficacy and futility bounds for interim and final analysis 80
Appendix C. List of Approved Devices to be used in the SELECT2 Protocol: 82

Protocol Synopsis

SELECT 2: **A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke**	
Aims	To evaluate in acute ischemic stroke patients due to a large vessel occlusion in the anterior circulation (MCA M1 and ICA): • If thrombectomy, as compared to medical management, will be efficacious and safe in patients with large core on either CT (ASPECTS: 3-5) or advanced perfusion imaging ([rCBF<30%] on CTP or [ADC<620] on MRI: ≥50cc), treated within 0-24 hours from last known well. • Second aim: to look at the correlation of imaging profiles with thrombectomy clinical outcomes and treatment effect. This will be evaluated by comparing the outcomes in patients with discordant imaging profile and assessing if thrombectomy outcome rates and treatment effect will differ in patients with discordant imaging profiles (favorable CT/unfavorable perfusion imaging and unfavorable CT/favorable perfusion imaging) a. Evaluate good clinical outcome (90-day mRS 0-2) rates in patients with discordant imaging profile (unfavorable CT/favorable perfusion imaging vs favorable CT/unfavorable perfusion imaging) treated with thrombectomy. b. Evaluate the heterogeneity of thrombectomy treatment effect in patients with favorable CT/unfavorable perfusion and unfavorable CT/favorable perfusion imaging.
Study Design	A prospective, randomized, international, multicenter, assessor-blinded controlled trial
Study Sites	Up to 40 total sites, up to 30 US sites
General Inclusion Criteria	1. Adults (18-85 years) with the final diagnosis of an acute ischemic stroke 2. NIHSS ≥ 6 3. Last known well to groin puncture or medical management between 0 to 24 hours 4. Pre-stroke modified Rankin Scale score (mRS) of 0-1 5. Eligible for thrombectomy or medical management 6. Signed Informed Consent obtained 7. Subject willing to comply with the protocol follow-up requirements 8. Anticipated life expectancy of at least 3 months

General Exclusion Criteria	1. Inability to undergo CT angiography and/or CT perfusion imaging (e.g., renal insufficiency, iodine/contrast allergy) 2. Co-morbid psychiatric or medical illnesses that would confound the neurological assessments 3. Treatment with IV thrombolytic therapy beyond 4.5 hours from last known well 4. Treated with IV thrombolytic therapy 3-4.5 hours 3-4.5 hours after last known well **AND** any of the following: 1) age >80, 2) current anticoagulant use, 3) history of diabetes AND prior stroke, 4) NIHSS >25, 5) ischemic involvement of > 1/3 MCA territory 5. Current participation in another investigational drug or device study.
Imaging Inclusion Criteria	1. Proven large vessel occlusion in ICA or MCA-M1 occlusion (carotid occlusions can be cervical or intracranial, with or without tandem MCA lesions) determined by MRA or CTA 2. Large infarct-core lesion on at least one of the following 2.1. Non-Contrast CT (ASPECTS of 3-5), 2.2. CT perfusion (rCBF<30% ≥50cc), 2.3. MRI-DWI (ADC<620 ≥50cc)
Imaging Exclusion Criteria	1. Patients who have both ASPECTS of 6-10 on non-contrast CT **AND** core volume <50 cc on perfusion imaging 2. Patients with very large core on non-contrast CT i.e. ASPECTS ≤ 2 3. Evidence of intracranial tumor (except small meningioma), acute intracranial hemorrhage, neoplasm, or arteriovenous malformation 4. A significant mass effect with midline shift 5. Evidence of internal carotid artery dissection that is flow limiting or aortic dissection 6. Intracranial stent implanted in the same vascular territory that precludes the safe deployment/removal of the neurothrombectomy device 7. Acute symptomatic arterial occlusions in more than one vascular territory confirmed on CTA/MRA (e.g., bilateral MCA occlusions, or an MCA and a basilar artery occlusion). 8. Signs of established infarct and large area of cerebral edema on non-contrast CT
Primary Outcome	1. Modified Rankin Scale (mRS) at 90 (+/- 15) days. The primary outcome is a shift on 90-day mRS. 2nd primary outcome is favorable clinical outcomes: mRS score of 0-2.
Secondary Outcomes	1. Safety measured by the incidence of symptomatic intracranial hemorrhage (sICH per SITS-MOST), mortality and groin (or arterial access site) hematomas, infections or any vascular injury caused by the endovascular procedure 2. Rates of recanalization (complete and partial) using the modified TICI system (score ≥ 2b defined as favorable reperfusion)

	3. Length of hospital stay 4. Discharge location 5. NIHSS 6. Neuro-QoL
Imaging Outcomes	1. Infarct volume on MRI DWI sequence (or CT if MRI not feasible) 24 hours to 7 days after randomization 2. Lesion growth between the RAPID identified ischemic core on baseline imaging and the infarct volume 3. Successful reperfusion defined as DWI lesion volume minus Tmax>6 seconds greater than 50% 4. Recanalization of the primary arterial occlusive lesion, assessed by a modified Thrombolysis in Cerebral Infarction scores of 2b (50% to 75% reperfusion), 2c (>75% to 99% reperfusion) or 3 (complete reperfusion).
Imaging Assessments	1. CT images will be read by the appropriately trained clinicians as well as by the iSchemaView automated ASPECTS. ASPECTS for patient selection will be determined independently by the clinicians prior to any assessment with automated ASPECTS. In cases where there is disagreement, the physician reading will override the automated software reading. 2. CTP images with mismatch determination will be read by iSchemaView automated RAPID software. 3. All the images will be adjudicated by a blinded core lab at McGovern Medical School at UTHealth.
Randomization	Randomization will be done in the emergency room using a web-based dynamic randomization system. Covariate adaptive randomization will be conducted to balance the distribution of the randomization by age (<60, 60-69, 70-79, 80-85 years old), presentation NIHSS (6-9, 10-15, 16-20, >20), center, clot location (M1, ICA), treatment time window (0-8, 9-16, 17-24 hours from onset to randomization time), CTP/MRP core volume (<50cc, 50-100cc, >100cc), presence or absence of target mismatch profile (mismatch ratio ≥ 1.8 & mismatch volume ≥ 15 cc) and hemisphere (right, left). The randomization algorithm we are going to implement is the algorithm developed by Pocock and Simon (1975), i.e., minimization method. Through this algorithm, the assignment of a new patient to a treatment group is determined so as to minimize the differences between the groups in terms of these important key baseline variables. Unlike traditional stratified randomization, the minimization method works toward minimizing the total imbalance for all factors together instead of considering mutually exclusive subgroups, that is, we will not be creating these mutually exclusive subgroups during the randomization. Therefore, this approach is not restricted by the number of variables and the possible combinations of levels of balancing factors.

	Patients with large core on either CT (ASPECTS 3-5) or perfusion imaging (CTP: rCBF<30% or MRP: ADC<620 ≥50cc) or both within 0-24 hrs from last known well will be randomized into thrombectomy plus medical management vs medical management alone.
Interventions	**Endovascular Thrombectomy:** Patients randomized to endovascular thrombectomy, will be treated with thrombectomy stent-retrievers and/or aspiration devices currently cleared by the FDA. The choice of thrombectomy method, primary approach/technique, whether primary aspiration or primary stent-retriever with or without aspiration, will be left up to the interventionalist, with any of the FDA-approved devices approved in the study protocol or a combination of them (Appendix C). Standard medical therapy, based on current AHA guidelines, will also be provided for all patients. **Medical Management:** Patients randomized to medical management only will receive standard medical therapy based on current AHA guidelines. Patients will receive IV thrombolytic therapy available for use according to practice guidelinesif presented within the first 3 hours from last known well and meeting other FDA label criteria, or up to 4.5 hours from last-seen-normal and meeting other AHA guidelines. No procedures or tests required by the protocol will delay fastest possible delivery of thrombolytic therapy to potentially eligible subjects. For thrombolysis treated patients, the sites' post-thrombolysis protocol will be followed. The non-thrombolysis treated patients will be treated with aspirin, 325 mg on Day 1, and 81-325 mg/day (investigator's preference) on day 2-5, unless an indication for early anticoagulation is present (as determined by the patient's attending physician). All patients will receive standard DVT prevention therapy.
Assessment and Visits	Clinical assessments will be done at baseline, 24-hours after randomization, day 5-7 or hospital discharge (whichever is earlier), 30 days, and 90 days: 1. Baseline: demographics and medical history, CT/CTA/CTP/MRP imaging, lab work, hourly blood pressure, NIHSS, mRS 2. 24 hours (+/- 6 hrs): hourly blood pressure, NIHSS 3. 24 hour – 7 days post-procedure imaging (MRI or CT if MRI not feasible) 4. Day 5-7 or discharge (whichever is earlier): NIHSS, mRS 5. Day 30 (+/- 15 days): mRS 6. Day 90 (+/- 15 days): mRS, Neuro-QoL

Protocol

1. Scientific Background

Endovascular thrombectomy efficacy and safety was established initially up to 6 hours from stroke onset (the early time window) from several randomized controlled trials (MR CLEAN[1], REVASCAT[2], ESCAPE[3], SWIFT PRIME[4,] and EXTEND-IA[5]). These trials' inclusion criteria focused only on patients with favorable imaging profiles (minimal ischemic changes) on CT defined as ASPECTS ≥ 6 and on perfusion imaging defined as small core infarct with a large area of mismatch. Later, two trials (DAWN[6] and DEFUSE 3[7]) extended the safety and efficacy up to 24 hours (the late time window). The late window trials utilized advanced perfusion images with the same criteria of small core infarct and a large area of mismatch. As a result, these inclusion criteria excluded patients with unfavorable imaging profiles (significant ischemic changes), including patients with ASPECTS <6 or core infarct volume > 50-70 cc. Thus, thrombectomy efficacy and safety in these patients with unfavorable profiles (large core) on imaging is not established.

Moreover, the different trials used different imaging modalities for including or excluding patients, simple imaging with non-contrast CT head (ASPECTS ≥ 6) and/or advanced perfusion imaging with small infarct core and mismatch, with the vast majority of the patients having favorable imaging profile on at least one modality (CT and/or perfusion imaging). Thus:

1. The correlation between the different imaging profiles and thrombectomy outcomes is not established and the optimal imaging selection prior to thrombectomy is unknown.
2. Many patients were not represented in the trials, especially those with discordance between the two imaging modalities.

1.1. Thrombectomy in Patients with Unfavorable Imaging Profiles (i.e. Large Core)

Endovascular thrombectomy is safe and efficacious in selected patients with acute ischemic strokes (AIS) due to large vessel occlusion (LVO) in the anterior circulation up to 24 hours after the stroke onset. The majority of the early window trials used simple imaging with CT with ASPECTS ≥ 6 as inclusion criteria[2-4]. EXTEND-IA[5] was the only early window trial that solely used perfusion imaging criteria (core infarct volume < 70cc with a mismatch ratio of > 1.2 & mismatch volume > 10 cc). The trial only enrolled 70 patients. Most of the SWIFT PRIME[4] patients were included based on perfusion imaging with limited infarct core but some were included based only ASPECTS ≥ 6. Only the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial included a limited number of patients with an ASPECTS < 6. Based on the results of these trials, the American Heart Association recommended the use of thrombectomy in patients with large vessel occlusions presenting with CT ASPECTS ≥ 6 in the early treatment window (0-6 hours)[8].

Both the trials assessing thrombectomy safety and efficacy in the late time window used perfusion imaging. The DAWN[6] only included core infarct volume of up to > 50 cc on perfusion images and the trial excluded patients with involvement of >1/3rd of MCA territory on simple CT. The DEFUSE 3[7] trial excluded patients with ASPECTS < 6 or ischemic core volume ≥ 70 cc and required a mismatch ratio of ≥ 1.8 and mismatch volume of ≥ 15 cc. As a result, the safety and efficacy of late window thrombectomy is only established in patients with a small core, CT ASPECTS ≥ 6 and an infarct core < 50 cc on perfusion imaging. In fact, most of the patients in the late window trials had very small infarct core, with median (IQR) core infarct volume of 8 (2-18) cc in the DAWN[6] trial and 9 (2-25) cc in DEFUSE 3[7].

Despite the lack of data on patients with low ASPECTS, the American Heart Association has concluded that thrombectomy may be reasonable in patients with CT ASPECTS< 6 presenting within 6 hours of symptom onset while suggesting the need for additional randomized trial

data[8]. This population of patients represents a good portion of the patients encountered in daily practice without strong evidence from randomized trials to support treatment decision.

Data from a few prospective and retrospective non-randomized studies reported reasonable rates of good clinical and safety outcomes after thrombectomy in patients with unfavorable imaging profiles. In our recently concluded 'Optimizing Patient Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT): A Prospective Multicenter Cohort Study of Imaging Selection', investigators were allowed to enroll patients with unfavorable imaging profiles/large core on either CT or advanced perfusion imaging or both. The treatment decision in these patients, thrombectomy vs. medical management, was not randomized and rather based on the discretion of the site investigators. The study found that patients with unfavorable imaging profile on either or both imaging modalities formed a significant proportion of the daily clinical practice with up to 1/4th of patients demonstrating significant ischemic changes on one or both imaging modalities. In SELECT, thrombectomy was associated with improved functional independence in patients with an unfavorable profile on one or both imaging modalities (EVT: 30% vs MM: 13%, Adjusted OR: 2.92, 95%CI=1.00-7.91, p=0.041). Thrombectomy was also associated with a significant shift towards better outcomes across the full distribution of modified Rankin Scale scores (adjusted OR: 2.01, 95%CI=1.00-4.03, p=0.049). (Figure 1).

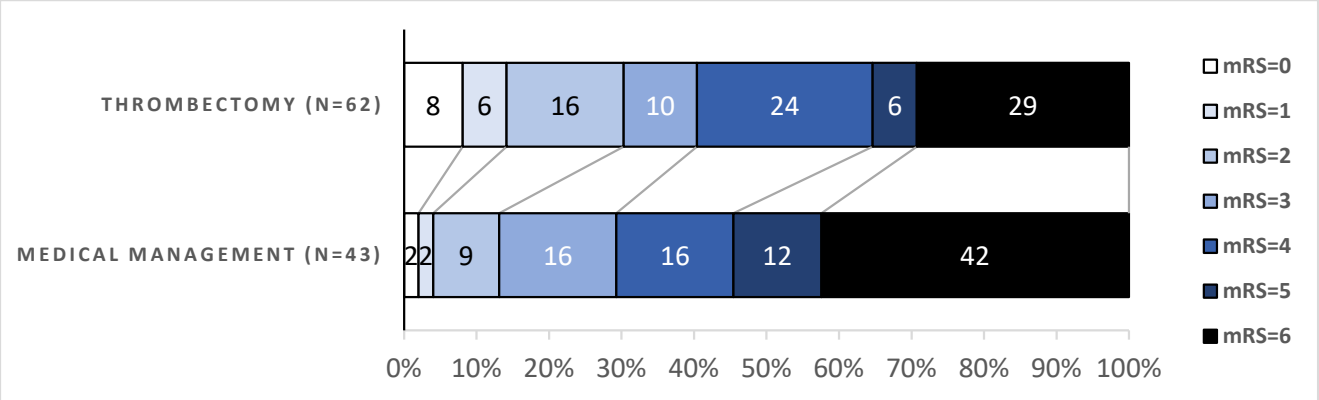


Figure 1. Modified Rankin Scale (mRS) distribution bars representing 90day clinical outcomes in patients with unfavorable profile on one or both imaging modalities, stratified by thrombectomy vs medical management only.

For safety outcomes, symptomatic intracranial hemorrhages rates (EVT: 7% vs MM only: 13%, p=0.26) and mortality (EVT: 29% vs MM only: 42%, p=0.17) did not statistically differ between thrombectomy and medical management only arms.

In a post-hoc analysis of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands (MR CLEAN), the investigators compared the rates of good outcome in patients with CTP ischemic core volume>70 cc, who received thrombectomy or medical management. The rate of good outcome (mRS 0-2) was 8% in the thrombectomy vs 0% in the medical management group. The rate of mortality was 38% versus 33%, respectively[10]. In another secondary analysis of MR CLEAN trial, thrombectomy patients with ASPECTS 0-4 had 9% rate of good outcome (mRS=0-2), compared to 0% in medical therapy patients. Mortality rate was lower in the thrombectomy group (36% vs 42%). Similarly, in patients with ASPECTS 5-7, thrombectomy patients had 32% good outcome versus 13% in medical management patients with a slightly lower mortality rate (24% vs 26%, respectively)[11].

In a retrospective multicenter study[12], the outcome rates in patients who received thrombectomy were compared between those with CT ASPECTS<7 versus those with CT ASPECTS≥7. The study showed similar outcomes between thrombectomy patients with unfavorable and favorable CT profiles. There was no statistically significant difference in good clinical outcome mRS 0-2 (ASPECTS<7=37% vs ASPECTS≥7=47%, p=0.8), symptomatic intracerebral hemorrhage (9% vs 9%, p=1.0), or mortality (20% vs 22%, p=0.8).

Rebello et al. (2017) compared the outcomes of patients with unfavorable CTP profile [rCBF <30%] >50 cc who underwent thrombectomy versus matched controls who had medical management only[13]. The results showed that compared to medical management, thrombectomy was statistically associated with favorable shift in the distribution of 90-day modified Rankin scale (mRS) (odds ratio: 2.56; 95%CI: 2.50-8.47; p=0.04), higher rates of good

clinical outcome (mRS=0-2) (thrombectomy=25% vs medical therapy=0%; p=0.04), as well as smaller infarct volumes (mean [SD], thrombectomy=87 [77] vs medical therapy=242 [120] mL; p<0.001). There were no statistically significant differences between the groups for safety outcomes including parenchymal hematoma type 2 (p>0.99), hemicraniectomy (p=0.10), and 90-day mortality (p=0.75).

These contrasting results with some reporting a potential signal for benefit and others reporting no difference in good outcome rates between thrombectomy and medical management alone, along with the lack of higher level of evidence from randomized trials support the need for randomized trials to test the efficacy and safety of thrombectomy in patients with unfavorable imaging profiles. The current status of inadequate evidence results in different treatment approaches in patients with unfavorable imaging profiles, with some patients being treated with thrombectomy while the majority receiving medical management only.

We hypothesize that endovascular thrombectomy is safe and efficacious in patients with acute ischemic strokes due to large vessel occlusion in the anterior circulation (ICA, MCA/M1) with large ischemic lesion volumes on simple (non-contrast CT head) or advanced perfusion imaging (CT or MRI perfusion) as compared to medical management only up to 24 hours.

1.2. Rationale for randomization in patients with favorable CT profile (ASPECTS 6-10) and unfavorable perfusion imaging profile (CTP: rCBF <30% volume or MRP: ADC <620 ≥50cc)

Most of the early window (0-6 hours) trials limited the use of perfusion imaging for patient selection. Only SWIFT PRIME[4] and EXTEND – IA[5] used perfusion imaging to exclude patients with the larger ischemic core (> 50-70 cc). Recently a patient-level meta-analysis of early window trials examining the impact of perfusion imaging parameters was published, including more than 1700 patients from 6 randomized controlled trials[14]. The study demonstrated 8% good outcome in patients with ischemic core volume of 70 cc or more treated with

thrombectomy compared to 0% in patients treated with medical management only. In a univariate shift analysis, the study showed the benefit of thrombectomy, which disappeared once adjusted for confounders. No difference in symptomatic ICH (EVT – 0%, MM – 12%, p=0.24) was reported. Thus, true evidence of efficacy in this patient group is still lacking. The recommendation for using only simple CT imaging for patient selection in the early window (within 6 hours) was recently rescinded from the American Heart Association stroke guidelines[8].

In an analysis of our recently concluded SELECT trial within early window (thrombectomy within 6 hours of stroke onset), functional independence rates were 101/173 (58%) in patients with ASPECTS score of 6 or more and with ischemic core volume of < 50cc. This rate reduced to 6/18 (33%) in patients with ASPECTS scores of 6 or more but ischemic core volume of 50-100 cc, which approached the medical management only rates reported in early window thrombectomy trials. The safety outcomes – symptomatic ICH (8/173 (5%) vs 3/18 (17%), p=0.072), neurological worsening (14/173 (8%) vs 5/18 (28%), p=0.023) and mortality (15/173 (9%) vs 7/18 (39%), p=0.001) also significantly increased in the subgroup when ischemic core volume was large. Thus, in these patients the outcomes changed significantly as the infarct core volume increased on perfusion imaging: the good outcomes reduced in half, while the safety outcomes doubled. With a limited representation of this subgroup in clinical trials assessing thrombectomy in the early window, no conclusive evidence is available and there is equipoise to justify randomization between thrombectomy and medical management alone.

In the late window, no randomized evidence exists for the efficacy of thrombectomy in these patients. Two randomized controlled trials (DAWN[6] & DEFUSE 3[7]) assessing the efficacy and safety of thrombectomy in the late window used both simple (CT) as well as advanced perfusion imaging to exclude patients. The DAWN[6] study only included patients with ischemic core volume of up to 50cc, while the DEFUSE 3[7] trial included patients with up to 70 cc of ischemic core volume. However, only 18 of the 182 randomized patients had ischemic core

volume between 50-70cc. Thus, no substantial conclusion of efficacy and safety of thrombectomy can be made within this subgroup for the late window as well.

1.3. Rationale for including patients with very large core on advanced perfusion (CTP: rCBF (<30%) volume or MRP: ADC < 620 >100cc)

Limited non-randomized evidence of thrombectomy efficacy is available in the published literature. A recently published study, a meta-analysis of 7 early window randomized controlled trials by Campbell et al.[14] has suggested benefit of thrombectomy in patients presenting with infarct core of >100 cc. Campbell et al. demonstrated that although functional independence rates remain very low, these patients continue to benefit from thrombectomy. For infarct core volumes up to 125 cc, the number needed to treat for any benefit remains below 10 for most functional outcomes and less than 5 for any functional improvement. In the light of these recently available evidence, these patients may have a low likelihood of functional independence but could still have better functional outcome than patients treated with medical management only. Thus, the protocol was amended to include these patients in the study. Stringent safety monitoring of mortality and symptomatic ICH is employed to ensure patient safety. The amended inclusion criteria will allow for:

1) Assessment of population with CTP/MRP core infarct >100cc
2) More generalizability of the study findings
3) No dependency on perfusion criteria, which will allow for the population to be treated based on non-contrast CT only. Providing data on the efficacy and safety of thrombectomy selection based on a non constrast CT, which is more readily available, would result in an increased thrombectomy availability to centers without perfusion imaging.

Although no upper limit is specified for infarct core volume measurements on CT or MR perfusion imaging, the infarct size is still expected to be limited, to an extent, given imaging exclusion criteria of “Patients with very large core on non-contrast CT i.e. ASPECTS ≤ 2” and

patients with "signs of established infarct and large area of cerebral edema on non-contrast CT".

1.4. Rationale for excluding patients with very large core on CT (ASPECTS 0-2)

There are no previously published data to describe the outcomes in this patient population. We did not have any patients with ASPECTS 0-2 who received a thrombectomy in SELECT trial. The 90-day mRS distribution for patients with ASPECTS 0-2 is shown in Figure 2. Since, no data for thrombectomy efficacy and safety is available, these patients were excluded from the trial.

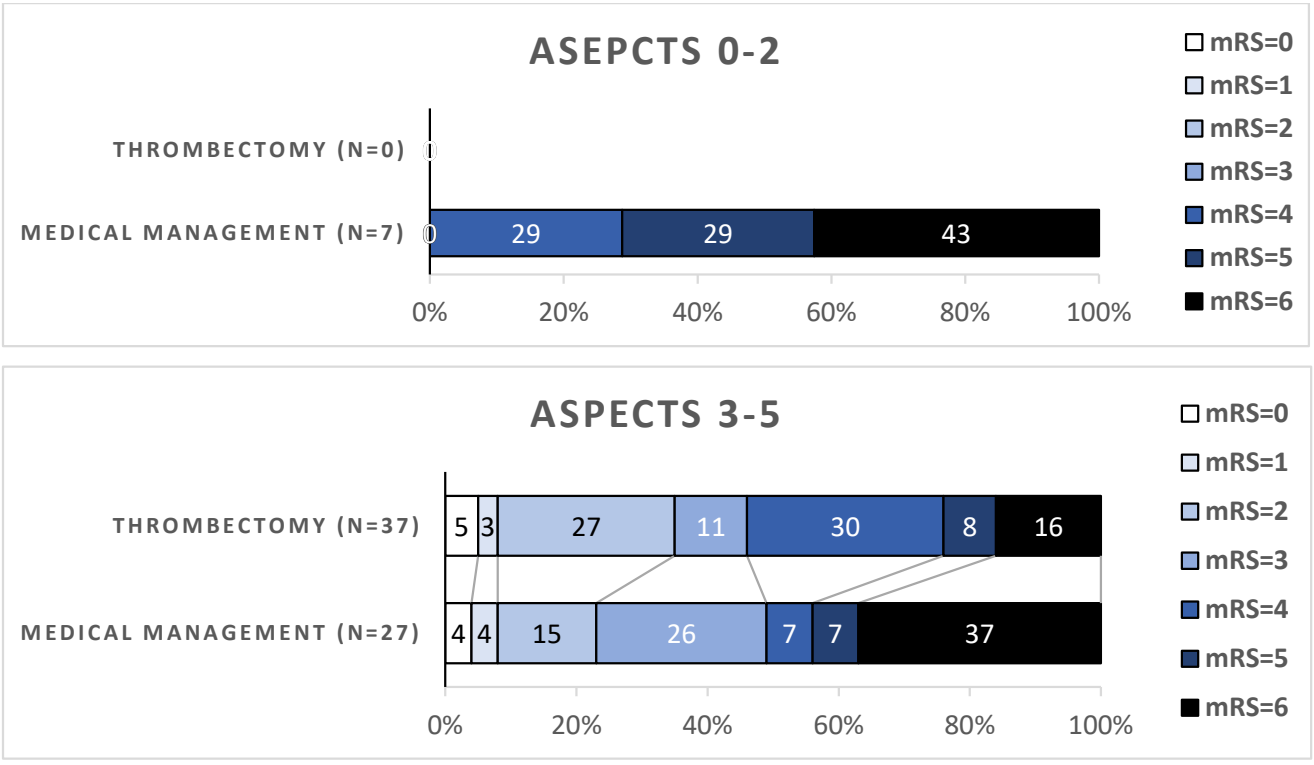


Figure 2. Modified Rankin Scale (mRS) distribution bars representing 90day clinical outcomes in large core patients stratified by ASPECTS score.

1.5. Imaging selection for thrombectomy

Thrombectomy is a highly effective treatment for anterior circulation LVO patients based on the results of several recent randomized clinical trials[1-7]. However, the imaging modalities and the patient populations enrolled, varied between the studies. For example, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)[1] used non-contrast head CT (NCCT) with the inclusion criteria of less than one third of the MCA, while the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment trial (SWIFT PRIME)[4] and the Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT)[3], in spite of using NCCT, applied a more stringent inclusion criterion of the Alberta Stroke Program Early CT Score (ASPECTS) of ≥ 6. Some of the patients in SWIFT PRIME[4] were treated by CT-Perfusion/ iSchemaView RAPID (CTP/RAPID), while some in REVASCAT[3] were treated based on MRI ASPECTS (≥ 7). Thrombectomy for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE)[2] used more specific imaging criteria focusing on NCCT ASPECTS (≥ 6) and CT-Angiography collaterals, as well as placing some consideration of the CT-Profusion profile. Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial trial (EXTEND-IA)[5] was the sole early window trial that purely based imaging selection on advanced perfusion imaging using CTP/RAPID.

This resulted in uncertainty in regards to optimal patient selection when it comes to imaging modality prior to thrombectomy as reflected in the current AHA guidelines, and the guideline recommending against using advanced perfusion imaging for patients presenting in early time window was recently rescinded[8].

The recent trials evaluating thrombectomy effectiveness in the late time window - Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With TREVO (DAWN)[6] and Endovascular Therapy Following Imaging Evaluation For Ischemic Stroke 3 (DEFUSE3)[7] used advanced imaging perfusion (CTP and MR-Perfusion) utilizing the RAPID software along with NCCT criteria to select patients. As a result, the recent AHA guidelines also recommend the use of both CT and advanced perfusion imaging for patient selection in thrombectomy[8].

In conclusion, the optimal imaging selection modality prior to thrombectomy is still unknown. Furthermore, the restrictive imaging inclusion criteria and correlation with outcomes, both functional independence, and safety outcomes are still yet undetermined. To measure the correlation between the two different imaging modalities and clinical outcomes, patients with discordant imaging profiles should be compared.

The highest level of evidence comes from a randomized controlled trial comparing thrombectomy outcome rates as well as safety parameters in patients selected by CT only vs CT plus perfusion imaging. However, a randomized trial is not feasible given the level of evidence from RCTs in the late window patients treated based on favorable perfusion imaging profiles (DAWN[6] and DEFUSE 3[7]). Additionally, the current AHA guidelines recommend the use of perfusion imaging for selection of patients in the late window[8].

Since the clinical trials evaluating thrombectomy largely included patients with favorable profiles on both CT and perfusion imaging, the vast majority of the currently available data is on these patients. Thus, the correlation between the thrombectomy outcome rates with different imaging profiles, specifically with discordance profiles between CT and perfusion images, is not well established. However, those patients with discordant imaging profiles on both modalities are frequently encountered in real-world practice. There is currently no evidence from randomized trials to guide the treatment decision in these patients. Many of these patients

may be excluded from the treatment based on the unfavorable profile on one imaging modality as preferred by the treating center or physician. Moreover, it is unclear if a favorable profile on advanced perfusion imaging with an unfavorable profile on non-contrast CT will provide improved prognostic value of thrombectomy when compared to patients with unfavorable perfusion imaging and favorable CT, or vice versa.

The SELECT trial was the first and only study to document discordance between imaging selection profiles. In SELECT, we observed that the two imaging modalities (CT and CT perfusion) had an agreement with favorable profiles in 81% of patients and an unfavorable profile on both modalities in 4% of patients. Discordance between the two imaging modalities was observed in 15% of patients with 7% showing favorable CT but unfavorable CTP and 8% showing unfavorable CT but favorable CTP. The agreement between imaging modalities and outcomes are shown in Figure 3.

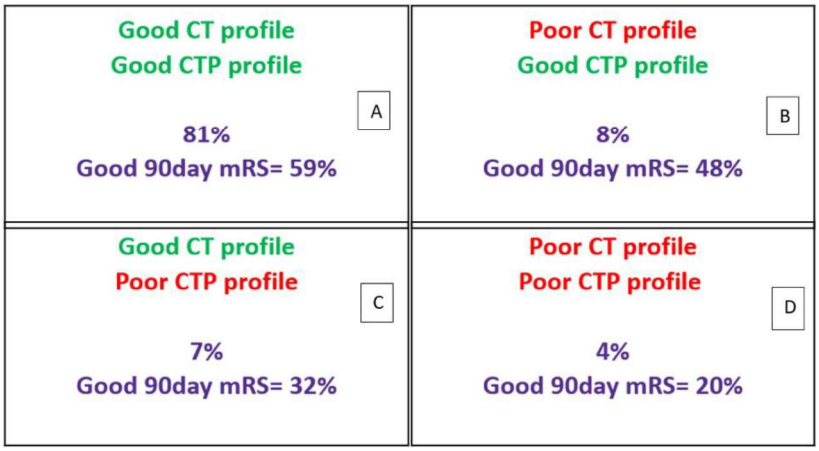


Figure 3. Illustration of patients' imaging profiles, as determined by the core lab, and their outcomes. A (Favorable CT & Favorable CTP): High agreement between **CT and CTP profiles** prior to thrombectomy. Similar profile to patients enrolled in prior RCTs; B (Unfavorable CT & Favorable CTP): Patients who would have been excluded by CT but treated based on favorable CTP; C (Favorable CT & Unfavorable CTP): Patients who would have been excluded by CTP but qualified by favorable CT; D (Unfavorable CT & Unfavorable CTP).

As shown above, discordance between imaging profiles was not uncommon and clinical outcomes differed based on the presence and type of discordant imaging profiles. Patients with discordant profiles showed outcomes better than patients with both imaging modalities demonstrating an unfavorable profile.

The two groups where both imaging modalities (CT and perfusion imaging) agree:

1. Unfavorable profiles on both: the results would not contribute to the comparison of imaging selection.
2. Favorable profile on both: there is, as detailed, strong evidence from RCTs supporting thrombectomy in both early and late time windows; thus randomizing these patients to compare imaging selection for thrombectomy is unethical and not feasible.

In SELECT 2, in order to compare the outcomes between imaging selection modalities, we propose to examine the correlation between the discordance in imaging profile and outcome rates, both functional independence as well as safety outcomes. We also propose to examine if there is a heterogeneity of treatment effect of thrombectomy in patients with discordant imaging profile (favorable CT/unfavorable perfusion imaging and unfavorable CT/favorable perfusion imaging).

Based on the SELECT trial results, patients with unfavorable CT/ favorable CTP had 48% good outcomes vs favorable CT/unfavorable CTP with 32% good outcomes (16% absolute difference). A superiority margin at 15% will be set between the two discordance groups and good outcome rates between patients with discordant imaging profiles will be compared. If those differences do not reach the statistical margin, then among patients with discordant imaging profile who met the inclusion criteria for SELECT 2 and treated with thrombectomy, the outcome rates did not differ.

In addition to comparing the rates of good outcomes between patients treated with thrombectomy in patients with discordant profiles, thrombectomy treatment effect heterogeneity will be assessed in patients with favorable CT/ unfavorable perfusion imaging and those with unfavorable CT/favorable perfusion imaging. If no heterogeneity exists, then thrombectomy benefit is not modified in the two scenarios when the two imaging modalities disagree.

1.6. Thrombectomy efficacy and safety in patients with favorable CT but unfavorable perfusion imaging profile

Early window trials demonstrated the superiority of thrombectomy over standard medical management in patients selected by either favorable CT (ESCAPE and REVASCAT) or favorable perfusion imaging (EXTEND-IA and a portion of SWIFT-PRIME). Thus, in patients with favorable CT profile, thormbectomy is proven superior to standard medical management in early window. Late window trials, DAWN[6] and DEFUSE 3[7] proved thrombectomy efficacy and safety in patients with favorable CT and perfusion imaging profiles. If thrombectomy is proven better than medical management only in patients with favorable CT but unfavorable perfusion imaging, then regardless of the perfusion imaging findings, patients with favorable CT would benefit from thrombectomy and thus, should be treated with thrombectomy.

1.7. Rationale and use of iSchemaView RAPID and iSchemaView RAPID ASPECTS

iSchemaView RAPID: At the conclusion of the CT/MR Perfusion scan, the technologist sends the sequences from the console to RAPID for automated processing. The RAPID software was developed based on data from DEFUSE 1 and was prospectively validated in DEFUSE 2. The system provides fully automated processing of brain images. The RAPID output maps, which identifies the volume and location of ischemic core and perfusion lesions, are emailed to

investigators (protected health information is automatically removed) and auto-sent to PACS for viewing within 5 minutes of completion of the scan. Immediately after the images are available, the investigator will review the results of the RAPID mismatch map, simple (Non-contrast) CT and the CTA to determine assignment in the specified group. The accuracy of the software for identifying the size and location of perfusion and diffusion lesions has been established by extensive validation and testing on blood flow phantoms; the software received FDA 510K clearance for clinical use in 2013. The agreement between local investigators and the Imaging Core Lab for identification of the mismatch profile in DEFUSE 2[15] was 97%, κ 0·92; 95% CI 0·83–1·0. Identification of core and penumbral volumes will be done in accordance with the procedures followed in DAWN[6] and DEFUSE 3[7] trials.

iSchemaView RAPID ASPECTS: Inter-rater reliability of ASPECTS score has been shown to be fair[16]. In a recent study, Automated ASPECTS has been shown to have a much higher agreement (k = 0.896) with the predefined gold standard sources (reporting of results by two board-certified neuroradiologists) compared to human readers (k = 0.574 and k = 0.556)[17]. The automated ASPECTS score is included as an investigational tool in the study. ASPECTS for patient selection will be determined independently by appropriately trained clinicians prior to any assessment with automated ASPECTS. In case of disagreements, ASPECTS scores provided by the clinicians will override the ASPECTS score by iSchemaView RAPID ASPECTS. In addition, the use of perfusion imaging in all patients will also help verify if a large core is present in these patients.

1.8. Rationale for including patients with exctracranial ICA occlusion:

Patients with extracranial ICA occlusion, as of now, do not have a proven treatment for revascularization and the rates of recanalization achieved by the only currently FDA approved treatment, IV tissue plasminogen activator have been poor[18-19]. Another issue with these patients is the potential of so called “Psuedoextracranial occlusion.” In a significant proportion

of cases with intracranial ICA occlusion, because of low flow, the contrast used for obtaining CT angiogram does not reach the level of occlusion and thus the occlusion appears to be extracranial on the conventional CT angiogram[20]. The only way to confirm the diagnosis of psuedoextracranial occlusion is to obtain an angiogram using fluoroscopy in the angio suite. Such cases form a significant number of patients presenting with extracranial occlusion who may benefit from the thrombectomy procedure, but are excluded from the trial based on the appearance on CT angiogram. Including cases with extracranial ICA occlusion on CTA will allow for enrollment of these patients. Randomized controlled trials such as ESCAPE and REVASCAT reported 40 (12.7%) and 31 (10.3%) patients with extracranial ICA occlusions. EXTEND-IA in early window and DEFUSE 3 in late time window also allowed for inclusion of patients with extracranial ICA, though did not report the number of patients enrolled with extracranial ICA.

2. Study Question, Aim, and Hypothesis

Study aims: are to evaluate in acute ischemic stroke patients due to a large vessel occlusion in the anterior circulation (MCA M1 and ICA):

- Primary aim: If thrombectomy plus medical management as compared to medical management alone will be efficacious and safe in patients with large core on either CT (ASPECTS 3-5) or perfusion imaging (CTP: rCBF<30% or MRP: ADC <620 ≥50cc), treated within 0-24 hours from last known well. We hypothesize that patients with unfavorable profiles (large core) treated with thrombectomy on either imaging modality will have significantly better outcomes than large core patients treated with medical management only.

- Second aim: The second aim is to look at the correlation of imaging profiles with thrombectomy clinical outcomes and treatment effect. It will be evaluated by comparing the outcomes in patients with discordant imaging profile and assessing if thrombectomy outcome rates and treatment effect will differ in patients with

discordant imaging profiles (favorable CT/unfavorable perfusion imaging and unfavorable CT/favorable perfusion imaging).

A) Evaluate good clinical outcome (90-day mRS 0-2) rates in patients with discordant imaging profile (unfavorable CT/favorable perfusion imaging vs favorable CT/unfavorable perfusion imaging) treated with thrombectomy.

B) Evaluate the heterogeneity of thrombectomy treatment effect in patients with favorable CT/unfavorable perfusion and unfavorable CT/favorable perfusion imaging.

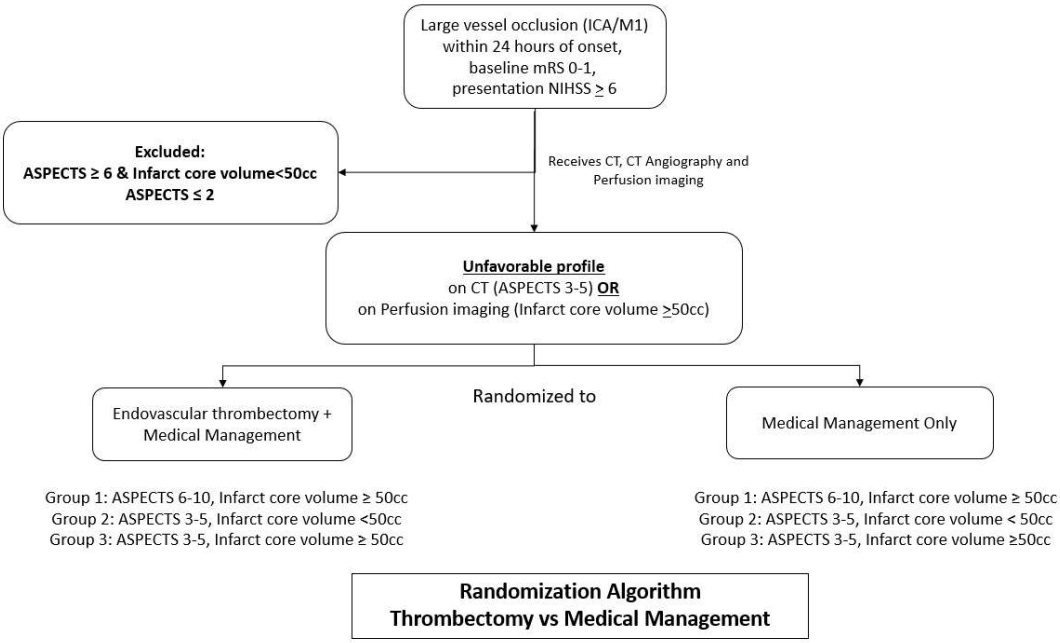
3. Methods

3.1. Study Design

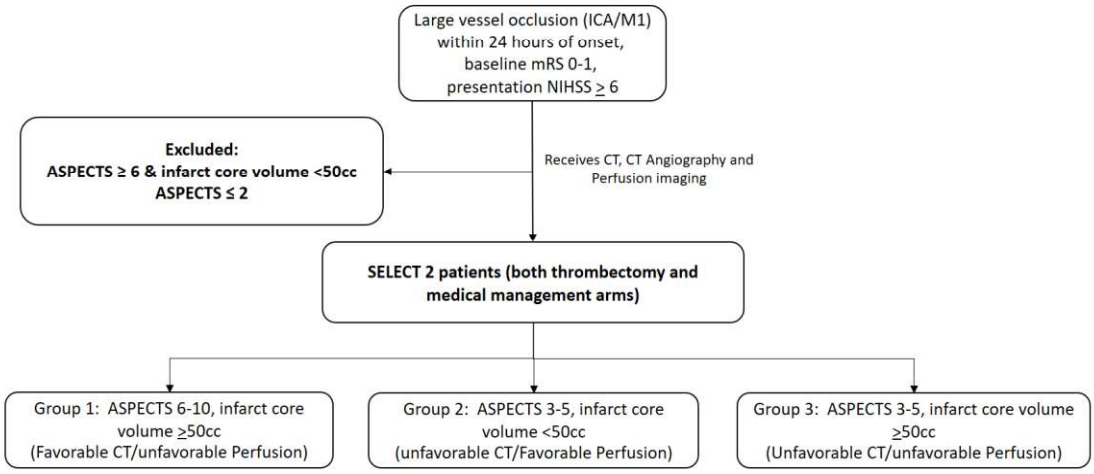
SELECT 2 is a prospective, multicenter, randomized open-label clinical trial evaluating: 1) the efficacy and safety of thrombectomy in patients with unfavorable imaging profiles (large core) on either CT or perfusion imaging or both treated within 0 to 24 hours from last-known-well; and 2) the correlation between CT and CT/MR perfusion imaging profiles and 90 day clinical outcomes (good mRS scores, 0-2) in LVO patients treated with thrombectomy within 0 to 24 hours from last-known-well.

On presentation to the EVT capable center enrolling patients in SELECT 2 trial, patients will receive a simple (non-contrast CT), CT angiography and CT/MR Perfusion with mismatch determination using automated RAPID software. The physicians will evaluate the CT scans and provide ASPECTS score. The CT image will also undergo processing by iSchemaView RAPID ASPECTS software as an investigational tool and the results will be available to the physicians for review. ASPECTS for patient selection will be determined independently by appropriately trained clinicians prior to any assessment with automated ASPECTS.

Patients with unfavorable imaging profiles on either CT (ASPECTS 3-5) or perfusion imaging (CTP: rCBF<30% or MRP: ADC <620 ≥50cc) or both within 0-24 hrs from last-known-well will be randomized into thrombectomy plus medical management vs medical management alone.



Randomization Algorithm
Thrombectomy vs Medical Management



Analysis 1: good outcomes rate in thrombectomy patients in Group 2 different to Group 1: 15% margin
Analysis 2: heterogeneity of treatment effect of thrombectomy between Group 2 and Group 1
Analysis 3: EVT superior to MM in patients with Favorable CT/Unfavorable CTP

Imaging Algorithm
Thrombectomy and Medical Management Patients

3.2. Enrollment Inclusion and Exclusion Criteria

Adult patients with AIS due to LVO in the anterior circulation (ICA and MCA occlusions in the M1 segment) who are normal or with minimal deficits at the time of their strokes (mRS 0-1), have received the pre-specified imaging profile (NCCT, CTA and CTP/MRP) prior to the treatment decision, and will be treated with thrombectomy (groin puncture time) plus medical management or medical management alone within 24 hrs from their last-known-well are eligible for the study (Table 1). A screening log of all patients with LVO presenting within 24 hours of symptom onset who receive thrombectomy, in addition to non-enrolled patients who qualify for SELECT 2 large core definition on imaging, will be kept. Clinical data will be collected to evaluate which method best correlates with patient outcome after thrombectomy. Mechanical thrombectomy includes the use of stent retrievers (e.g. Trevo®, Solitaire®, EmboTrap Revascularization Devices) and/or aspiration devices (e.g. MicroVention SOFIA Catheter, and Penumbra) as recommended by AHA (American Heart Association) guidelines. Please review Appendix C for a list of all approved devices.

Table 1. The SELECT 2 study inclusion and exclusion criteria

Inclusion Criteria	1) Adults (18-85 years) with the final diagnosis of an acute ischemic stroke
	2) NIHSS ≥ 6
	3) Last known well to groin puncture or medical management between 0 to 24 hours
	4) Pre-stroke modified Rankin Scale score of 0-1
	5) Eligible for thrombectomy or medical management
	6) Signed Informed Consent obtained
	7) Subject willing to comply with the protocol follow-up requirements
	8) Anticipated life expectancy of at least 3 months

Exclusion Criteria	1) Inability to undergo CT-Angiography and/or CT/MR Perfusion imaging (e.g., renal insufficiency, iodine/contrast allergy) 2) Co-morbid psychiatric or medical illnesses that would confound the neurological assessments 3) Treatment with IV thrombolytic therapy beyond 4.5 hours from last known well 4) Treated with IV thrombolytic therapy 3-4.5 hours after last known well **AND** any of the following: - age >80 - current anticoagulant use - history of both diabetes AND prior stroke - NIHSS >25 - ischemic involvement of more than third of the MCA territory 5) Current participation in another investigational drug or device study.

3.2.1.1. Specific Neuroimaging Inclusion Criteria

1. Proven large vessel occlusion in ICA or MCA-M1 occlusion (carotid occlusions can be cervical or intracranial, with or without tandem MCA lesions) determined by MRA or CTA
2. Large infarct-core lesion <u>on at least one of the following</u>

   2.1. Non-Contrast CT (ASPECTS of 3-5)*,

   2.2. CT perfusion (rCBF<30% ≥50cc),

   2.3. MRI-DWI (ADC<620 ≥50cc),

**ASPECTS 0-2 are not included in this study due to the expected poor outcome in these patients.*

3.2.1.2. Specific Neuroimaging Exclusion Criteria

1. Patients who have both ASPECTS of 6-10 on non-contrast CT **AND** core volume <50 cc on perfusion imaging
2. Patients with very large core on imaging on non contrast CT i.e. ASPECTS ≤ 2

3. Evidence of intracranial tumor (except small meningioma) acute intracranial hemorrhage, neoplasm, or arteriovenous malformation
4. Significant mass effect with midline shift
5. Evidence of internal carotid artery dissection that is flow limiting or aortic dissection
6. Intracranial stent implanted in the same vascular territory that precludes the safe deployment/removal of the neurothrombectomy device
7. Acute symptomatic arterial occlusions in more than one vascular territory confirmed on CTA/MRA (e.g., bilateral MCA occlusions, or an MCA and a basilar artery occlusion).
8. Signs of established infarct and large area of cerebral edema on non-contrast CT

3.3. Enrollment and Randomization

All patients who meet the clinical criteria listed above are eligible for SELECT 2 clinical enrollment. This includes both patients who are directly admitted to the study site and patients who are transferred from an outside hospital. The time of enrollment is the time when the informed consent is signed by the patient or their authorized legal representative. All patients or their surrogates will provide written informed consent. If a surrogate has provided informed consent, an attempt will be made to assess the competence of the patient again at day 1, discharge and at every follow-up in-person visit within 90 days of the procedure with the study team, if an in-person visit is feasible. If the patient is able to provide consent, informed written consent procedure will be reattempted, if an in-person visit is feasible.

3.4. Remote consent procedure:

A remote consent process to prevent delay in treatment is developed and included in the SELECT 2 protocol for participating sites that may want to implement such process. This remote consenting process will be utilized in cases when the patient himself/herself cannot provide an informed consent with the surrogate not being present on enrollment site. The key requirements of the process include provision of information regarding the study procedure in entirety followed by opportunity to ask questions and provision of contact information, and

receive completed ICF document with signature by the surrogate. An example of such process is described below. In places where only a legally authorize representative can consent for a research study, appropriate modifications will be made to the process described below.

1. **Provision of information regarding the study procedure in entirety followed by opportunity to ask question:**
   1.1. This can be achieved by an audio call, a video call or a teleconferencing service. The identity of the surrogate should be confirmed by providing acceptable ID documents before providing patients' related identifiable information.
   1.2. The surrogate should be encouraged to ask question. A contact number should be provided to the surrogate in case they have any further questions as they consenting process progress or later on.
2. **Complete ICF document:**
   2.1. The treating center should transmit all pages of ICF document to the surrogate. All pages of ICF document, completed by the surrogate should be received by the treating center prior to enrollment and randomization of the patient.
   2.2. Documents with incomplete information, i.e. absence of signature, absence of full legal name and absence of date and time of informed consent or missing pages of ICF document would not be considered adequate and must be received en-block and completed prior to enrollment and subsequent randomization into the study.
3. **Confirmation of the identity:**

   The surrogate identity should be confirmed by providing acceptable ID documents before any identifiable information is shared and tthe completed informed consent form is transmitted.
4. **Transmission of the information through a HIPAA compliant medium:**
   4.1. A HIPAA compliant secure medium should be used to transmit the data to the surrogate and receive the ICF back from the surrogate. These can include a secure institutional email with implemented HIPAA security features, Adobe Sign platform

approved for transmission of healthcare information or a fax number that is in possession of the intended recipient .

4.2. If the surrogate is present at the remote site, where the patient was first received before being transferred to the treatment center, the secured email from the Health Service Provider (HSP) at remote treatment site or fax machine under direct control and access of the HSP for the patient at remote treatment site can be used to transmit the information to and from the LAR.

5. Decreasing the burden of responsibilities from the surrogate as much as possible:

5.1. The study will ensur that ethe surrogate will receive assistance from the on-site ER physician/Nurse/research coordinators to decrease the burden of the consenting process including connecting with the surrogate, transferring the study information to the surrogate and returning the signed form to the study enrollment site. Use video conferencing if possible to establish the contact with the surrogate, provide ample opportunity to ask questions and answer all questions in detail. Request assistance from on-site healthcare personnel whenever available, provide protocol training to them beforehand and consider including them as the study personnel. Follow-up with another video call 15-20 minutes after the first contact to provide another opportunity to ask questions and assist in the process of signing and transmitting the ICF.

6. Documentation in the ICF

6.1. A complete documentation of the consenting process including the surrogate's name, relationship to the patient, method of transmission of ICF, mode of communication and verification of identity should be included in the ICF.

An example of such a procedure is provided below:

- Contact the appropriate surrogate by telephone/videoconferencing.
- Confirm the identity of the surrogate and how he/she is related to the patient.
- Discuss the study details, including procedures, study device and potential risks and benefits. Discuss the ICF and give instructions about where the surrogate needs to sign and date/time. The study will ensure that the surrogate will receive assistance from the on-site ER physician/Nurse/research coordinators to decrease the burden of the consenting process including connecting with the surrogate, transferring the study information to the surrogate and returning the signed form to the study enrollment site.
- Provide the ICF through a secure medium (Adobe Sign/email/fax).
- Provide the surrogate with a phone number to call you back in the event that she/he has questions. Follow-up with a phone/videoconferencing call after 15-20 minutes if they have any questions or need any help completing and returning the ICF.
- The surrogate should return the entire, signed and dated ICF back. The ICF is not valid and you cannot proceed with study enrollment unless all pages are received and appropriately filled out/signed/dated/timed.

After obtaining consent and ensuring all inclusion and exclusion criteria are met, randomization will be done in the emergency room prior to treatment using a web-based dynamic randomization system. Our randomization algorithm will be accessible to the study investigators and staff through a separate web page accessible only through the REDCAP database module. Covariate adaptive randomization will be used to balance the distribution of age (<60, 60-69, 70-79, 80-85 years old), presentation NIHSS (6-9, 10-15, 16-20, >20), center, clot location (M1, ICA), treatment time window (0-8, 9-16, 17-24 hours from onset to randomization time), CTP/MRP core volume (<50cc, 50-100cc, >100cc), presence or absence of target mismatch profile (mismatch ratio ≥ 1.8 & mismatch volume ≥ 15 cc) and hemisphere (right, left) between the two treatment groups.

The randomization algorithm we are going to implement is the algorithm developed by Pocock and Simon (1975)[27], i.e., minimization method. Through this algorithm, the assignment of a new patient to a treatment group is determined so as to minimize the differences between the groups in terms of these important key baseline variables. Unlike traditional stratified randomization, the minimization method works toward minimizing the total imbalance for all factors together instead of considering mutually exclusive subgroups, that is, we will not be creating these mutually exclusive subgroups during the randomization. Therefore, this approach is not restricted by the number of variables and the possible combinations of levels of balancing factors. Further details about Randomization can be found in Appendix A.

Eligible patients will be randomized into thrombectomy plus medical management vs medical management alone at a 1:1 ratio. The minimization algorithm is intended to balance the baseline characteristics between the two study arms, thrombectomy vs. medical management. The algorithm is not intended at the level of imaging profile subgroup. When a new patient is enrolled, the site will enter the stratification factor values into the dynamic randomization webpage and the treatment assignment will be determined immediately. An emergency 1-800 number will be provided if web-based randomization is not available due to exigent circumstances.

The assignment of the patients based on site assessment will be considered final for the primary analysis. A 1-800 number will be provided to the study investigators, where the case and imaging can be discussed with highly experienced vascular neurologists. A pre-specified secondary analysis based on core lab imaging assessment will be performed to address the cases where the core lab assessment differs from the site imaging assessment.

3.5. Endovascular Thrombectomy

The goal for femoral artery puncture will be within 45 minutes of randomization; femoral artery puncture must occur within 90 minutes of the completion of the qualifying imaging. Patients will be treated with thrombectomy devices (stent-retrievers) and/or suction (aspiration) thrombectomy systems currently cleared by the FDA for thrombus removal in patients experiencing an acute stroke within 24 hours of symptom onset following the published instructions for use for these devices. The devices which will be used are FDA-approved stent retrievers: the Trevo Retriever, the Solitaire Revascularization Device, EmboTrap Revascularization Device and Tigertriever Revascularization Device; and/or the aspiration devices approved by the FDA (e.g. MicroVention SOFIA Catheter, and the Penumbra thrombectomy system) permitted in the study. Please review Appendix C for a list of all approved devices. The choice of thrombectomy method, primary approach/technique, whether primary aspiration or primary stent-retriever with or without aspiration, will be left up to the interventionalist, with any of the FDA-approved devices approved in the study protocol or a combination of them (Appendix C). The study database will collect the thrombectomy method, and the devices used in the thrombectomy procedure.

Standard medical therapy, based on current AHA guidelines, will also be provided for all patients. Although any cleared neurothrombectomy device (Appendix C) can be used in the study, only the Solitaire Revascularization Device and Trevo Retriever are FDA-cleared to be indicated as a treatment in acute ischemic stroke patients to reduce their disability from the stroke. Individual investigators may use any of these devices or any combination of these devices to remove thrombus from the ICA, MCA M1 segment or, if needed, from M2 segments of the intracranial circulation. These are all approved anatomic locations for these devices. The use of thrombectomy devices should be performed in accordance with the indications for use and within the trial protocol. Any deviation from the on-label use of the device outside of the SELECT 2 protocol should be recorded in the appropriate case report form in detail. If there is severe stenosis of the common carotid artery or the proximal internal carotid artery,

investigators may also use devices for angioplasty or for stenting of the carotid artery as deemed appropriate. The use of adjuvant intra-arterial (IA) thrombolytic medication is not currently approved by the FDA for stroke treatment and cannot be used in SELECT 2.

Sites will use local protocols for femoral access, sedation, heparin infusion, monitoring, etc. Sites will perform a cervical injection of the involved carotid circulation as a baseline angiogram. At the conclusion of the procedure, a post-treatment angiogram as a cervical injection of the involved carotid circulation will also be obtained. Imaging will cover the full region of the normal circulation in AP and lateral projections at 2-3 films per second through the entire venous phase. All brain imaging from stroke onset through hospital discharge, including the MRI, CTP/MRP, and CT, as well as angiographic images obtained for the diagnostic and therapeutic portions of the procedure, will be transmitted to the core lab. The use of general anesthesia is left to the local investigators but discouraged by the study given the concerns of worse outcomes associated with that.
In cases of extracranial ICA occlusions, immediate stenting will be discouraged and delayed stenting (beyond 72 hours) will be preferred to reduce the risk of hemorrhagic transformation because of requirements of antiplatelet therapy/heparin to prevent re-occlusion.

3.6. Medical Management

Patients randomized to medical management alone will receive standard AHA guideline-directed medical therapy, which will include IV thrombolytic therapy available for use according to practice guidelines in patients presenting within the first 3 hours from last-seen-normal and meeting other FDA label criteria, or up to 4.5 hours from last-seen-normal and meeting other AHA guidelines. No procedures or tests required by the protocol will delay fastest possible delivery of thrombolytic therapy to potentially eligible subjects. The study database will collect the names of all thrombolytic drugs administered during the study, the route, the time of start of administration, and the dose administered. For non- thrombolysis treated patients, this will include aspirin 325 mg on day 1 followed by aspirin 81 mg or 325 mg

thereafter, which will be determined by treating physician, and standard deep venous thrombosis prevention therapy. Equivelent regimens of the aspirin will be allowed in countries where aforementioned doeses are not commercially available. Intravenous anticoagulation and dual anti-platelet therapy will be discouraged without clear documented reasoning. Post-thrombolysis patients will be treated based on standard study site protocols for these patients.

3.7. Outcome Measures

3.7.1.1. Primary Outcome

The primary outcome #1 will be the distribution of mRS scores at 90 days. The primary outcome #2 will be the percentage of good outcome (mRS 0-2) at 90 days. The definition of favorable primary clinical outcomes is the patients' functional outcomes at 90 (+/- 15) days, measured by a modified Rankin scale (mRS) score of 0-2. The determination of mRS scores will be performed by certified raters unaware of the treatment arm or the baseline clinical and radiographic characteristics of the individual patient by in person interview or by telephone if in-person visit is not possible.

The shift in the modified Rankin Scale score is better equipped to capture potential improvement in the functional outcomes as compared to a binary (dichotomized) outcome with intervention. Since the study population is composed of acute stroke patients with significant ischemic changes (unfavorable imaging profiles), the potential shift across modified Rankin Scale Score categories, not only the functional independence, is of clinical significance. For details, a change of mRS score of 5 – completely bedridden to mRS score of 4 – ambulating with a wheelchair and to mRS score of 3 – ambulating with a cane is a successful outcome for thrombectomy. We will still have the dichotomized outcome as our second primary outcome.

3.7.1.2. Secondary Outcomes

Secondary outcome measures include: 1) safety as measured by the incidence of symptomatic intracranial hemorrhage (sICH) (SITS-MOST)[21], neurological worsening (defined as a ≥4-point

increase on the NIHSS score within 24 hours due to the stroke itself), mortality and groin (or arterial access site) hematomas, infections or any vascular injury caused by the endovascular procedure, 2) rates of recanalization (complete and partial) using the modified TICI system (score ≥ 2b defined as favorable reperfusion), 3) length of hospital stay, and 4) discharge location. 5) significant improvement of ≥8 points on NIHSS at 24 hours of presentation or an NIHSS of 0-1

3.7.1.3. Imaging Outcomes

Imaging endpoints are: 1) infarct volume on MRI DWI sequence (or CT if MRI not feasible) 24 hours to 7 days after randomization; 2) lesion growth between the RAPID identified ischemic core on baseline imaging and the infarct volume; 3) successful reperfusion defined as DWI lesion volume minus Tmax>6 seconds greater than 50%; and 4) the proportion of subjects with recanalization of the primary arterial occlusive lesion. The technical efficacy of the endovascular procedure will be assessed by a modified Thrombolysis in Cerebral Infarction scores of 2b (50% to 75% reperfusion), 2c (>75% to 99% reperfusion) or 3 (complete reperfusion).[22]

3.8. Clinical and Imaging Evaluations

Clinical assessments will be performed at baseline, 24 hours after randomization, hospital discharge, 30 days, and 90 days (Table 2). Clinical assessments include the modified Rankin Scale, the NIHSS, and quality of life measure (Neuro-QoL).[23]

CT images will be read by appropriately trained clinicians as well as by the iSchemaView automated ASPECTS prior to randomization. ASPECTS for patient selection will be determined independently by the clinicians prior to any assessment with automated ASPECTS. In cases where there is disagreement, the physician reading will override the automated software reading. CTP images with mismatch determination will be read by iSchemaView automated RAPID software. All the images including baseline and follow-up MRI and CT images will be assessed independent of each other and blinded to treatment allocation at the core imaging laboratory at SELECT 2 Core Lab at McGovern Medical

School at UTHealth at Houston. Angiographic studies from the endovascular procedure will be assessed at SELECT 2 Core Lab.

3.9. Table 2. Schedule of Events

PROCEDURES	Screening	Enrollment	Baseline/ randomization	Thrombectomy	Day 1 (24 hrs +/-6 hrs)	5-7 Day follow-up (or discharge)	Day 30 (+/-15 days)	Day 90 (+/-15 days)	Day 365 (+/-60 days)
Screen Failure Log	X								
Inclusion and Exclusion Criteria	X								
Randomization			X						
Informed Consent		X							
Demographics			X						
Physical Exam[a]			X						
Vital Signs[b]			X						
Baseline Labs[c]			X						
Serum HCG (if applicable)			X						
Medical History			X						
Baseline Medications			X						
Baseline Characteristics			X						
NIHSS[e]			X		X	X			
Modified Rankin Scale[d]			X			X	X	X	X
Neuro-QoL[d]								X	X
Thrombectomy Timepoints/Procedural Data				X					
Post Treatment Hourly Blood Pressure Form (Treatment + 24 hrs)[e]			X	X	X				
Baseline Imaging (Head CT/CTA/CTP/MRI)			X						
Post Procedure Imaging (MRI 24 hours-7 days or CT if MRI not feasible)					X				
Image CRF completion by core lab (CT ASPECTS Score, CT Angio ASPECTS score, CT perfusion score, Angio mTICI, Capillary Index Score, Post-			X	X	X	X			

treatment/procedural, hemorrhage)[f]									
AE Reporting					X	X	X	X	
SAE Reporting					X	X	X	X	
Crossover explanations			X						
Protocol Deviation			X		X	X	X	X	

a. Physical exam at baseline as per standard of care (SOC). **b.** Vital Signs (BP and HR) recorded at baseline as per SOC. **c.** Labs (evaluation includes CBC with Platelets, Creatinine, Glucose, INR, activated PTT, and Pregnancy test (if applicable): at baseline as per SOC. **d.** If possible, 30 and 90-day visits should be completed in person. The telephone is allowed if the only option. **e.** for medical arm: recording blood pressure readings starts from either thrombolytics administration (if applicable) or randomization, for EVT arm recording blood pressure readings starts from the end of the thrombectomy procedure. **f.**Head CT/CTA/CTP/MRI: will be read centrally.

3.10. Assessment and Follow-up Visits

Baseline visit: The inclusion/exclusion page of the case report form must be completed to determine if the patient meets the eligibility requirements for the study. If the patient is eligible, then the consent form will be obtained by the patient or authorized representative.

24-hour visit (+/- 6 hours): The items listed for this visit in Table 2 should be performed between 18 and 30 hours from the time of the procedure.

Discharge visit: The items listed for this visit in Table 2 should be performed either on day 5/7 or the day of hospital discharge (whichever comes first).

30-day visit (+ / - 15 days): The items listed for this visit in Table 2 should be performed on day 30 (+/-15) days. The mRS score must be performed by an mRS certified evaluator who is blinded to treatment allocation. If possible, this visit should be completed in person. Telephone is allowed if the only option.

90-day visit (+ / - 15 days and preferably an in-person visit): The items listed for this visit in Table 2 should be performed on day 90 (+/- 15) days. The mRS score must be performed by an

mRS certified evaluator who is blinded to treatment allocation. The Neuro-QoL will also be completed on 90-day visit by an evaluator who is blinded to treatment allocation. If possible, this visit should be completed in person. Telephone is allowed if the only option.

365-day visit (+ / - 60 days): The mRS score must be performed by an mRS certified evaluator who is blinded to treatment allocation. The Neuro-QoL will also be completed on 360-day visit by an evaluator who is blinded to treatment allocation. Patients who were enrolled in the study at a date before the addition of the 365-day follow up visit, will be consented (remotely or in person) to complete the visit. The supplemental informed consent can be obtained verbally or in-written for patients who already provided their consents (or their LAR's consent) to participate in the study.

Neurological worsening: If clinical worsening (defined as a ≥4 point increase on the NIHSS score) occurs prior to discharge, a CT scan or MRI should be obtained as soon as possible.Neurological worsening is a reportable adverse event.

4. Sources of Materials

Information on the clinical status of patients will be obtained from the patient's medical record. Study coordinators at the site will complete the SELECT 2 case report forms to collect basic demographic and medical information about the patients. Data will subsequently be entered into the REDCAP electronic data capture system. Imaging data will be uploaded on DICOM (all patient identifiers are removed by the software prior to exporting the data outside of the site's firewall). All study sites will complete a screening log that documents all acute stroke patients treated by thrombectomy in the cath lab as well as patients who met the imaging criteria but were not enrolled in the study at their center, and the reason for exclusion of patients not enrolled. Serious adverse events (SAEs) will be reported within 24 hours of the event in the REDCAP electronic data capture system.

5. Site Approval and Monitoring Plan

Site approval: The University of Texas Health Science Center at Houston is the administration center and conducts data monitoring, core image lab reading and statistical analyses. Sites are selected for participation based on their experience in conducting clinical trials, their acute stroke treatment, and thrombectomy volumes, and only after an extensive discussion and vetting process by the principal investigator and documentation of interventionist experience, prior clinical trial enrollments, well-established research infrastructure, commitment to conducting clinical research, fast treatment times and efficient workflow. Sites will have a requirement of at least 100 thrombectomy procedures/year. Sites will commit to randomization and treatment criteria based on agreed upon contract. Selected sites will have access to emergent CT/CT perfusion and/or MR imaging 24/7. Prior to activating a site, we will verify that RAPID is functional at the site. Sites will be activated for enrollment after test cases processed with RAPID have ensured good quality maps.

Monitoring for imaging quality: The Imaging Core Lab will monitor image quality throughout the study. If significant inadequacies or protocol errors are noted at a site, enrollment will be halted. Enrollment will resume after all imaging problems have been resolved and repeat dummy runs have been obtained that demonstrate adequate image quality.

Monitoring for bias: A detailed site-monitoring plan has been developed to detect bias. This plan will protect the study from enrollment, randomization, and treatment bias. Sites will report their volume of endovascular stroke procedures (within 24 hrs) each month on a screening log. If a SELECT 2 eligible patient is treated with endovascular thrombectomy outside the SELECT 2 study, an explanation will be required detailing why the patient was not enrolled. The second component of the plan involves tracking of patients who are consented but not randomized. These patients will require an explanation of why the patient was not randomized as well as documentation whether endovascular thrombectomy was performed outside of the study. A third component involves monitoring of crossover after randomization. The Executive

Committee will review the data described above for each site every 6 months. If evidence of enrollment bias is suspected, it will be investigated. If confirmed, the site will be placed on probation. If additional incidents of suspected bias are confirmed, the site will be withdrawn. Routine monitoring of the clinical sites for the source to database verification will be performed by the UT Houston site.

6. Sample Size Calculation and Statistical Analysis Plan

6.1. Sample Size justification, Adaptive Enrichment Design, and Statistical Analysis Plan

The study will implement a novel adaptive enrichment design that will not only allow the trial to stop early for efficacy but also allow to select and evaluate the treatment effect in a most promising subpopulation if futility rule is triggered at the interim (or final) analyses in the overall population. This adaptive design has been developed, well-studied, and implemented for the DEFUSE 3 studies[24]. The details and theory of this adaptive enrichment design are summarized in Lai et al (2014)[25] and Lai et al (2018)[26]. This adaptive enrichment design is an extension of standard group sequential design with an enrichment feature[25]. It will test for efficacy or futility with two interim analyses and a final analysis. This adaptive design was chosen because the preliminary data from the SELECT study suggest a potential heterogeneity in thrombectomy treatment effect based on the different imaging profiles. By adopting this adaptive design, we expect to reallocate future accrual and study treatment effects only in a most promising subpopulation when there is evidence to show that EVT is futile in the overall population at interim (or final) analyses. By limiting the subsequent enrollment only in the most promising subpopulation, a larger number of patients will eventually be enrolled in this subgroup for efficacy testing compared to traditional designs.

This design uses the Generalized Likelihood Ratio (GLR) statistic (Kullback-Leibler criterion) as criteria to identify the subgroup, which has the best chance of showing a benefit from EVT.

Through these criteria, it can achieve optimal balance simultaneously between the estimated size of the treatment effect and the sample size of the subgroup. By considering the CTP core volume and treatment time window, the patients are split into six disjoint groups, that is Group 1 (ASPECTS 3-5 and CTP/MRP core volume <50cc) at early time window 0-12 hours (denoted as **G1A**), Group 1 at late time window 12-24 hours (denoted as **G1B**), Group 2 (ASPECTS 6-10 and CTP/MRP core volume ≥50cc) at early time window (denoted as **G2A**), Group 2 at late time window (denoted as **G2B**), Group 3 (ASPECTS 3-5 and CTP/MRP core volume ≥50cc) at early time window (denoted as **G3A**), and Group 3 at late time window (denoted as **G3B**). Considering a prior assumption that the EVT effect is largest in the patients with good imaging profile and treated within the shortest time window, we assume that the highest effect of EVT will be observed in G1A. Then the effects get decreased gradually in G1B, G2A, G2B, G3A, and the lowest effect will be observed in G3B. According to this adaptive design, when a most promising subgroup needs to be selected at the time of interim (or final) analysis, we will compare the GLR statistic among five cumulative groups, that is, G1A, G1A+G1B (i.e., Group 1), G1A+G1B+G2A, G1A+G1B+G2A+G2B (i.e., Group 1+Group 2), and G1A+G1B+G2A+G2B+G3A.

Primary analysis: The primary endpoint is the distribution of scores on the modified Rankin Scale (mRS) at day 90. The null hypothesis will be tested at the interim and final analysis using a normal approximation of the Wilcoxon-Mann-Whitney test (the GLR test). The principle of the intention to treat will be applied for the primary analysis. An additional analysis of the primary endpoint will be the same rank-based analysis comparing the 90-day mRs distribution between treatment groups while stratifying for prognostically important covariates. We will use the Generalized Cochran-Mantel-Haenszel test (CMH) to evaluate whether there is a uniform shift on the mRS distribution from one group to the other after stratification. The CMH test will be stratified by these variables used in the covariate adaptive randomization. For age, NIHSS, treatment time window, and CTP core volume, we will consider them as continuous variables in this adjusted analysis.

Power and sample size considerations Based on prior reported data, the following distributions were projected on the mRS at 90 days in EVT and MM groups for SELECT 2 in the overall population.

	mRS at day 90							
	0	1	2	3	4	5	6	Total
Endovascular group	4%	8%	12%	16%	19%	13%	28%	**100%**
Medical group	1%	4%	9%	14%	19%	10%	43%	**100%**

This distribution corresponds to a standardized effect of 0.34 for the primary analysis. Based on these data, the fixed sample size for a non-adaptive design requires a total of 376 patients (188/arm) to have 90% power at an alpha of 5% (Wilcoxon-Mann-Whitney test); We add additional 184 patients for the adaptive design to reach a maximum sample size of 560. We will conduct two interim analyses when we reach the number of patients at 200 and 380. Through extensive simulation studies, we have shown that with 560 patients in total for the adaptive design, we will have around 91% power to test for a standardized effect size of 0.34 in the overall population (assuming homogeneous EVT effect across six disjoint groups) by controlling an overall (one-sided) Type I error rate at 2.5%.

Efficacy and futility bound At each analysis (two interim analyses and the final analysis), an efficacy bound will be set to decide if the study should be stopped for efficacy while controlling the overall (one-sided) Type I error rate at 2.5%. At each interim analysis, a futility bound will be set to decide if the study should continue recruitment in the overall group, shift accrual and testing to a subgroup, or stop the trial entirely. When the futility bound is crossed and the optimal subgroup is selected, the maximum analyzed sample size will not be fixed but a random variable (smaller than the fixed maximum sample size 560). Due to the reduction in the maximum number of patients available for analysis at the end of the study, our design allows

an easier futility stop after subgroup selection. Further details regarding efficacy and futility bounds at interim and final analyses is provided in Appendix B.

First interim analysis (n=200 randomized and completed 90-day follow-up): The null hypothesis is tested in the entire patient cohort:

1. If neither efficacy nor futility bound is crossed, the trial continues enrollment to the 2nd interim analysis.
2. If the efficacy bound is crossed, the trial stops and efficacy is declared in the overall cohort.
3. If the futility bound is crossed, the optimal subgroup is selected based on the GLR statistic and the null hypothesis is tested in this selected subgroup:
   - 3.1. If neither bound is crossed, the trial will continue with enrollment limited to the selected subgroup
   - 3.2. If the efficacy bound is crossed, the trial stops and efficacy is declared in the selected subgroup
   - 3.3. If the futility bound is crossed, the trial stops for futility.

   Note: the futility bound is relaxed as described above, based on the expected maximum number of patients in the trial at completion (i.e. 560 minus the number of patients already enrolled in the groups that will no longer be open for enrollment).

Second interim analysis (n=380 randomized and completed 90 day follow-up): After the first interim analysis, the trial proceeds to this stage under two scenarios: (1) continuing enrollment in the overall population (i.e., option 1 above) and (2) limiting enrollment to a selected subgroup (i.e., option 3.1 above). When scenario (1) happens, the testing at the 2nd interim analysis is identical to the first interim analysis. When scenario (2) happens, the null hypothesis is tested in that selected subgroup:

1. If neither bound is crossed, the trial continues to the final analysis with an enrollment of 560-380=180 additional patients limited to the selected subgroup

2. If the efficacy bound is crossed, the trial stops and efficacy is declared in the selected subgroup
3. If the futility bound is crossed, the trial stops for futility.

Final analysis (n=560 randomized and completed 90-day follow-up): After the 2nd interim analysis, the trial proceeds to the final stage under two scenarios: (1) continuing enrollment in the overall population and (2) limiting enrollment to a selected subgroup.

When scenario (1) happens, the null is tested in the overall population:

1. If the efficacy bound is crossed, EVT is declared efficacious in the overall population.
2. If the efficacy bound is not crossed, the optimal subgroup is selected and the null is tested in that group:
   2.1. If the efficacy bound is crossed, EVT is declared efficacious in that subgroup
   2.2. If the efficacy bound is not crossed, EVT will be declared of no benefit.

When scenario (2) happens, that is, limiting enrollment to a subgroup (either selected at the 1st or 2nd interim analyses), the null hypothesis is tested in that selected subgroup only. Efficacy or lack thereof will be declared as per options 2.1 and 2.2 above.

Operating characteristics of the adaptive design: We have conducted simulations (5000 simulated trials) to evaluate the performance of the adaptive design (max n=560) and compare it to a traditional fixed sample-size design (fixed n=560) under various scenarios (see **Table 3**, below). For the simulations the effect size is expressed as a standardized effect with normal approximation, where a standardized effect of 0.32 or 0.30 corresponds to a conservative projected effect of EVT (anticipated effect 0.34; see section of Power and sample size considerations). We assume that we will observe the number of patients in G1A, G1B, G2A, G2B, G3A, G3B with 14%, 6%, 14%, 6%, 42%, and 18%, respectively.

Scenario	Standardized effect in groups G1A, G1B, G2A, G2B, G3A, G3B						Average standard. effect	Adaptive Design		Fixed Design	
								Average No. randomized	Power	Number randomized	Power
#0	0	0	0	0	0	0	0	426	2.0%	560	2.5%
#1	0.32	0.32	0.32	0.32	0.32	0.32	0.32	376	86.0%	560	95.8%
#2	0.3	0.3	0.3	0.3	0.3	0.3	0.3	393	81.1%	560	93.3%
#3	0.4	0.4	0.4	0.4	0	0	0.16	500	74.1%	560	45.7%
#4	0.4	0.4	0.4	0.4	-0.1	-0.1	0.1	502	78.5%	560	21.2%
#5	0.4	0.4	0.3	0.3	0	-0.1	0.122	513	67.1%	560	29.2%
#6	0.5	0.5	0	0	0	0	0.1	503	70.6%	560	21.2%
#7	0.5	0	0	0	0	0	0.07	503	60.5%	560	12.8%

Table 3. Under the null (Scenario #0), the adaptive design controls the total Type 1 error below 2.5%, stops early for futility 59.1% of the time, and the average number of randomizations is 426. If the effect is uniform across cells at 0.32 (scenario #1), the fixed-sample design is optimal, but the adaptive design results in only a small loss of power (from 95.8% to 86.0%), but reduced the expected sample size (from 560 to 376). We observed similar findings when the effect is uniform across cells at 0.3 (scenario #2). The adaptive design performs much better (higher power and smaller expected sample size) than the fixed-sample design when the effect size distribution across the subgroups is in accord with the biological assumptions (scenarios #3, #4 and #5). If the effect is concentrated only in Group 1 (scenario #6) or Group 1A (scenario #7), the adaptive design maintains power (70.6% in scenario #6 and 60.5% in scenario #7) while the conventional design collapses (21.2% power in scenario #6 and 12.8% in scenario #7).

Secondary analyses: Our secondary endpoint is the proportion of patients with mRS 0-2 at day 90 (indicating functional independence). The difference in the proportions of patients with mRS 0-2 between treatment arms will be assessed using logistic regression. We will adjust for the variables we used in adaptive randomization program in the logistic regression model. Other secondary endpoints include (1) the safety outcomes measured by the incidence of sICH, neurological worsening, mortality, groin hematomas, infections or vascular injury, (2) infarct volume, lesion growth, successful reperfusion, and recanalization rate, (3) length of hospital stay, and (4) discharge disposition. The exploratory analyses on secondary outcomes will include descriptive statistics (mean [± standard deviation, SD] or median and interquartile range for continuous variables and frequency [percentage] for discrete variables) and appropriate test for secondary outcome variables between two groups. For binary outcomes (e.g., sICH, neurological worsening, mortality, groin hematomas, infections or vascular injury, successful reperfusion, recanalization), Chi-square or Fisher's exact test where appropriate will be used to compare the incidence between two treatment groups for large core patients. We will also apply the logistic regression model on these outcomes after adjusting for the variables we used in adaptive randomization program. The adjusted odds ratio (OR), as well as 95% confidence interval will be reported. For the length of stay, mean ± SD and median (Interquartile range) will be calculated for each group. For continuous variables (e.g., the length of stay and infarct volume), two sample t-test or Wilcoxon rank sum test as appropriate will be applied to compare them between two groups. For discharge disposition, frequency and percentage of each disposition will be reported and Chi-square test or Fisher's exact test where appropriate will be applied to compare its distribution between two groups.

Subgroup analyses: Subgroup analyses of the effect of thrombectomy on the primary and secondary endpoints will be performed. Subgroups will be defined based on the stratification variables, key demographic factors (such as race and ethnicity), thrombolysis vs. no thrombolysis, CTP vs. MRI selection, and witnessed vs. unwitnessed symptom onset, wake-up vs non-wake-up stroke, and TICI 0-2a vs. TICI 2b/3 results in the cath lab. An additional

subgroup analysis will be performed in patients who present with extracranial ICA occlusion. Also, an additional subgroup analysis will be performed in patients based on thrombolytic therapy received.

6.2. Statistical plan for the second aim

The second aim is to compare outcomes in patients with discordant imaging profiles. Good outcome rates (90-day mRS 0-2) will be compared between EVT patients with favorable CTP/unfavorable CT and EVT patients with unfavorable CT/favorable CTP. Logistic regression model will be applied and odds ratio as well as 95% CI will be calculated. If there is a significant difference in the outcome, we will evaluate whether any patient characteristics could be potential confounders and can explain these differences.

We will also assess the heterogeneity of the treatment effect of thrombectomy comparing to medical management between patients with favorable CT/unfavorable CTP and patients with unfavorable CT/favorable CTP. We will assess the heterogeneity by evaluating the interaction effect in the logistic regression model between treatment groups (EVT vs MM) and imaging profile (favorable CT/unfavorable CTP vs unfavorable CT/favorable CTP). If the interaction term is statistically significant, we will examine patient characteristics and other baseline clinical characteristics for possible correlations or confounding factors.

6.3. Poolability analysis across centers

The data from all investigative sites will be pooled based on the assumption of comparable clinical aspects such as the common protocol used, adequate monitoring on protocol compliance, and the centralized data gathering and validation systems across all study sites.

We will assess the poolability across the sites by evaluating the interaction effect between treatment groups and sites. If the interaction term is statistically significant, we will examine patient characteristics and other baseline clinical characteristics for possible correlations or confounding factors. Sites with fewer than five subjects will be combined based on geographic region.

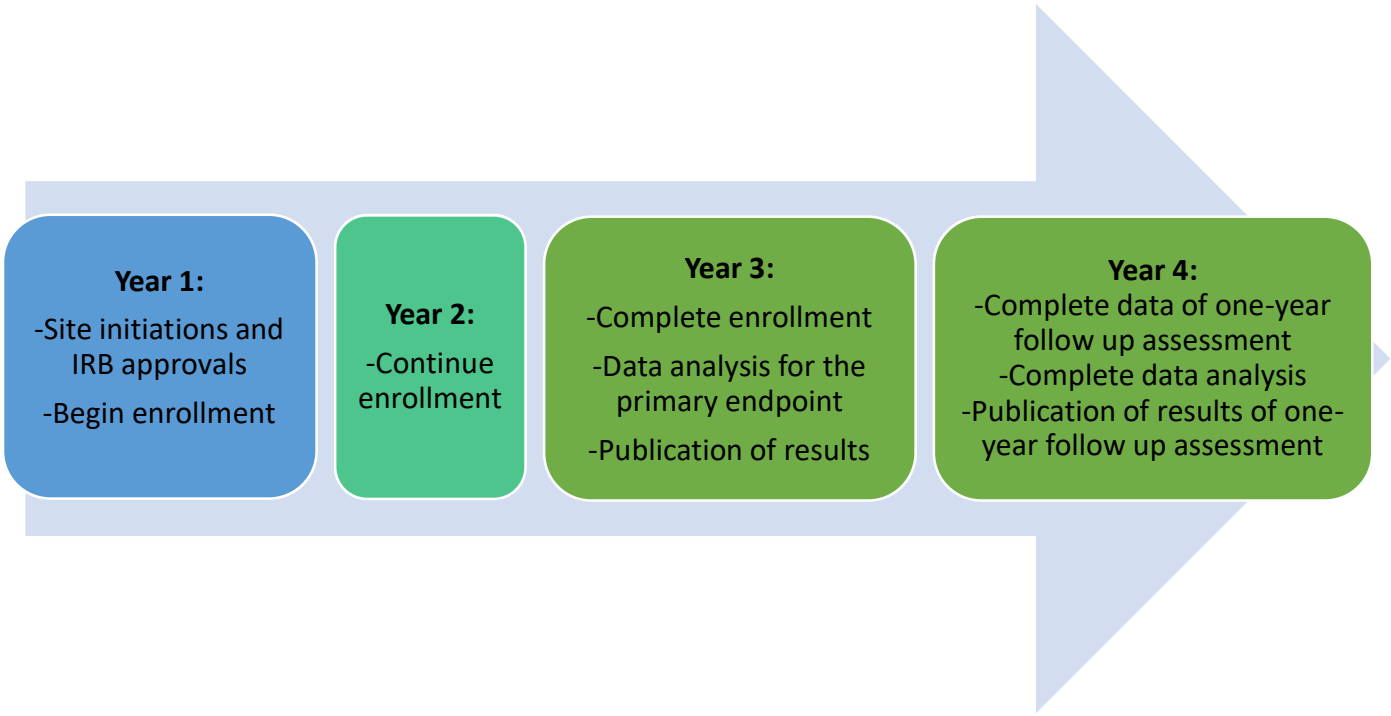
6.4. Feasibility of enrollment

The study is planning to involve 30 high volume centers with volumes of 150-200 thrombectomies/site/year. Based on SELECT data, roughly 20% of the patients have unfavorable imaging profiles on either CT or CTP, with ~30 patients/site/year eligible to participate in the study. Assuming 50% of the patients consenting to participate in the study and at 30 sites coming onboard in a gradual fashion, the study will complete the enrollment target (560 patients) in nearly 2 years.

6.5. Missing Data/Lost to Follow-up (LTFU)

All effort is put forth to ensure near complete follow-up, in particular with the assessment of the primary outcome (mRS at 90 days), death (mRS=6), and stroke recurrence. If the primary outcome (mRS at 90 days) cannot be assessed in the clinic, it will instead be obtained by phone using a structured interview. If the subject's mRS cannot be obtained in clinic or by phone within the window of 60 to 120 days from randomization, we will use multiple imputation method to impute 90-day mRS. Specifically, using the data from patients with available 90-day mRS, we will build ordinal logistic regression based on patient baseline features and prior mRS scores to impute 90-day mRS.

7. SELECT 2 Timetable



8. Risk Analysis

Description and analysis of all increased risks to the research subjects:

Potential complications of MRI scan include localized twitching sensation due to the magnetic field changes during the scan, anxiety due to claustrophobia and allergic reaction to the contrast agent. The allergic reaction may include headache, nausea, rash, hives, nasal congestion, sneezing, itching or swelling. If a severe reaction occurs, swelling of the throat, chest tightness, or a marked drop in blood pressure may occur. In addition, pain, bleeding, bruising, coldness or inflammation at the injection site may occur. Precautions will be taken for early detection and rapid treatment if such reactions occur.

Potential complications of CT scan include radiation exposure and allergic reaction to CT contrast agents. The iodinated contrast administration may also result in transient and rarely permanent renal failure due to nephrotoxicity.

Radiation doses:

Combined scanning with comprehensive stroke imaging, which includes a non-contrast head CT scan, perfusion imaging, and CT angiography of the cervicocranial vessels starting at the aortic arch results in a dose of approximately 7-10 mSv (Diekmann et al. 2010). According to the National Council on Radiation Protection and Measurement, the average annual radiation dose per person in the U.S. is 620 millirem (6.2 milliSieverts).

Reactions to contrast agents:

Mild

Nausea, Vomiting**,** Headache**,** Cough**,** Nasal stuffiness, altered taste**,** Flushing**,** Itching**,** Rash, Hives**,** Sweats**,** Swelling of eyes or face

Moderate

Mild hypotension, Tachycardia or Bradycardia, Bronchospasm, Wheezing, Dyspnea, Laryngeal edema, Generalized or diffuse erythema

Severe

Cardiopulmonary arrest, clinically manifested arrhythmias, profound hypotension, Convulsions, Unresponsiveness, Respiratory failure, Laryngeal edema. The rate of major reactions (e.g., anaphylaxis, death) is very low, estimated at one in 170,000 administrations.

Potential complications of endovascular thrombectomy include stroke; new clot in an artery; total blockage of an artery; infection and pain in the region of insertion site; lack of blood flow to the brain; rupture or puncture of an artery; significant tearing of the vessel wall; bleeding requiring blood transfusion; allergic reaction to contrast dye; abnormal low blood pressure requiring treatment; temporary closing of the artery (vessel spasm); formation of or dislodgments of clots which block the arteries (embolism). In rare circumstances, the procedure could result in death. At the puncture site in the groin, a blood clot or other blood vessel injury

may occur and require blood transfusion or surgical repair. Infection may occur at the puncture site; this could cause pain and require additional medications. There is some chance of an allergic reaction or renal injury due to the x-ray contrast (dye) used during the angiogram procedure. Minor allergic reactions may include a rash or hives. There is also the possibility of a serious allergic reaction that could include shortness of breath and swelling, drop in blood pressure, and even death. Patients will be closely monitored for these reactions and receive prompt treatment to reverse any allergic reactions.

9. Methods to mitigate risks to subjects in the trial

Methods to mitigate risks to subjects in the trial include the exclusion of subjects with bleeding disorders and selection of subjects via neuroimaging to minimize the risk of symptomatic intracranial hemorrhage. Computed Tomography (CT) scans will be performed for neurological deterioration (≥ 4 point increase in National Institutes of Health Stroke Scale (NIHSS) score) to identify new strokes, hemorrhage, or edema. Hospitals will follow their local standard of care safety procedures in order to reduce the risk of kidney dysfunction caused by contrast agents. Only investigators who are trained and experienced with the use of the devices allowed within the trial are eligible to participate. The adaptive design will eliminate subgroups with an unfavorable therapeutic response. Patients will be carefully screened for CT, MRI, and endovascular treatment contraindications according to the inclusion/exclusion criteria and excluded from enrollment if any are present. Radiation exposure during all tests will be minimized by optimizing the imaging protocols and by limiting fluoroscopy-time during the endovascular procedure. All CT sequences, including the CTP sequence, meet all FDA guidelines for radiation exposure.

To address the concerns of safety in early window for patients with favorable CT / unfavorable CTP profile in early window treated with medical management, consecutive monitoring of safety outcomes will be carried out for these patients. If the rates of safety outcomes e.g. mortality increases by >20% in patients treated by medical management only compared to

thrombectomy, enrollment within the group will be halted pending data safety monitoring board recommendations.

Although no upper limit is specified for infarct core volume measurements on CT or MR perfusion imaging, the infarct size is still expected to be limited, to an extent, given that the imaging exclusion criteria of "Patients with very large core on non-contrast CT i.e. ASPECTS ≤ 2" and patients with "Signs of established infarct and large area of cerebral edema on non-contrast CT".

To reduce the risk of hemorrhagic transformation in cases with extracranial ICA occlusion, immediate stenting of the extracranial lesion will be strongly discouraged and stenting beyond 72 hours of procedure will be strongly encouraged. Use of dual antiplatelet therapy and heparin will also be discouraged.

10. Stopping rules or safety triggers for the study

All participating centers are carefully selected to include only centers with high-volume and experienced interventionalists. The study PI reserves the right to terminate sites that significantly deviate from standard-of-care. Further, sites that violate the study inclusion or fail to produce timely data will be subject to possible termination.

The SELECT 2 has established the following two-step stopping rules for safety based on sICH and mortality rates using Bayesian method (Thall, Simon, and Estey, 1995)[28].
Since it is plausible that the safety concerns will increase with increment in ischemic core volume, consecutive monitoring of symptomatic ICH and mortality will be carried out in endovascular patients with CTP/MRP core volume of >100 cc and endovascular patients with CTP/MRP core volume ≤100cc separately.

For sICH:

1) **Step 1 for sICH:** check whether the posterior probability that the rate of symptomatic ICH (NIHSS worsening of 4 or more points associated with sICH per SITS-MOST definition assessed within 24 hours after randomization) in one of the endovascular group is >35% exceeds the cut-off 0.95. That is, check whether Pr{ $\pi_S^E >$ 0.35 | data} > 0.95, where the sICH rate in this endovascular group is denoted as π_S^E.

In the event that Step 1 for sICH in one of the endovascular group is triggered, step 2 for sICH for that group will be executed. Otherwise, continue the trial.

2) **Step 2 for sICH:** if Step 1 for sICH in one of the endovascular group is triggered, check whether the posterior probability that the sICH rate in this endovascular group is higher than the corresponding medical management by 10% exceeds the cut-off 0.95. That is, check whether Pr{ $\pi_S^E > \pi_S^M$ +10% | data} > 0.95, where the sICH rate in the corresponding medical management group is denoted as π_S^M.

In the event that Step 2 for sICH in of the endovascular group is triggered, patient enrollment will be placed on hold and a meeting of the DSMB will be conducted to discuss the events and make a determination on the continuation of the trial.

For endovascular patients with CTP/MRP core volume ≤100cc, we will conduct the two-step stopping rules for sICH after we enroll 50, 100, 150, 200, and 250 in this group (the maximum number of patients to be enrolled into the endovascular group is 280 and we expect 80% of patients' CTP/MRP core volume will ≤100cc**.**). We assign a weakly informative prior distribution for both π_S^E and π_S^M, that is, a beta distribution with two shape parameters at 0.35 and 0.65, which centers at 0.35 with an effective sample size of 1.

The rule of step 1 for sICH in this group can be pre-determined in the following table.

Find your number of **patients with CTP/MRP core volume ≤100cc in the endovascular group** in the left-side column. The step 1 for sICH will be triggered if the number of sICHs is in the range in the right-side column (the range is inclusive):

# of patients with CTP/MRP core volume ≤100cc in the endovascular group	# of sICHs
50	24-50
100	44-100
150	63-150
200	82-200
250	101-250

For endovascular patients with CTP/MRP core volume >100cc, we will conduct the two-step stopping rules for sICH after we enroll 20 patients in this group and then conduct monitoring after every 10 patients in this group (We expect 20% of patients' CTP/MRP core volume will >100cc, that is, among 280 endovascular patients, around 56 endovascular patients are with CTP/MRP core volume >100cc.). Similarly, we assign a weakly informative prior distribution for both π_S^E and π_S^M, that is, a beta distribution with two shape parameters at 0.35 and 0.65, which centers at 0.35 with an effective sample size of 1.

The rule of step 1 for sICH in this group can be pre-determined in the following table.

Find your number of **endovascular patients with CTP/MRP core volume >100cc** in the left-side column (we provide the table up to 100 patients, but if we enroll more than 100 patients in this group, we will run the algorithm and identify the # of sICHs which will trigger the rule). The step 1 for sICH will be triggered if the number of sICHs is in the range in the right-side column (the range is inclusive):

# of patients with CTP/MRP core volume >100cc in the endovascular group	# of sICHs
20	11-20
30	16-30
40	20-40
50	24-50
60	28-60
70	32-70
80	36-80
90	40-90
100	44-100

For endovascular patients with Extracranial Occlusions, we will conduct the two-step stopping rules for sICH after we enroll 20 patients in this group and then conduct monitoring after every 10 patients in this group (We expect 10% of patients will have isolated extracranial ICA occlusions, that is, among 280 endovascular patients, around 28 endovascular patients are with extracranial ICA occlusions). Similarly, we assign a weakly informative prior distribution for both π_S^E and π_S^M, that is, a beta distribution with two shape parameters at 0.35 and 0.65, which centers at 0.35 with an effective sample size of 1.

The rule of step 1 for sICH in this group can be pre-determined in the following table.

Find your number of **endovascular patients with Extracranial ICA occlusions** in the left-side column (we provide the table up to 100 patients, but if we enroll more than 100 patients in this group, we will run the algorithm and identify the # of sICHs which will trigger the rule). The step 1 for sICH will be triggered if the number of sICHs is in the range in the right-side column (the range is inclusive):

# of patients with extracranial ICA occlusions	# of sICHs
20	11-20
30	16-30
40	20-40
50	24-50
60	28-60
70	32-70
80	36-80
90	40-90
100	44-100

For mortality,

1) **Step 1 for mortality**: check whether the posterior probability that the rate of mortality at Day 90 in one of the endovascular group is > 40% exceeds the cut-off 0.95. That is, check whether Pr{ $\pi_m^E >$ 0.40 | data} > 0.95, where the mortality rate in this endovascular group is denoted as π_m^E.

In the event that Step 1 for mortality in one of the endovascular group is triggered, step 2 for mortality in this group will be executed. Otherwise, continue the trial.

2) **Step 2 for mortality**: if Step 1 for mortality in one of the endovascular group is triggered, check whether the posterior probability that the mortality rate in this endovascular group is higher than the corresponding medical management by 10% exceeds the cut-off 0.95. That is, check whether Pr{ $\pi_m^E > \pi_m^M$ +10% | data} > 0.95, where the mortality rate in the corresponding medical management group is denoted as π_m^M.

In the event that Step 2 for mortality in one of the endovascular group is triggered, patient enrollment will be placed on hold and a meeting of the DSMB will be conducted to discuss the events and make a determination on the continuation of the trial.

For endovascular patients with CTP/MRP core volume ≤100cc, we will conduct the two-step stopping rules for mortality after we enroll 50, 100, 150, 200, and 250 in this group (the maximum number of patients to be enrolled into the endovascular group is 280 and we expect 80% of patients' CTP/MRP core volume will ≤100cc**.**). We assign a weakly informative prior distribution for both π_m^E and π_m^M, that is, a beta distribution with two shape parameters at 0.4 and 0.6, which centers at 0.4 with an effective sample size of 1.

The rule of step 1 for mortality in this group can be pre-determined in the following table. Find your number of **patients with CTP/MRP core volume ≤100cc in the endovascular group** in the left-side column. The step 1 for mortality will be triggered if the number of deaths is in the range in the right-side column (the range is inclusive):

# of patients with CTP/MRP core volume ≤100cc in the endovascular group	# of deaths
50	26-50
100	49-100
150	71-150
200	92-200
250	113-250

For endovascular patients with CTP/MRP core volume >100cc, we will conduct the two-step stopping rules for mortality after we enroll 20 patients in this group and then conduct monitoring after every 10 patients in this group (We expect 20% of patients' CTP/MRP core volume will >100cc, that is, among 280 endovascular patients, around 56 endovascular patients

are with CTP/MRP core volume >100cc.). Similarly, we assign a weakly informative prior distribution for both π_m^E and π_m^M, that is, a beta distribution with two shape parameters at 0.4 and 0.6, which centers at 0.4 with an effective sample size of 1.

The rule of step 1 for mortality in this group can be pre-determined in the following table. Find your number of **endovascular patients with CTP/MRP core volume >100cc** in the left-side column (we provide the table up to 100 patients, but if we enroll more than 100 patients in this group, we will run the algorithm and identify the # of deaths which will trigger the rule). The step 1 for mortality will be triggered if the number of deaths is in the range in the right-side column (the range is inclusive):

# of patients with CTP/MRP core volume >100cc in the endovascular group	# of deaths
20	12-20
30	17-30
40	22-40
50	26-50
60	32-60
70	35-70
80	40-80
90	44-90
100	49-100

For endovascular patients with Extracranial ICA occlusions, we will conduct the two-step stopping rules for mortality after we enroll 20 patients in this group and then conduct monitoring after every 10 patients in this group (We expect 10% of patients to have isolated extracranial ICA occlusion, that is, among 280 endovascular patients, around 28 endovascular patients are with extracranial ICA occlusions). Similarly, we assign a weakly informative prior

distribution for both π_m^E and π_m^M, that is, a beta distribution with two shape parameters at 0.4 and 0.6, which centers at 0.4 with an effective sample size of 1.

The rule of step 1 for mortality in this group can be pre-determined in the following table. Find your number of **endovascular patients with Extracranial ICA occlusions** in the left-side column (we provide the table up to 100 patients, but if we enroll more than 100 patients in this group, we will run the algorithm and identify the # of deaths which will trigger the rule). The step 1 for mortality will be triggered if the number of deaths is in the range in the right-side column (the range is inclusive):

# of patients with Extracranial ICA occlusions	# of deaths
20	12-20
30	17-30
40	22-40
50	26-50
60	32-60
70	35-70
80	40-80
90	44-90
100	49-100

These rules only serve as guides and do not substitute for the independent decision-making of the DSMB in the determination of whether the study should be stopped for safety reasons. The decision to stop the study will be made by the DSMB after review of all adverse events based on its own independent decision making. The investigators and the sponsor will not be informed of the interim grouped results.

11. Imaging Core Lab

All baseline and follow-up CTs, CT-Angiograms (CTAs) and CTP/MRP images will be reviewed by a central lab core at UTH. Dr. Clark Sitton, Associate Professor, Diagnostic and Interventional Imaging and Dr. Roy Riascos, Professor, Diagnostic and Interventional Imaging at UT McGovern Medical School will serve on the imaging core lab. All images will be sent to the central lab core in a de-identified manner. All radiology interpretations will occur independently of any knowledge of clinical factors. Blinding of imaging core lab at UT Houston will be ensured. We have several neuroradiologists at the institute and the neuroradiologist for the core lab will not participate in the care of a patient enrolled in the trial. Also, the neuroradiologists, while evaluating images will assess the CT images at a different time than the MRIs. They will also not be aware of the treatment and other clinical variables.

A) Parenchymal (e.g., non-contrast head CT) Imaging - the ASPECT score will be determined (baseline study only). Follow up studies will be determined for stroke location as well as for the presence of any hemorrhage and hemorrhage grading.

B) CT-Angiograms of the head – identify the vessel occlusion location and collateral scoring system.

C) CTP-Advanced analysis through the RAPID software (RAPID, non-commercial research version iSchemaView, Inc.) will be utilized to identify potentially salvageable brain tissue. Brain tissue at risk for infarction will be distinguished from minimally hypo-perfused tissue if the time to maximum (Tmax) delay is more than 6 seconds. Irreversibly injured brain (hypo-perfused tissue will be diagnosed if the relative cerebral blood flow is less than 30% of that in normal tissue.

D) Conventional Angiograms – identify and grade reperfusion using the modified TICI scoring system.

12. National Data Management Center

Data management and site monitoring will be performed by the University of Texas at Houston (UTH). The UTH will create the database and set up the interface on the REDCAP where clinical site personnel will enter the data into the electronic CRF. Data quality assurance processes include: (1) logic and rule checks built into the database; (2) monitoring by the Data Manager at the UTH; (3) central monitoring by the statistical programmer at the UTH; and (4) risk-based source verification monitoring by the Study Coordinators.

13. Data Management Plan

Individual data elements will be collected locally and then entered into a password-protected web-based, secure central database, REDCAP. Biostatistics/Epidemiology/Research Design (BERD) Core at The University of Texas Health Science Center – Houston will act as the data coordination center. Data quality will be maintained by establishing a written Data Management Plan describing all applicable aspects of the data management process including:

Developing a database that meets all verification and validation requirements of FDA rule 21 CFR 11, including reference to all pertinent FDA-provided guidelines;

- Developing a Data Clarification Plan which describes
  - Edit check logic for all variables specified,
  - CRF pages referenced by edit check,
  - Types of query responses: manual, site notification and clinical query;
  - Query text;
- Establishing a data audit strategy and associated procedures.

The database, housed in a Zone 100 secure server at UT-Houston, will be frozen and data will be audited prior to database lock by the statistical center. All data will be identified and subjected to a 100% audit, with all errors corrected.

14. Compliant Handling Plan

All treatments will be performed following each stroke center's local standard of care using FDA-approved devices and medications. Any individual patient or family member complaints regarding adverse events or morbidity will be handled locally by each institution's patient safety center.

In the event dissemination of protected patient health information (PHI) or any other confidential information occurs, local investigators are bound to report to their risk management department as well as the coordinating site and study sponsor. On a case by case basis, the PI reserves the right to terminate any participating centers if mismanagement of such data is discovered.

15. Data Safety and Monitoring Board

SELECT 2 will have an independent Data and Safety Monitoring Board (DSMB) to oversee study safety. Patients in both study arms will be assessed for the incidence of stroke-related mortality at 90 days, the incidence of symptomatic intracranial hemorrhage per SITS-MOST definition within 24 hours after randomization (defined as a ≥ 4 point worsening of immediate pre-deterioration NIHSS neurological status vs. post deterioration and associated with brain hemorrhage), and the incidence of significant neurologic deterioration prior to discharge (defined as ≥ 4 point worsening of the immediate pre-deterioration NIHSS neurological status vs. post deterioration and not attributed to sedation). Patients in both arms will also be assessed for intra-procedural complications including intra-procedural mortality, vessel perforation, arterial dissection, access site complication requiring surgical repair or blood

transfusion, embolization and device failure. SAEs will be reported within 24 hours of awareness of the event.

The DSMB will meet in person or by teleconference, on a semi-annual basis, to monitor the cumulative safety data during participant follow-up. In no instance will more than 12 months elapse between DSMB reviews of cumulative safety data after the first participant has been enrolled. The DSMB will monitor the study according to the guidelines specified in the study protocol and the operating procedures established at the initial meeting unless the DSMB determines during the course of the trial that modification of the guidelines is in the best interest of the study and its participants. The DSMB charter can be found as an attachment to the protocol.

16. Independent Medical Safety Monitor

In addition to the DSMB, an independent Medical Safety Monitor (MSM) will be appointed for the SELECT2 trial. The independent MSM will not be involved in the study and will not have conflict of interest. He/she will be responsible for ongoing monitoring of reports of SAEs submitted by the clinical centers in real time to ensure good clinical practice and to identify safety concerns quickly. The MSM may suggest protocol modifications to prevent the occurance of particular AEs, e.g., modifying the protocol to require frequent measurement of laboratory values predictive of the event or to improve expeditious identification of the SAEs. In the event of unexpected SAEs or an unduly high rate of SAEs, the MSM will promptly contact the DSMB. In the event that MSM is unavailable for an extended period of time (i.e., extended vacation, sabbatical, illness, etc.), a back-up MSM will be nominated by the study PI and approved by the DSMB.

17. Adverse Event Reporting

Consideration of adverse events will hereafter consist of adverse events, serious adverse events, and adverse device effects, including anticipated adverse device effects and unanticipated adverse device effects.

- **Adverse event (AE)** is defined as any untoward/undesirable clinical occurrence in a clinical investigation of a subject, which does not necessarily have a causal relationship with the treatment under investigation. An adverse event can, therefore, be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a device product, whether or not considered related to the device product. Only abnormal laboratory values that are deemed clinically significant by the investigator will be classified as adverse events.
- **Serious adverse event (SAE)** is defined as any untoward/undesirable adverse experience that results in any of the following outcomes: 1) death; 2) a life-threatening adverse experience; 3) inpatient hospitalization or prolongation of existing hospitalization; 4) a permanent/persistent or significant disability/incapacity or a congenital anomaly/birth defect; 5) important medical events 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, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. This category includes the use of intra-arterial thrombolytics and/or intracranial stents.
- **Anticipated Adverse Device Effect (AADE)** is defined as any adverse effect related to the device or procedure, which is identified in the protocol or the instructions for use for the device.
- **Unanticipated Adverse Device Effects (UADEs)** is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other

unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

18. Reporting Procedures for All Adverse Events

All Adverse Events, whether or not attributed to the study and/or the devices, observed by the investigator or reported by the subject, will be recorded from the time of randomization through Day 90. All recorded adverse events will be provided to the data safety monitoring board (DSMB) at the time of review for decision-making.

The following attributes will be assigned by the reporting investigator:

1. Description of event
2. Date of onset
3. Date of resolution (if applicable)
4. Seriousness
5. Relationship to the study device and/or procedure(s)
6. Severity
7. Action(s) taken
8. Outcome(s)

Severity is defined as a measure of the intensity of a reaction, effect or experience. The measurement(s) are described as mild, moderate, severe, life-threatening or death. The event itself, however, may be of relatively minor medical significance. The severity of Adverse Events is assessed according to the following index scale:

- **Mild**

  Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

- **Moderate**

Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living.

- **Severe**

Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living.

- **Life-threatening consequences**

Urgent intervention indicated

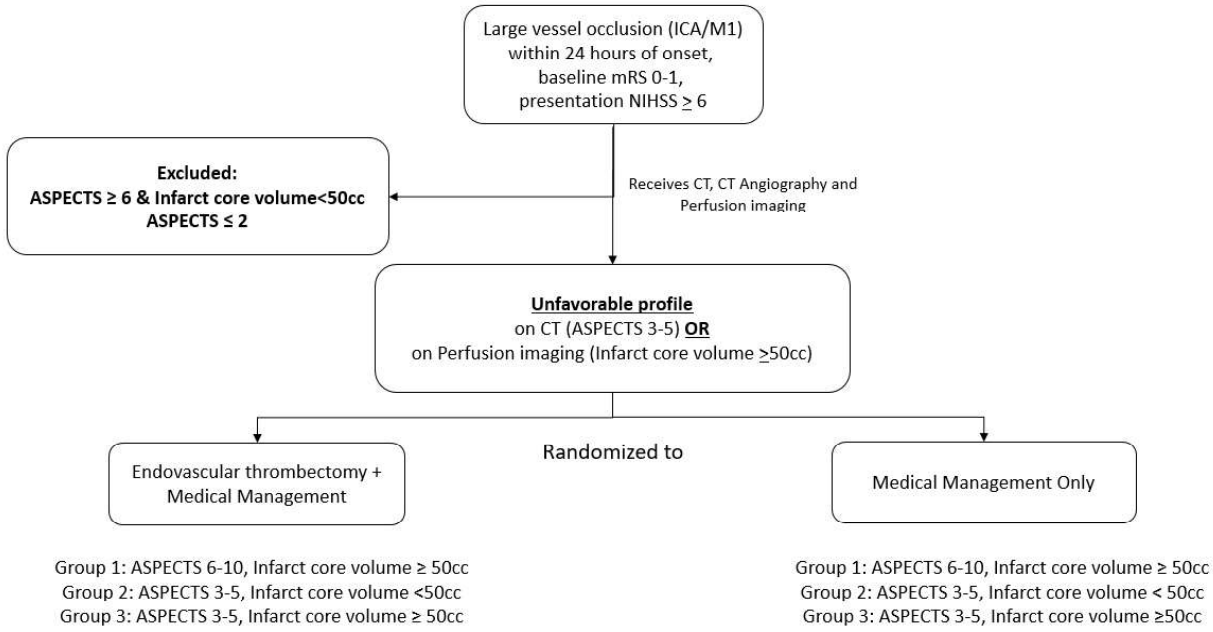
- **Death** related to AE

The relationship of an AE to the study device or procedure will be graded as follows:

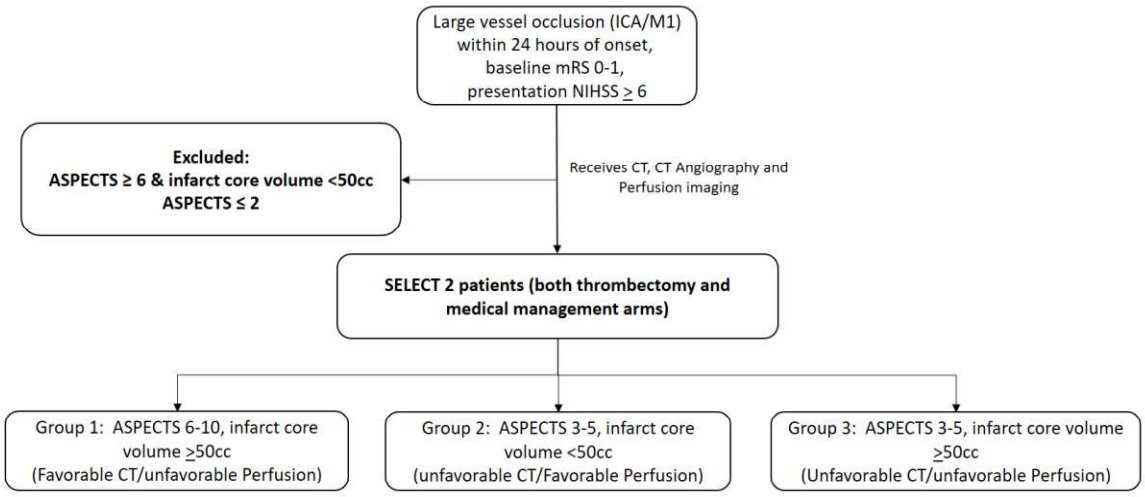
- Unrelated
- Unlikely
- Reasonable possibility
- Definitely

Serious Adverse Events All Serious Adverse Events and Unanticipated Adverse Device Effects including deaths will be reported to the MSM, the Coordinating Center (McGovern Medical School) and the FDA, as required.

19. Study Design



Randomization Algorithm
Thrombectomy vs Medical Management



Analysis 1: good outcomes rate in thrombectomy patients in Group 2 different to Group 1: 15% margin
Analysis 2: heterogeneity of treatment effect of thrombectomy between Group 2 and Group 1
Analysis 3: EVT superior to MM in patients with Favorable CT/Unfavorable CTP

Imaging Algorithm
Thrombectomy and Medical Management Patients

References

1. Berkhemer O, Fransen P, Beumer D et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. *New England Journal of Medicine*. 2015;372(1):11-20. doi:10.1056/nejmoa1411587

2. Jovin T, Chamorro A, Cobo E et al. Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke. *New England Journal of Medicine*. 2015;372(24):2296-2306. doi:10.1056/nejmoa1503780

3. Goyal M, Demchuk A, Menon B et al. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. *New England Journal of Medicine*. 2015;372(11):1019-1030. doi:10.1056/nejmoa1414905

4. Saver J, Goyal M, Bonafe A et al. Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke. *New England Journal of Medicine*. 2015;372(24):2285-2295. doi:10.1056/nejmoa1415061

5. Campbell B, Mitchell P, Kleinig T et al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. *New England Journal of Medicine*. 2015;372(11):1009-1018. doi:10.1056/nejmoa1414792

6. Nogueira R, Jadhav A, Haussen D et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *New England Journal of Medicine*. 2018;378(1):11-21. doi:10.1056/nejmoa1706442

7. Albers G, Marks M, Kemp S et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *New England Journal of Medicine*. 2018;378(8):708-718. doi:10.1056/nejmoa1713973

8. Powers W, Rabinstein A, Ackerson T et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the

American Heart Association/American Stroke Association. *Stroke*. 2018;49(3). doi:10.1161/str.0000000000000158

9. Sarraj A, Hassan A, Gupta R et al. Optimizing Patient Selection For Endovascular Treatment In Acute Ischemic Stroke (Select): A Prospective Non-Randomized Multicenter Cohort Study Of Imaging Selection - European Stroke Organisation Conference: Late Breaking Abstracts. *European Stroke Journal*. 2018;3(1_suppl):587-620. doi:10.1177/2396987318773967

10. Borst J, Berkhemer O, Roos Y et al. Value of Computed Tomographic Perfusion–Based Patient Selection for Intra-Arterial Acute Ischemic Stroke Treatment. *Stroke*. 2015;46(12):3375-3382. doi:10.1161/strokeaha.115.010564

11. Yoo A, Berkhemer O, Fransen P et al. Effect of baseline Alberta Stroke Program Early CT Score on safety and efficacy of intra-arterial treatment: a subgroup analysis of a randomised phase 3 trial (MR CLEAN). *The Lancet Neurology*. 2016;15(7):685-694. doi:10.1016/s1474-4422(16)00124-1

12. Logan C, Maingard J, Phan K et al. Borderline Alberta Stroke Programme Early CT Score Patients with Acute Ischemic Stroke Due to Large Vessel Occlusion May Find Benefit with Endovascular Thrombectomy. *World Neurosurgery*. 2018;110:e653-e658. doi:10.1016/j.wneu.2017.11.068

13. Rebello L, Bouslama M, Haussen D et al. Endovascular Treatment for Patients With Acute Stroke Who Have a Large Ischemic Core and Large Mismatch Imaging Profile. *JAMA Neurology*. 2017;74(1):34. doi:10.1001/jamaneurol.2016.3954

14. Campbell B, Majoie C, Albers G et al. Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. *The Lancet Neurology*. 2019;18(1):46-55. doi:10.1016/s1474-4422(18)30314-4

15. Lansberg M, Straka M, Kemp S et al. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. *The Lancet Neurology*. 2012;11(10):860-867. doi:10.1016/s1474-4422(12)70203-x

16. Gupta A, Schaefer P, Chaudhry Z et al. Interobserver Reliability of Baseline Noncontrast CT Alberta Stroke Program Early CT Score for Intra-Arterial Stroke Treatment Selection. *American Journal of Neuroradiology*. 2012;33(6):1046-1049. doi:10.3174/ajnr.a2942

17. Freidrich B, Monch s, Berndt M et al. Software-Based, Automated Calculation of the ASPECT Score In Patients Suffering From Emergent Vessel Occlusions in the Anterior Circulation – Clinical Feasibility And Reliability: European Stroke Organisation Conference: Late Breaking Abstracts. *European Stroke Journal*. 2018;3(1_suppl):587-620. doi:10.1177/2396987318773967

18. Wolpert SM, Bruckmann H, Greenlee R et al. *American Journal of Neuroradiology* Jan 1993, 14 (1) 3-13.

19. Pechlaner R, Knoflach M, Matosevic B et al. Recanalization of Extracranial Internal Carotid Artery Occlusion after i.v. Thrombolysis for Acute Ischemic Stroke. *PLoS ONE*. 2013;8(1):e55318. doi:10.1371/journal.pone.0055318.

20. Grossberg J, Haussen D, Cardoso F et al. Cervical Carotid Pseudo-Occlusions and False Dissections. *Stroke.* 2017;48(3):774-777. doi:10.1161/strokeaha.116.015427

21. Mazya M, Egido J, Ford G et al. Predicting the Risk of Symptomatic Intracerebral Hemorrhage in Ischemic Stroke Treated With Intravenous Alteplase. *Stroke*. 2012;43(6):1524-1531. doi:10.1161/strokeaha.111.644815

22. Zaidat O, Yoo A, Khatri P et al. Recommendations on Angiographic Revascularization Grading Standards for Acute Ischemic Stroke. *Stroke*. 2013;44(9):2650-2663. doi:10.1161/strokeaha.113.001972

23. Cella D, Lai J, Nowinski C et al. Neuro-QOL: Brief measures of health-related quality of life for clinical research in neurology. *Neurology*. 2012;78(23):1860-1867. doi:10.1212/wnl.0b013e318258f744

24. Albers G, Lansberg M, Kemp S et al. A multicenter randomized controlled trial of endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE 3). *International Journal of Stroke*. 2017;12(8):896-905. doi:10.1177/1747493017701147

25. Lai T, Lavori P, Liao O. Adaptive choice of patient subgroup for comparing two treatments. *Contemporary Clinical Trials*. 2014;39(2):191-200. doi:10.1016/j.cct.2014.09.001

26. Lai T, Lavori P, Tsang K. Adaptive enrichment designs for confirmatory trials. *Statistics in Medicine*. 2018;38(4):613-624. doi:10.1002/sim.7946

27. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical tria. *Biometrics.* 1975;31:103–115

28. Azur MJ, Stuart EA, Frangakis C, et al. Multiple imputation by chained equations: What what is it and how does it work? Int J Methods Psychiatr Res. 2011;20:40-49

Appendix A: Minimization Randomization Algorithm

Randomization will be done in the emergency room using a web-based dynamic randomization system. Covariate adaptive randomization is planned to be developed and implemented to balance the distributions of important key baseline variables between the two treatment arms. The key variables include **age (<60, 60-69, 70-79, 80-85 years old)**, **presentation NIHSS (6-9, 10-15, 16-20, >20)**, **center**, **clot location (M1, ICA)**, **treatment time window (0-8, 9-16, 17-24 hours from onset to randomization time)**, **CTP/MRP core volume (<50cc, 50-100cc, >100cc), presence or absence of target mismatch profile (mismatch ratio ≥ 1.8 & mismatch volume ≥ 15 cc)** and **hemisphere (right, left)**.

The randomization algorithm we are going to implement is the algorithm developed by Pocock and Simon (1975), i.e., minimization method. Through this algorithm, the assignment of a new patient to a treatment group is determined so as to minimize the differences between the groups in terms of these important key baseline variables. Unlike traditional stratified randomization, the minimization method works toward minimizing the total imbalance for all factors together instead of considering mutually exclusive subgroups, that is, we will not creating these mutually exclusive subgroups during the randomization. Therefore, this approach is not restricted by the number of variables and possible combinations of levels of balancing factors.

Details of the minimization randomization algorithm and its implementation

Part I: Specification

This section provides a general framework for a study with the implementation of the minimization algorithm proposed by Pocock and Simon (1975).

Assumptions and Notations:

Assume there are K treatments denoted as $T_1, T_2, \dots, T_K$ with the randomization ratio as 1:1:…:1.

Assume there are S variables to be balanced in the minimization algorithm denoted as $X_1, X_2, \dots, X_S$.

For the variable X_f, suppose there are Q_f levels and denote the level of X_f as $Z_f \in \{1, \dots, Q_f\}$.

Algorithm:

When a new patient enters to the study, denote the observed level of the variable X_f for this patient as l_f, $f = 1, \dots, S$.

Step 1: Calculate the number of existing patients who are at the same level of the variable X_f as this patient in treatment k, denoted as $N_k(Z_f = l_f)$, $k = 1, \dots, K$. So we can obtain $N_1(Z_f = l_f)$, $N_2(Z_f = l_f)$,…, $N_K(Z_f = l_f)$.

Step 2: Regarding to the variable X_f, if we assign this patient to treatment k, we should have $N_k(Z_f = l_f)$+1 patients at treatment k who have the same level of the variable X_f as this patient. We obtain the amount of imbalance which would arise by assigning the patient to treatment k as

$$I_k(Z_f = l_f) = D(N_1(Z_f = l_f),\dots, N_k(Z_f = l_f) + 1,\dots, N_K(Z_f = l_f)).$$

Here, $D(\boldsymbol{a})$ is a function to measure the amount of variation for any set of non-negative integers $\boldsymbol{a}$. Then we can calculate the overall imbalance for all S variables arising when assigning the patient to treatment k by taking a weighted average, that is,

$$G_k = \sum_{f=1}^{S} w_f I_k(Z_f = l_f), k = 1, \ldots, K,$$

where w_f denotes the weight for the variable X_f.

Step 3: Find k^*=$\underset{k}{\operatorname{argmin}}\, G_k$ and assign the patient to treatment $k^*$with the highest probability among all treatments.

If we consider variance function for D, according to Freedman and White (1978), the total imbalance arising when assigning the patient to treatment k can be simplified as follow

$$G_k = 2(\sum_{f=1}^{S} w_f N_k(Z_f = l_f))/(K-1) + constant,\ k = 1, \ldots, K.$$

Therefore, k^*=$\underset{k}{\operatorname{argmin}} \sum_{f=1}^{S} w_f N_k(Z_f = l_f)$

Part II: Implementation in SELECT2

Two treatment groups: T_1 and T_2 with 1:1 ratio.

	Level	Weight
age	**<60, 60-69, 70-79, 80-85 years old**	4
presentation NIHSS	**6-9, 10-15, 16-20, >20**	4
clot location	**M1, ICA**	3
treatment time window from onset to randomization time	**0-8, 9-16, 17-24 hours**	3
CTP/MRP core volume	**<50cc, 50-100cc, >100cc**	2
Target mismatch profiles	**mismatch ratio ≥ 1.8 & mismatch volume ≥ 15 cc, mismatch ratio < 1.8 or mismatch volume < 15 cc or both**	

hemisphere	**right, left**	1
center		1

For the first patient to be enrolled, we assign this patient to one of the treatments using equal randomization. Then before we assign next patients, we will calculate G_1 and G_2, if $G_1 > G_2$, then assign next patient to T_2 with a probability p. Here, we set $p = 0.9$; if $G_1 = G_2$, then assign patient to T_2 with probability 0.5; if $G_1 < G_2$, then assign patient to T_2 with probability=1-$p = 0.1$.

References

Pocock, S.J. and Simon, R., Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics.* v31. 103-115.

Pocock, S.J., Allocation of Patients to Treatment in Clinical Trials. *Biometrics.* v35. 183-197

Freedman, L.S. and White, S.J., On the use of Pocock and Simon's method for balancing treatment numbers over prognostic factors in the controlled clinical trial. *Biometrics*. v32. 691-694

Appendix B. Efficacy and futility bounds for interim and final analysis

At the lth interim analysis, let W_i^l be the sum of the ranks of Rankin scores from the endovascular group in the patient subgroup Π_i, $j = 1, \dots, J$. In our trial, we defined J =6 groups with Π_J denotes the entire patient population and $\Pi_1 \dots, \Pi_5$ denote the subgroups of G1A, G1A+G1B, G1A+G1B +G2A, G1A+G1B +G2A +G2B, G1A+G1B +G2A +G2B +G3A, respectively.

The standardized Wilcoxon statistic for patient subgroup Π_i is

$$Z_i^l = \left\{ W_i^l - \frac{n_i^l\left(n_i^l + n_{0i}^l + 1\right)}{2} \right\} / \left\{ \frac{n_i^l n_{0i}^l\left(n_i^l + n_{0i}^l + 1\right)}{12} \right\}^{1/2},$$

where, n_i^l and n_{0i}^l denote the numbers of patients enrolled into the endovascular group and medical management group at the lth interim analysis, respectively.

At the lth interim analysis, we will terminate the trial and claims efficacy for the endovascular group if the following efficacy bound is crossed, that is,

$$Z_J^l \geq b.$$

Otherwise, we will proceed to the subgroup selection if the following futility bound is crossed, that is,

$$\widetilde{Z_J^l} \leq \tilde{b},$$

where

$$\widetilde{Z_J^l} = \left\{ W_i^l - \frac{n_i^l\left(n_i^l + n_{0i}^l + 1\right)}{2} - n_i^l n_{0i}^l \theta \right\} / \left\{ \frac{n_i^l n_{0i}^l\left(n_i^l + n_{0i}^l + 1\right)}{12} \right\}^{1/2}.$$

When the above criteria is satisfied, a subgroup $\hat{I}$ with the largest value of Z_i^l for $i \neq J$ is chosen. The future enrollment of the trial will include patients of this subgroup only, while the maximum total sample size is still N=560.

Similar to testing the efficacy and futility in the entire population, at stage l', we will terminate the trial and claim efficacy for the endovascular group in this selected subgroup if the following efficacy bound is crossed

$$Z_{\hat{I}}^{l'} \geq b.$$

We may also terminate for futility if

$$\widetilde{Z_{\hat{I}}^{l'}} \leq \tilde{b}.$$

If neither the efficacy nor futility bound for the entire population ever occurs, the trial proceeds to the final stage and we terminate the trial and claim efficacy for the endovascular group if

$$Z_J^{l=3} \geq c.$$

Under our design setting (maximum sample size N=560 and conducting interim analysis at N=200 and N=380 with type I error at 0.025 and power at 0.9), we obtain $b = 2.604, \tilde{b} = -1.897, c = 2.772$ for our efficacy and futility boundaries. We assume θ to be the projected treatment effect given the maximum sample size for testing the hypothesis: $H_0: P(Y \leq X) = \frac{1}{2}$, $H_A = P(Y \leq X) = \frac{1}{2} + \theta$ using the fixed-sample-size test and is calculated as $\frac{(Z_{1-\alpha}+Z_{1-\beta})}{\sqrt{3N}} = 0.0791$. Here, Y denotes the Rankin score in the medical management group and X denotes the Rankin score in the endovascular group. The rationale of this set-up is detailed in section 3.1 of Lai et al (2014).

Reference

Lai T, Lavori P, Liao O. Adaptive choice of patient subgroup for comparing two treatments. *Contemporary Clinical Trials*. 2014;39(2):191-200. doi:10.1016/j.cct.2014.09.001

Lai T, Lavori P, Tsang K. Adaptive enrichment designs for confirmatory trials. *Statistics in Medicine*. 2018;38(4):613-624. doi:10.1002/sim.7946

Appendix C. List of Approved Devices to be used in the SELECT2 Protocol:

Stent-Retriever Devices:

1. K173352 - Trevo ProVue Retriever and Trevo XP ProVue Retriever
2. K162539 - Solitaire 2 Revascularization Device
3. K173452 - EmboTrap II Revascularization Device
4. K203219 - Trevo XP ProVue Retriever, Trevo NXT ProVue Retriever
5. K193576 - Solitaire Platinum and Solitaire X Revascularization Devices
6. K193063 - Embotrap III Revascularization Device
7. K203592 - Tigertriever and Tigertriever 17 Revascularization Device

Aspiration Devices:

1. K173761 - Penumbra System (Reperfusion Catheter JET 7)
2. K173200 - SOFIA Plus Aspiration Catheter
3. K183464 - AXS Universal Aspiration System
4. K191768 - AXS Vecta Aspiration System
5. K190338 - Zenith Flex Aspiration System
6. K193380 - Cerenovus Large Bore Catheter; Cerenovus Aspiration Tubing Set
7. K201689 - Riptide Aspiration System
8. K202182 - ZOOM Reperfusion Catheters; ZOOM Aspiration Tubing
9. K211476 - ZOOM 71 Reperfusion Catheter; ZOOM Aspiration Tubing