THUNDER: Acute Ischemic Stroke Study with the Penumbra System® including **Thunder**bolt™ Aspiration Tubing

Protocol

CLP 21340.D

Date of Protocol

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Product Name

Penumbra System including Thunderbolt Aspiration Tubing

Sponsor

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CLP 21340.D Protocol Synopsis	
Study Title:	**THUNDER**: Acute Ischemic Stroke Study with the Penumbra System® including **Thunder**bolt™ Aspiration Tubing
Study Objective:	The objective of this study is to demonstrate the safety and efficacy of the Penumbra System including Thunderbolt Aspiration Tubing (Thunderbolt) in a population presenting with acute ischemic stroke (AIS) secondary to intracranial large vessel occlusion (LVO) who are eligible for mechanical thrombectomy.
Study Design:	Prospective, single-arm, multi-center study that will enroll up to 235 participants at up to 35 sites
Indication:	As part of the Penumbra System, the Thunderbolt Aspiration Tubing is indicated to connect the Penumbra Reperfusion Catheters to the Penumbra Aspiration Pump.
Patient Population:	Patients presenting with acute ischemic stroke (AIS) secondary to intracranial large vessel occlusion (LVO) who are eligible for aspiration based mechanical thrombectomy.
Study Device:	Penumbra System including Thunderbolt Aspiration Tubing
Study Duration:	It is anticipated this study will take approximately 2-3 years. All participants will be followed for approximately 90 days or to outcome (e.g. withdrawal, death), whichever occurs first. Participants enrolled that did not receive intervention with the Penumbra System including Thunderbolt will be followed out to 72 hours of enrollment or discharge (whichever comes first) for safety.
Follow-up:	Participants will undergo follow-up at the following timepoints: 24 hours, 7-10 days and/or discharge, 30- and 90-days post-procedure
Inclusion Criteria:	1. Patient age 18 - 80 years 2. Treatment within 8 hours of symptom onset 3. Pre-stroke mRS 0-2 4. Patient experiencing acute ischemic stroke secondary to intracranial large vessel occlusion in the internal carotid, middle cerebral (M1 or M2), basilar, or vertebral artery

CLP 21340.D Protocol Synopsis	
Study Title:	**THUNDER**: Acute Ischemic Stroke Study with the Penumbra System® including **Thunder**bolt™ Aspiration Tubing
	5. If patient is eligible for thrombolytic therapy, it was administered as soon as possible, and no later than 3 hours from stroke symptom onset 6. Planned frontline treatment with Penumbra System including Thunderbolt modulated aspiration 7. Informed consent obtained per Institution Review Board/Ethics Committee requirements
Exclusion Criteria:	1. Stenosis, excessive tortuosity, or any occlusion in a proximal vessel requiring treatment or preventing access to the thrombus 2. Alberta Stroke Program Early CT Score (ASPECTS) ≤6 or core infarct volume >50 mL on MRI or CT-based imaging (for anterior circulation strokes) 3. Pregnant patient 4. Life expectancy < 90 days due to comorbidities 5. Current participation in an interventional drug or device study that may confound the results of this study. Studies requiring extended follow-up for products that were investigational but have since become commercially available are not considered investigational studies 6. Other medical, behavioral, or psychological conditions that in the opinion of the Investigator could limit the patient's ability to participate in the study, including compliance with follow-up requirements, or that could impact the scientific integrity of the study
Primary Endpoint:	• Angiographic revascularization of the occluded target vessel at immediate post-procedure as defined by mTICI 2b or higher.
Secondary Endpoints:	• Angiographic revascularization of the occluded target vessel after first pass as defined by mTICI 2b or higher • Angiographic revascularization of the occluded target vessel at immediate post-procedure as defined by mTICI 2c or higher • Time to revascularization • Modified Rankin Scale (mRS) 0-2 at 90 days

CLP 21340.D **Protocol Synopsis**	
Study Title:	**THUNDER**: Acute Ischemic Stroke Study with the Penumbra System® including **Thunder**bolt™ Aspiration Tubing
	• Occurrence of symptomatic intracranial hemorrhages (sICH) at 24 hours • All-cause mortality at 90 days • Incidence of device related, and/or procedure related Serious Adverse Events (SAEs) within 24 hours post-procedure
Statistical Analysis:	**Efficacy:** The null hypothesis of a mTICI 2b-3 less than or equal to 71.5% ($H_0 : p_{TICI} \leq 0.715$) will be tested against the alternative hypothesis of a mTICI2b-3 greater than 71.5% ($H_1 : p_{TICI} > 0.715$) with a one-group binomial test at the one-sided $\alpha = 0.025$ level.
Sample Size Justification	**Efficacy:** Assuming 80% of participants achieve mTICI 2b or higher, a sample size of 211 participants has 80% power to detect an mTICI 2b-3 rate that is greater than 71.5%. The sample size was adjusted to 235 participants to account for up to 9% attrition. Up to 235 patients will be enrolled in order to provide 211 evaluable participants treated with Thunderbolt.

1 Introduction and Rationale

Approximately 800,000 people in the United States and 1.1 million people in Europe experience a new or recurrent stroke each year.[1,2] Of these, approximately 87% are ischemic and 13% are hemorrhagic.[1] Strokes account for 1 in every 20 deaths in the United States, resulting in an annual mortality of 133,103 deaths/year.[1] The literature suggests that the majority of these deaths are caused by intracranial large vessel occlusions (LVO).[3] Occlusions of the basilar artery, internal carotid artery terminus, and the M1 segment of the middle cerebral artery (MCA) are associated with particularly high mortality rates.[4-6]

Substantial evidence in the published literature suggests that early recanalization of the occluded vessel improves clinical outcome.[7] The likely basis for this correlation is that although some brain tissue experiences near immediate and irreversible infarction during acute stroke, there remains a region of ischemic penumbra surrounding this area where at-risk tissues can be salvaged.[8] If timely recanalization can be affected and reperfusion established, then damage to the penumbra region might be reversed, leading to reduced neurologic deficit and reduced stroke-related mortality and morbidity.[9-13]

The Penumbra System® is a mechanical neuro-thrombectomy system and was the first system specifically designed to remove thrombus through aspiration.[14,15] The Penumbra System received 510(k) clearance from the US FDA for an acute ischemic stroke (AIS) revascularization indication, CE-mark for commercialization in Europe, and approval in specific Asian countries based on data from the Penumbra Pivotal Stroke Trial.[15] The results indicated that the Penumbra System was able to revascularize the site of primary occlusion in over 80% of the patients with a favorable procedural event rate when compared to the published rates for other intra-arterial interventions for acute stroke.[16-19] The safety and efficacy of the Penumbra System were confirmed in a multicenter post-market trial in Europe and the US,[14] and more recently completed concurrent randomized controlled trials showing the superior safety and efficacies of the mechanical thrombectomy devices.[20-23]

Further Penumbra System technology advancements enabled the development of new aspiration thrombectomy approaches including ADAPT (A Direct Aspiration First Pass Technique) – aspiration alone applied directly at the face of the clot using a 5MAX reperfusion catheter as the primary device.[24]

The ASTER and COMPASS trials provided additional evidence of ADAPT as an effective frontline thrombectomy treatment with similar safety and functional outcomes to stent retrievers. In the ASTER trial[25] (a European multi-center randomized trial), 85.4% of patients undergoing aspiration as frontline therapy (primarily using the Penumbra System with ACE64 or 5MAX) achieved the primary endpoint of TICI 2b/3 at the end of the procedure compared with 83.1% of patients in the stent retrievers group ($p = 0.53$), with no difference in groups for mRS scores or for rates of symptomatic intracranial hemorrhage (sICH) at 24 hours or procedure-related adverse events.[25] The results of the COMPASS trial, a prospective randomized multicenter trial of stroke patients treated with either

ADAPT (primarily using the Penumbra System with ACE68 or ACE64) or stent retriever as frontline approach, demonstrated no difference in primary outcomes between the groups.[26] The trial enrolled 270 patients across 15 centers with anterior circulation stroke who presented within 6 hours of onset. Good functional outcome (mRS 0-2) at 90 days in the aspiration group was 52% vs 49% in stent retriever group (p=0.0014 for non-inferiority). The safety outcomes including 90-day all-cause mortality (22% vs 22%), any ICH (36% vs 34%) and sICH (6% vs 6%) were similar between the aspiration and stent retriever groups. Time to successful revascularization was faster with aspiration (22 mins vs 33 mins, p = 0.02) and rate of successful revascularization was similar between groups (92% aspiration vs 89% stent, p = 0.54). Additionally, the investigators concluded that there was a significant benefit towards ADAPT in terms of cost reduction as compared to a stent-retriever frontline approach.

Another thrombectomy technique that emerged is the combined technique – use of a stent retriever (e.g. Penumbra 3D Revascularization Device) together with aspiration through a reperfusion catheter at the site of occlusion for thrombus extraction. The randomized multi-center Penumbra 3D trial included second-generation 4MAX, 5MAX, and ACE60 reperfusion catheters and demonstrated that treatment with the Penumbra 3D Revascularization Device and aspiration was non-inferior to aspiration alone with 15% non-inferiority margin.[27] There was no difference in safety, functional outcome, mortality, and sICH between the two groups. Successful reperfusion immediately post-procedure was reported in 87.2% (3D with aspiration) and 82.3% (aspiration alone) of patients with a difference of 4.9% (90% CI, -3.6% to 13.5%) between both groups. In a meta-analysis of MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT from the HERMES collaboration, the control group receiving best medical therapy (n=653) showed 26.5% functional independence, while the endovascular therapy (EVT) group, which primarily used currently available stent retrievers, (n=634) showed functional independence in 46.0%.[28] In the 3D study, both groups demonstrated higher functional independence at 45.3% (3D with aspiration) and 45.8% (aspiration alone) than the HERMES control group of patients with best medical therapy, but these rates were comparable to the EVT group treated with other intra-arterial mechanical thrombectomy devices.[27]

PROMISE, a prospective, single-arm, multi-center European study enrolling 204 patients across 20 sites, provided evidence in support of ADAPT using the Penumbra System with larger bore (ACE68 and ACE64) reperfusion catheters as a frontline approach in AIS patients. Successful revascularization was achieved in 93.1% of patients post-procedure – 70.6% with aspiration alone. A stent retriever was used as an adjunctive device after aspiration in 21% of participants. The median procedure time was 31 minutes (interquartile range [IQR], 20–53 min). Good functional outcome at 90 days was achieved in 61% of patients. The low mortality rate (all-cause mortality at 90 days, 7.5%) and strong safety profile (sICH at 24 hours, 2.9%; embolization in new territories [ENT], 1.5%) affirmed that aspiration is a safe and effective frontline treatment.[29]

COMPLETE, a global registry, provided evidence in support of safety and performance of Penumbra system with 3D Revascularization device or ADAPT technique with larger bore reperfusion catheters (primarily ACE68, Penumbra JET 7 and Penumbra JET D) as frontline approach in patients with acute ischemic stroke. It was a prospective, single-arm, multi-center study that enrolled 650 patients with anterior or posterior circulation stroke and including a cohort of patients with ASPECTS<6 across 42 US and European centers. The rate of successful revascularization was 87.8%, the rate of good functional outcome at 90 days was 55.8%, and the rate of all-cause mortality at 90 days was 15.5%. Median procedure time was 27 mins (IQR 16–44 min). Procedural complication rates were low, with an sICH rate of 3.8% and ENT rate of 2.8%, providing evidence that aspiration with larger bore catheters is a safe and effective frontline treatment.

Modulated or cyclical aspiration has been studied as a possible method for improving the efficiency of clot removal. An initial proof of concept study involving a flow model, a three-way valve, and vacuum source found that modulated aspiration outperformed sustained aspiration in overall clot removal and removal speed ($p < 0.001$).[30] Similarly, a benchtop study involving modulated aspiration (18-29 inHg, 0.5 Hz) with the digital CLEAR Aspiration System (Insera Therapeutics, Sacramento, CA) compared to static aspiration (29 inHg) found that modulated aspiration increased the rate of complete clot ingestion and that complete clot ingestion was associated with significantly higher rates of complete first pass recanalization compared to partial ingestion ($p < 0.0001$).[31] Device is approved in EU (CE Mark) and not available for commercial use in US.

In 2021, Kalousek et al published results of a prospective observational cohort study of 40 consecutive patients who underwent modulated aspiration thrombectomy using the CLEAR Aspiration System.[32] Of the 38 patients who met criteria for LVO, first pass recanalization to TICI 2c or 3 was achieved in 76% (29/38) compared with the historical control rate of 28% (2440/9082); $p = 0.0001$.[32] Additionally, at 90 days, they observed high rates of good functional outcomes (mRS 0-2, 85% [32/38]) and low mortality (5% [2/38]).[32] There were no symptomatic intracerebral hemorrhages and no device-related serious adverse events.[32]

Mechanisms to achieve complete recanalization with a single thrombectomy device pass (i.e. First Pass Effect [FPE]) may become increasingly important as a means to reduce procedure times and improve clinical outcomes. In their analysis of the North American Solitaire Acute Stroke Registry database, Zaidat et al found that patients in the FPE group had significantly faster median time to revascularization (34 versus 60 minutes, $p = 0.0003$) and that FPE was an independent predictor of good clinical outcome (mRS 0-2 at 90 days was achieved in 61.3% with FPE versus 35.3% for non-FPE, $p = 0.013$ [OR 1.7, 95% CI 1.1 to 2.7]).[33]

With the results of Penumbra's 3D trial, ASTER, COMPASS, PROMISE, and COMPLETE, the ADAPT technique is considered a safe and effective treatment

for patients with LVO. The latest Penumbra System technology will be utilized in this study.

2 Study Device

2.1 Penumbra System® with Thunderbolt™ Aspiration Tubing (Thunderbolt)

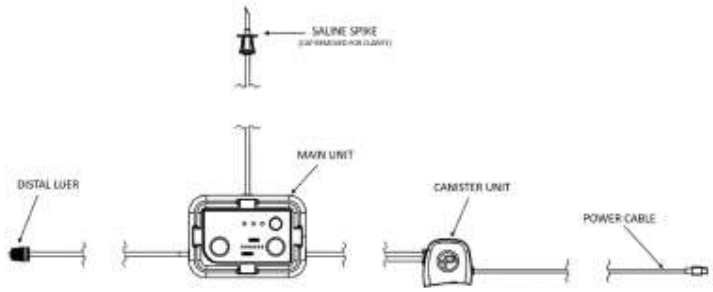
The Penumbra System, which includes Penumbra Reperfusion Catheters and the Penumbra Aspiration Pump, is a medical device system designed to remove thrombus and restore blood flow in the neurovasculature using aspiration. The Thunderbolt Aspiration Tubing (Thunderbolt) will be a component of the Penumbra System and is designed to serve as a conduit to assist in thrombus removal and restoration of blood flow in the vasculature. Thunderbolt can provide modulated aspiration or continuous aspiration. The device facilitates the transfer of vacuum between the Reperfusion Catheter and Penumbra Aspiration Pump; and can modulate the pressure delivered to the catheter by alternating between connecting the catheter to the Penumbra Aspiration Pump vacuum and ambient pressure saline in a predetermined modulated aspiration sequence.

Thrombus removal is accomplished using the aspiration components of the Penumbra System. A Reperfusion Catheter is advanced into the thrombus and Thunderbolt Aspiration Tubing is connected to the Reperfusion Catheter via a luer connection. The flow path is completed by attaching the Thunderbolt Canister Top Unit to the Penumbra ENGINE Pump / Canister via the Suction Connector and inserting the Saline Spike into a saline bag. Control buttons on the Thunderbolt Main Unit allow the physician to control flow. Thrombus is removed using aspiration.

There are potential clinical benefits using Thunderbolt. The Thunderbolt Aspiration System may lead to the removal of clot from the brain in a single pass. It may also ingest clot all the way into the clot cannister. By ingesting clot into the canister, physicians may be able to reduce catheter exchanges, further reducing procedure times. This could potentially reduce the risk of clot breaking off and traveling distally within the vessel as it is pulled into the guide catheter.

In addition, through its dynamic modulated technology, the Thunderbolt Aspiration System may allow physicians to utilize smaller, more navigable catheters which could potentially allow them to track to the site of the clot more efficiently, possibly reducing overall case times.

Figure 1: Thunderbolt



3 Risk Analysis

Testing has been completed to ensure that the Thunderbolt does not pose a significant risk. Safety has been demonstrated through pre-clinical testing in both bench-top and in vivo models. A thorough risk analysis was performed in accordance with quality system regulations under 21 CFR 820. Risk management activities performed in accordance with ISO 14971 did not identify any different risks or risk levels compared to other currently marketed devices.

3.1 Angiography

An angiographic procedure requires that a catheter be placed into the body, and in this case, threaded through the body to the neurovasculature. Once the catheter is in the proper position, contrast media is infused through the catheter to examine the vessels. Patients may encounter bleeding from vessel perforation, vessel spasm, swelling, or bruising at the access site where the catheters are placed in the body (usually the groin area). Additionally, once the catheter reaches the neurovasculature, there is a chance that the catheter could cause bleeding, hematoma, vessel thrombosis, dissection, distal embolization, pseudoaneurysm, and arteriovenous fistula formation. Patients who are allergic to contrast media are at further risk and may experience a reaction that may include hives, itching, nausea, or breathing difficulty. Contrast media may also cause kidney damage in some patients. The above risks of angiography are well known and generally unlikely to occur. However, if any of the above risks occur and are severe enough, patient death is possible.

3.2 Computed Tomography Scan (CT Scan) and Magnetic Resonance Imaging (MRI)

The risks encountered during a CT scan are low. The risks mentioned above for contrast media allergy are possible with a CT scan. There is also a slight risk of injury from being exposed to the radiation associated with a CT scan; however, the levels of radiation, and the risks associated with radiation exposure are low.

MRI does not use ionizing radiation. There are no known harmful side effects associated with temporary exposure to the strong magnetic field used by MRI scanners.

3.3 Thrombectomy

Possible complications (potential adverse events) include, but are not limited to the following:

- allergic reaction and anaphylaxis from contrast media
- acute occlusion
- air embolism
- arteriovenous fistula
- death
- device malfunction
- distal embolization
- emboli
- false aneurysm formation
- hematoma or hemorrhage at access site
- inability to completely remove thrombus
- infection
- intracranial hemorrhage
- ischemia
- kidney damage from contrast media
- neurological deficits including stroke
- vessel spasm, thrombosis, dissection, or perforation
- radiation exposure that may lead to cataracts, skin reddening, burns, alopecia, or neoplasia from x-ray exposure

Testing has been completed to ensure that the Penumbra System does not pose a significant risk. Testing includes both in vitro and in vivo testing. These anticipated adverse events are also listed in the Investigational Instructions for Use (IFU).

In addition, within this study, the following will be performed to minimize the risks:

- As per usual site practice, patients will be evaluated before entering the study to ensure that the location of the occlusion and the collaterals flow are appropriate for treatment with the Penumbra System.
- All sites will be assessed prior to being selected to ensure that either a stroke unit operating according to national stroke guidelines, or a physician experienced in treating patients presenting with AIS is available.
- Patients will be monitored as per site routine care and the study required follow-up period. The Investigator will examine and perform various diagnostic tests before, during, and after the procedure, at 7-10 day and/or at hospital discharge, 30 days, and 90 days after the procedure.

Use of the Penumbra System offers several potential benefits, which may include a higher success rate of revascularization with an acceptable device-related serious adverse rate. Based on the above information, the benefits of the Penumbra System outweigh the potential risks associated with its clinical use.

4 Study Overview

The primary aim of mechanical thrombectomy (MT) for the treatment of AIS due to LVO is to achieve a quick removal of blood clot from the brain arteries to achieve a higher rate of revascularization with an acceptable device and procedure-related serious adverse event rate. The purpose of this study is to collect data on the Penumbra System including Thunderbolt in a patient population with acute

ischemic stroke (AIS) secondary to intracranial large vessel occlusion (LVO) eligible for mechanical thrombectomy.

4.1 Study Design

This is a prospective, multicenter, single-arm study assessing the safety and efficacy of the Penumbra System including Thunderbolt in a patient population with AIS from LVO.

Data for each participant will be collected at the time of enrollment through final follow-up. Please refer to the Schedule of Assessments (Table 1) below for details.

4.2 Study Objectives

4.2.1 Primary Endpoint

- Angiographic revascularization of the occluded target vessel at immediate post-procedure as defined by mTICI 2b or higher.

4.2.2 Secondary Endpoints

- Angiographic revascularization of the occluded target vessel after first pass as defined by mTICI 2b or higher
- Angiographic revascularization of the occluded target vessel at immediate post-procedure as defined by mTICI 2c or higher
- Time to revascularization
- Modified Rankin Scale (mRS) 0-2 at 90 days
- Occurrence of symptomatic intracranial hemorrhages (sICH) at 24 hours
- All-cause mortality at 90 days
- Incidence of device related and/or procedure related Serious Adverse Events (SAEs) within 24 hours post-procedure

5 Study Population

The patient population will include patients with acute ischemic stroke (AIS) secondary to intracranial large vessel occlusion (LVO) eligible for mechanical thrombectomy.

5.1 Inclusion Criteria

1. Patient age 18 - 80 years
2. Treatment within 8 hours of symptom onset
3. Pre-stroke mRS 0-2
4. Patient experiencing acute ischemic stroke secondary to intracranial large vessel occlusion in the internal carotid, middle cerebral (M1 or M2), basilar, or vertebral artery

5. If patient is eligible for thrombolytic therapy, it was administered as soon as possible, and no later than 3 hours from stroke symptom onset
6. Planned frontline treatment with Penumbra System including Thunderbolt modulated aspiration
7. Informed consent obtained per Institution Review Board/Ethics Committee requirements

5.2 Exclusion Criteria

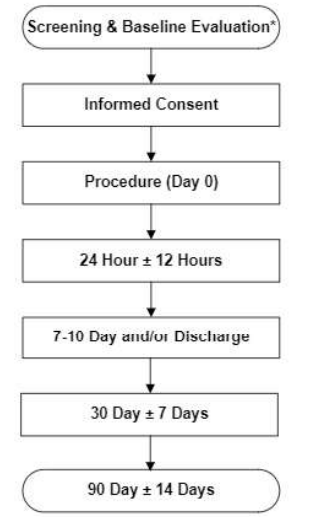
1. Stenosis, excessive tortuosity, or any occlusion in a proximal vessel requiring treatment or preventing access to the thrombus
2. Alberta Stroke Program Early CT Score (ASPECTS) ≤6 or core infarct volume >50 mL on MRI or CT-based imaging (for anterior circulation strokes)
3. Pregnant patient
4. Life expectancy < 90 days due to comorbidities
5. Current participation in an interventional drug or device studythat may confound the results of this study. Studies requiring extended follow-up for products that were investigational but have since become commercially available are not considered investigational studies.
6. Other medical, behavioral, or psychological conditions that in the opinion of the Investigator could limit the patient's ability to participate in the study, including compliance with follow-up requirements, or that could impact the scientific integrity of the study.

6 Study Procedures

6.1 Study Flow

The study allows for enrollment up to 235 participants at up to 35 sites.
Patients presenting with acute ischemic stroke (AIS) secondary to intracranial large vessel occlusion (LVO) should be assessed for eligibility. If a patient is enrolled, they will go through the visits outlined in Figure 2.

Figure 2: Study Flow



6.2 Study Visits

Participants enrolled in this study will follow the visit schedule:

- Screening and Baseline Evaluation
- Procedure
- 24-Hour Follow-Up (± 12 hours)
- 7-10 Day Follow-Up and/or Discharge (whichever comes first)
- 30 Day Follow-Up (± 7 days)
- 90 Day Follow-Up (± 14 days)

6.3 Screening

All sites will keep a screen failure log of all potential study candidates who are screened and not enrolled or screened, consented, and not enrolled. Reason(s) for exclusion will be recorded. Screening information including screen failures will be reported in Electronic Data Capture System (EDC).

Recruitment rates will be tracked over time for each site. The actual recruitment rates will be useful for planning further clinical trials and determining the widespread impact of the therapy.

6.4 Informed Consent

The Investigator or designee will obtain informed consent prior to the procedure from the patient or participant representative, using the current Institutional Review Board (IRB)/ Ethics Committee (EC) approved consent form per IRB/EC policy. A verbal consent using an IRB/EC approved oral script and short form is permitted.

All informed consent documents used under this protocol will be consistent with applicable elements of Good Clinical Practice (ICH E6), ISO 14155 Clinical investigation of medical devices for human subjects – Good Clinical Practice (GCP) and 21 CFR Part 50 Protection of Human Subjects and will be approved by the site's reviewing IRB/EC prior to study initiation.

Any modification to the FDA approved sample informed consent form made by the study site must be approved by the Sponsor and the IRB/EC before use. If essential elements of the informed consent template are removed, FDA approval will be required prior to use. Each study site will provide the Sponsor with a copy of the IRB/EC approved consent forms. Informed consent completion will be monitored regularly by the Sponsor.

6.5 Enrollment

A patient is considered enrolled once they or their representative have provided consent and all eligibility criteria have been confirmed. Participants enrolled but that did not receive intervention with the Penumbra System including Thunderbolt will be followed out to 72 hours of enrollment or discharge (whichever comes first) for safety.

Date of the procedure is day zero for calculating follow-up windows.

6.6 Baseline Evaluation

The participant will be clinically evaluated in the same manner as any patient presenting with AIS secondary to intracranial LVO. The medical history screen, available clinical/neurological exams (vital signs, NIHSS, and pre-stroke mRS) obtained, and imaging information will be evaluated to determine patient eligibility.

The CT or MR imaging performed to provide an initial diagnosis of AIS secondary to LVO. NCCT is the preferred modality. CT or MR image obtained closest to the procedure should be used for data entry in EDC.

The following assessments, at a minimum, will be performed:

- Vitals and review of medical history
- A pre-stroke mRS to assess the participant's level of function prior to the AIS
  - May not be performed by investigator performing the mechanical thrombectomy procedure
- The National Institutes of Health Stroke Scale (NIHSS)
  - May not be performed by investigator performing the mechanical thrombectomy procedure
- Non-Contrast Computed Tomography (NCCT), MR or CTA
- Digital Subtraction Angiography (DSA)
  - Define the angio-architecture of the occluded vascular segment
  - An assessment of collateral blood flow, particularly in cases of terminal internal carotid artery occlusion
  - Modified Thrombolysis in Cerebral Infarction **(**mTICI**)** scores
    - CTA or MRA is not an acceptable substitute for this assessment

    - Initial assessment of mTICI flow in the target vessel territory
- Record thrombolytic, antiplatelet, and anticoagulant medication use

6.7 Index Procedure

The angiogram will be performed prior to any treatment. mTICI scores are to be assessed throughout the procedure and in the final angiographic run using DSA. Index procedure DSA should be uploaded per Section 7.5 Image Upload. The intra-arterial (IA) procedure will then start as per routine care of the operator in performing mechanical thrombectomy with Penumbra System through a femoral access approach. If femoral access is not achieved, please document on the case report form access details. Frontline treatment is defined by devices used during the first pass of the mechanical thrombectomy procedure. Perioperative and post operative care will be dictated by the existing AHA guidelines for the management of stroke patients. Procedures should be performed as early as possible to ensure benefit, anesthetic technique should be determined based on individual assessment of patient risk factors as per 2019 Guidelines for Management of AIS and BP should be maintained at ≤180/105 during and for 24 hours after the procedure.[34]

Thunderbolt usage must follow the Investigational Instructions For Use.

The following data, at a minimum, will be captured:

- Type of Sedation
- Select intra-procedural meds
- Adverse Events
- Treatment Technique
- Device Accountability

6.8 24 Hour (± 12 Hours) Post-Procedure Follow-Up

The following assessments, at a minimum, will be performed:

- Neurological NIHSS status
    - Must be performed by blinded assessor that does not have previous knowledge of subject medical history or prior mRS and NIHSS scores. May not be performed by investigator performing the mechanical thrombectomy procedure
- NCCT/MR to assess hemorrhagic transformation based on ECASS definitions. NCCT is the preferred image modality.
    - NCCT/MR images should be uploaded per Section 7.5 Image Upload.
- Antiplatelet and anticoagulant medication use
- Adverse Event Review

In addition, any neurological deterioration should be evaluated by CT/MR scan and other evaluations as indicated according to Investigator/hospital routine care. Additional images related to Adverse Events may be requested for upload. This follow-up visit window is calculated from time of arterial puncture.

6.9 7-10 Day and/or Discharge

The following assessments, at a minimum, will be performed either at 7-10 days or at discharge if participant is discharged within 6 days post:

- Antiplatelet and anticoagulant medication use
- Adverse Event Review

In addition to the assessments above for all participants the following will be collected at discharge, at a minimum:

- The discharge location and date
- Antiplatelet and anticoagulant medication use
- Adverse Event Review

6.10 30 Day Follow-Up (± 7 Days)

30 Day Follow-up can be done in-person or over the telephone/telehealth.

The following assessments, at a minimum, will be performed:

- Adverse Event Review including mortality

6.11 90 Day Follow-Up (± 14 Days)

90 Day Follow-up can be done in-person or over the telephone/telehealth.

The following assessments, at a minimum, will be performed:

- mRS
  - Must be performed by blinded assessor that does not have previous knowledge of subject medical history or prior mRS and NIHSS scores. May not be performed by investigator performing the mechanical thrombectomy procedure
- Adverse Event Review

6.12 Follow-Up Post Study Completion

Investigators should conduct any follow-up after study completion in accordance with their routine care.

Table 1: Schedule of Assessments

ACTIVITY	Pre-Admission Evaluation	Screening & Baseline Evaluation	Procedure	24-Hr Follow-Up (± 12 hours)	7-10 Day and/or Discharge[4]	30 Day Follow-Up (± 7 Days)[5]	90 Day Follow-Up (± 14 Days)[5]
Informed[1] Consent		X					
Medical History		X					
Vitals		X					
CT/MR		X		X			
DSA		X	X				
ASPECTS		X					
mTICI[2]		X	X				
NIHSS		X[6]		X[6,7]			
mRS	X[6]						X[6,7]
Procedure			X				
Device Accountability			X				
Concomitant Medications[3]		X	X	X	X		
Adverse Event Review			X	X	X	X	X

1: Informed consent must be obtained prior to enrollment in the study
2: From DSA
3: Concomitant Medications to be recorded include thrombolytics, antiplatelet(s), and anticoagulant(s)
4: If discharge is before day 7, all assessments should be completed at discharge
5: In-person or over the telephone/telehealth
6: May not be performed by investigator performing the mechanical thrombectomy procedure
7: Must be performed by blinded assessor that does not have previous knowledge of subject medical history or prior mRS and NIHSS scores

7 Investigator Responsibilities

7.1 Institutional Review Board/Ethics Committee Approval

Prior to enrolling patients into the study, the investigator will ensure that proper IRB/EC approval is obtained in accordance with applicable local state and federal laws and regulations. The IRB/EC shall approve all study documents as appropriate, including but not limited to the final protocol, amendments to the protocol, IFU, and the informed consent, per 21 CFR 56; Institutional Review Boards or applicable EC requirements. The investigator should keep the IRB/EC informed of any serious adverse event, or serious device defects as per their policy.

The investigator will report to the Sponsor or designee immediately if the approval to conduct the investigation is withdrawn by the IRB/EC or Regulatory Authority. The report will include a complete description of the reason(s) for which approval was withdrawn.

7.2 Informed Consent

The investigator is responsible for ensuring that a completed informed consent form is obtained prior to conducting any research-related assessments in accordance with Section 6.4 of this protocol and country and local requirements.

7.3 Adherence to Protocol/Amendments and Applicable Law

The Investigator is responsible for overseeing and ensuring that the study is conducted according to this protocol and in accordance with the applicable aspects of ISO 14155, 21 CFR 812, Declaration of Helsinki, along with any conditions imposed by the reviewing IRB/EC, and all other applicable regulations. The Investigator shall approve and adhere to this protocol and any amendments that arise during the course of the study. The investigator is not allowed to deviate from the protocol except to protect the rights, safety, or well-being of human participants under emergency circumstances. No waivers from this protocol will be granted.

The Investigator has overall responsibility of the conduct of this study including oversight of all delegated individuals, tasks and all activities conducted under this protocol. It is the Investigator’s responsibility to ensure that site staff assisting with the study have the appropriate qualifications, are fully instructed on the study procedures, and will respect study confidentiality.

7.4 Case Report Form Completion

The Investigator and study staff shall complete the case report forms (CRFs) associated with this study. Participant numbers shall be used to identify individual participants in this study. The CRFs should be a complete and accurate record of participant data collected during the study according to relevant aspects of ISO 14155, 21 CFR 11, Electronic Records; Electronic Signatures and GCP requirements. It is the Investigator's responsibility to ensure the quality of the data collected and recorded is appropriate and collected in accordance with GCP and all applicable regulations. Data entry will be performed by the study site(s). Investigators are responsible for completion and timely submission of data to

Penumbra, Inc. Every reasonable effort should be made to complete data entry within 7 business days of data collection. If allowed by the site's Standard Operating Procedures (SOP) or policies, the Investigator and study staff may enter data directly into the CRFs. In this instance, the CRFs will be considered the primary data source. All sites who wish to enter data directly into the CRFs must document this decision in their Regulatory Binder.

7.5 Image Acquisition and Upload

Digital subtraction angiography (DSA) should be performed in AP and lateral projections for baseline evaluation, after each thrombectomy attempt, and to assess the final post-treatment result. DSA should be carried out at 2-3 frames per second through the venous phase and include the entire intracranial circulation.

NCCT should be performed using 3 to 5 mm thick sections, preferably 5 mm to minimize image noise (brain or soft tissue kernel reconstruction).

Pre-procedure and procedural DSA images as well as 24-hour CT scan will be uploaded to an image management system for Core Lab review. Additional images associated with adverse events may be uploaded, if collected per routine care. Required study images should be uploaded within 14 business days.

Study staff shall ensure that no images contain any personally identifying information about the participant or study site (e.g. Physician name, Institution name, participant name, address, insurance number, medical record etc.), procedural time stamps should remain.

7.6 Reporting

The investigator will be responsible for reporting the following:

7.6.1 Adverse Events

All adverse events (AE) must be assessed and recorded by the investigator, or designee, on the CRFs starting at enrollment through study exit.

Minimum requirements of data to be recorded are: adverse event term, event start date, seriousness, action taken, outcome and device or procedure-relatedness or causality.

To ensure prompt reporting of AEs, all reportable AEs (as well as all related study data) should be entered into the EDC within 7 business days. Any suspected UADE should be reported immediately upon site awareness by calling the Sponsor. All device related SAEs should be reported in the EDC within 48 hours of the site staff first being made aware of the occurrence of the SAE. Deaths should be reported immediately (within 24 hours) upon site awareness. If the EDC is unavailable, an email can be sent to Penumbra Inc.

The investigator must report adverse events to the IRB/EC according to their local reporting requirements. The investigator is responsible for reporting time frames and complying with local or national

requirements. In addition, the investigator will report to the sponsor and IRB/EC any device deficiencies that could have led to a SAE, if required by national regulations or by local authorities.

For the purposes of reporting within this protocol, pre-existing conditions or planned procedures for pre-existing conditions are not reportable as AEs unless there is worsening of the condition with an increase in severity or frequency during the study.

All deaths will be reported regardless of causality. When reporting a death, the primary condition or diagnosis that contributed to the fatal outcome should be reported as an SAE with an outcome of death. Only a single cause of death should be reported in EDC. If the cause of death is unknown, report “unknown cause of death” as an SAE.

7.6.2 Evaluation of Adverse Events

General adverse event and serious adverse event definitions can be found in the Appendix, Section 17.1.

A joint Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB) will be used for this study. A Sponsor Medical Monitor will review the pre-defined categories of adverse events as they are reported during the duration of the study. Based on the criteria listed in the CEC/DSMB Charter, the Sponsor Medical Monitor will request redacted source documents to assist in drafting adverse event(s) written narrative to be forwarded to the CEC/DSMB for adjudication. Additionally, aggregate reports of all adverse events, including SAEs, will be periodically reviewed by the CEC/DSMB to identify potential safety issues.

CEC/DSMB adjudication results will supersede the investigator-reported data in analyses of adverse events.

7.6.3 Relationship to the Study Device

A (S)AE is considered to be device-related when it is reasonable to believe that the event may have been caused by or is related to the study device performance.

The relationship between the use of the medical device and the occurrence of each adverse event shall be assessed and categorized. During causality assessment, clinical judgement shall be used and the relevant documents, such as the IFU, the Clinical Protocol or the risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed by these documents. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered. Relationship to the study device will

be classified for each (S)AE according to four different levels of causality. The definitions to be used to assess the relationship are found in Appendix, Section 17.2.

7.6.4 Device Deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of the study device including malfunction, use error or inadequacy in information supplied by the manufacturer shall be documented and reported through the standard commercial process (for commercial components) and/ or within the EDC. Investigators must report all possible device deficiencies with the device observed during the study. This includes unexpected outcomes or device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention has not be made or c) if circumstances had been less fortunate. Products with suspected device deficiencies should be returned to Penumbra Inc. for investigation.

Device manufacturers are required to report qualifying medical device incidents to the relevant national competent authorities. An incident is defined as “any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant or to a serious deterioration in their state of health.” A deterioration in state of health is not considered unanticipated if the condition leading to the event was considered in a risk analysis.

7.6.5 Protocol Deviation(s)

Deviations from the protocol identified by the Investigator, during monitoring, or through other means should be clearly documented in the CRF and source documents. Every reasonable effort should be made to report protocol deviations within 7 days of identification. For the purposes of this study, deviations being collected include, but are not limited to:

- Inclusion/exclusion criteria deviation(s)
- Informed Consent deviation(s)
- Missing endpoint visits
- Missing endpoint assessments
- Out of window endpoint assessments

7.7 Device Accountability

Sponsor or its designee will ship study devices to all sites. Devices must be stored in a secure area at the site and be accessible and controlled only by the assigned, trained study personnel at the site. The Investigator is

responsible for maintaining adequate records of the receipt and disposition of all study devices. These records should include:

- The type and quantity of the device, the date of receipt, and the study tracking number
- The names of all persons who received, used, or disposed of each device
- The number of devices that have been returned to Sponsor, discarded, or otherwise disposed of, and the reason for such action

A device accountability log will be provided for this purpose. When the study enrollment is complete, the Investigator shall return any unused devices.

The Investigator shall maintain records pertaining to device disposition which includes:

- Participant number
- Device lot number
- Expiration date
- Date used

The principal investigator will ensure that only trained and delegated physicians who are sub-investigators in this study will use Thunderbolt.

7.8 Records Retention

The investigator shall maintain the records associated with this study for a period of at least two years after either the date on which the investigation is completed or the date that the records are no longer required for supporting a premarket approval/notification submission, whichever is later.

The Investigator shall maintain the records associated with this study in accordance with the local/national regulations. These records may include but are not limited to the following:

- Correspondence with the Sponsor or designee, study committees, and other investigators
- Device accountability records
- Participant source records, including but not limited to: Informed Consent Forms, copies of all completed CRFs, and supporting documents (laboratory reports and reports of diagnostic tests, medical records, etc.)
- All versions of study protocol
- Documentation of protocol deviations
- Investigational IFU
- Reports of any serious adverse event or serious device effects
- A copy of all approvals related to the clinical investigation
- The approved, blank, informed consent form(s)
- All approval/acknowledgment letters from the IRB/EC for all versions of the study protocol, ICF and other documents

- Clinical Trial Agreement(s)
- Signed and dated curriculum vitae (CV) for study personnel
- Medical licenses or equivalent for the Principal Investigator and all participating sub-investigators
- Financial disclosure for the Principal Investigator and all participating sub-investigators
- All required regulatory documents such as, but not limited to, Delegation of Authority and training logs
- Signed Protocol Signature Page(s)

An electronic trial master file (eTMF) will be used as the master repository for Sponsor regulatory documents.

7.9 Financial Disclosure

The Investigator shall provide a financial disclosure to sponsor in accordance with 21 CFR 54. The investigator shall promptly update this information if any relevant changes occur during the investigation or for 1 year following completion of the study. Additionally, an updated financial disclosure form for each investigator will be collected at the completion of the study or if an investigator ends study participation prior to completion.

8 Sponsor Responsibilities

8.1 Training

The Sponsor is responsible for providing training on the protocol, study device, CRF completion, and image upload as applicable for all study staff per delegation of authority log or role on study.

8.2 Investigator List

The Sponsor shall keep a list of the names and addresses of the clinical investigators for the study, including the Investigator role.

8.3 Adverse Event Reporting

The Sponsor shall evaluate adverse event reports received from the study sites and found during data monitoring and shall report them to the appropriate regulatory bodies and other study sites as necessary.

8.4 Data Monitoring

The Sponsor is responsible for ensuring that the study is conducted according to the applicable aspects of the following regulations 21 CFR 812, ISO 14155. A list of monitors and respective contact information is maintained in the Sponsor eTMF. A Sponsor employee or designee will conduct the following site visits per the monitoring plan:

8.4.1 Site Qualification

Conducted to ensure the study site has the appropriate staff, facilities, and expertise to participate in the study. Investigator

agreement, Investigator CV and additional information on qualification of Investigators are collected prior to activation. To assess if Investigator was involved in termination or misconduct, publicly available websites are checked (e.g. FDA Debarment List). Site Qualification can be waived at the discretion of the sponsor.

8.4.2 Site Initiation

Conducted to train the study staff on use of the device, study requirements, and other relevant training.

8.4.3 Interim Monitoring

Conducted by Sponsor or designee per the monitoring plan, and/or as needed, to ensure the study site is operating in compliance with the protocol and local and federal regulations and continues to have the appropriate staff and facilities to conduct study related activities as indicated in the protocol.

To ensure that investigators and their staff understand and accept their defined responsibilities, the Sponsor will maintain regular correspondence and perform periodic monitoring visits during the course of the study to verify the continued acceptability of the facilities, compliance with the study plan, and maintenance of complete records. Clinical monitoring will include review and resolution of missing or inconsistent data and source document checks to ensure the accuracy of the reported data. Informed consent, CRFs and complete medical records for all enrolled and screen failed participants will be made available to the Sponsor for review and collection.

8.4.4 Site Close Out

Conducted to ensure all study, device, regulatory-related activities, and outstanding monitoring action items, have been resolved prior to site closure.

8.5 Data Management

CRFs will be used at all study sites. All study data will be entered into a commercially available web-based EDC system. Data entry will be performed by the study site personnel. Investigators are responsible for completion and timely submission of the data to the Sponsor. Every reasonable effort should be made to complete data entry within 7 days of data collection. This EDC system requires no on-site software installation or specific hardware to operate. Investigators, clinical coordinators, data managers, and Penumbra clinical personnel access project information and study data centrally via a web browser.

Automated data quality checks will display warnings for invalid data. Additionally, manual review of data listings may be performed, and manual queries created in the EDC system to highlight data discrepancies or inconsistencies for resolution by the study site. If CRF corrections are necessary, they will be made by the

Investigator or an authorized member of the Investigator's staff that is delegated to perform such activity in the EDC system. Questions or problems with submitted data will be addressed via queries in the EDC system, or through direct contact. The Investigator will review the CRFs for completeness and accuracy and provide his/her electronic signature and date to CRFs as evidence thereof. Any data items that have been changed after initial electronic signature will require reapplication of the electronic signature.

All study personnel will have an individual username and password to access the clinical study information based upon each individual's roles and responsibilities. The EDC system provides role-based user permissions for data entry, data viewing, and reporting.

All initial data entry and data updates, including the date and person performing the action, will be available via the audit trail, which is part of the EDC system.

All CRFs and data files will be secured to ensure confidentiality. Investigators are required to maintain source documents required by the protocol, including laboratory results, reports, supporting medical records, and Informed Consent Forms. The source documents will be used during the regular monitoring visits to verify information entered on the CRFs.

If the EDC system is unavailable, sites will complete a paper worksheet and provide it to the Penumbra clinical team for all reportable AE(s) and/or device deficiency(ies). The sites will be required to complete data entry in EDC system once the system is functional.

9 Ethical Requirements

9.1 Declaration of Helsinki

The study will be performed in accordance with the Declaration of Helsinki, ethical principles guiding physicians in medical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland (1964 and later revisions).

9.2 Informed Consent

The investigator is responsible for ensuring that a signed and dated informed consent is obtained in accordance with Section 6.4 of this protocol, as delegated by the site-specific Delegation of Authority, and according to country and local requirements.

9.3 Subject Data Protection

Every effort will be made to prevent data breach and protect participant's personal information within all applicable systems.

Each participant will be assigned a unique participant identification number at the time of enrollment. This participant identification number will be retained throughout the study. All CRFs will be tracked, evaluated, and stored using only the participant ID number. No personal identifying information will be included on the CRFs.

The informed consent form will notify participants that representatives of the sponsor and representatives of government agencies and ethics committees will have access to personal identifying information to ensure that data reported on the CRFs corresponds to the person who signed the consent form and the information contained in the source documentation.

10 Statistical Procedures

10.1 General Statistical Considerations

The efficacy analysis and safety analysis will be conducted in the modified intent-to-treat (mITT) population. The Statistical Analysis Plan (SAP) will provide details to further elaborate statistical methods as outlined in the protocol and will describe analysis conventions. The statistical analysis plan will be finalized prior to database lock.

All confidence intervals presented will be two-sided and statistical tests will be two-tailed with a significance level of 0.05 unless specified otherwise. Descriptive statistics will be provided for continuous variables (e.g. mean, standard deviation, median, inter-quartile range, minimum value, and maximum value) and frequency tables or proportions for discrete variables.

10.2 Sample Size Estimation for the Primary Outcome

The targeted sample size for this study 211 evaluable participants treated with Thunderbolt. To allow for up to 9% attrition, enrollment will be up to 235 participants.

The efficacy sample size estimate is based on an estimated incidence rate of 80% for the primary efficacy variable. This estimate is based on the mTICI 2b-3 post-Penumbra System rate seen in the 3D study All Patients Intent-to-Treat population. The efficacy performance goal for participants treated with Thunderbolt is 71.5%. A sample size of 211 participants has 80% power to detect a mTICI 2b-3 rate that is greater than 71.5%.

10.3 Control of Systematic Error and Bias

The study will be conducted under a common protocol for each study site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each study site.

For consistency of measurements and to reduce reader bias, an imaging Core Laboratory will be used for evaluation of pre-procedure, immediate post-procedure, and follow-up imaging. In determining patient eligibility for the study, the Investigator's assessment of pre-procedure imaging will be used. However, to control for intra-observer variability, the imaging Core Laboratory will determine the imaging results to be used in the data analysis.

An independent CEC/DSMB will be in place to review clinical events observed during the study.

The study secondary endpoint assessment of modified Rankin Scale (mRS) 0-2 at 90 days will be blinded. The NIHSS assessment for the secondary endpoint of symptomatic ICH at 24 hours will also be blinded.

10.4 Missing Data and Imputation Methods

Every effort is to be made to keep all missing data, particularly the secondary endpoint of modified Rankin Scale at 90 days, to a minimum. Despite the clinical sites' best efforts, some missing data may be inevitable mainly due to lost-to-follow-up. Analysis of the distribution of prognostic factors between participants with primary efficacy endpoint data and those without data will be reviewed for significance to assess selection bias. The primary analysis will be data as observed. Sensitivity analysis will be performed.

10.5 Definition of Populations

10.5.1 Screened

Screened patients are all patients considered for participation in the study, regardless of whether they complete informed consent.

10.5.2 Screen Failure

Screen failure patients are all patients considered for participation in the study, who failed to meet inclusion criteria or met exclusion criteria. These patients may or may not have signed an informed consent form.

10.5.3 Enrolled

Patients will be considered enrolled based on the criteria described in section 6.5.

10.5.4 Completed

All participants who were enrolled and completed the study follow-up or were known to have died prior to the follow-up timepoint are considered to have completed. The completed participant metric will be provided for the 72-hours or discharge follow-up for participants that did not receive intervention with the Penumbra System including Thunderbolt and the Day 90 follow-up for participants that received intervention with the Penumbra System attached to Thunderbolt.

10.5.5 Early Termination

Early termination participants are all participants who were enrolled but did not complete follow-up and were not known to have died. The early termination participant metric will be provided for the 72-hours or discharge follow-up for participants that did not receive intervention with the Penumbra System including Thunderbolt and the Day 90 follow-up for participants that received intervention with the Penumbra System including Thunderbolt.

10.6 Definition of Analysis Populations

10.6.1 Intent to Treat Sample

The ITT sample includes all participants who are enrolled. Participants are considered enrolled once they or their representative have provided consent and, all eligibility criteria have been confirmed whether or not Thunderbolt was used. Participants enrolled that did not receive intervention with the Penumbra System including Thunderbolt will be followed out to 72 hours of enrollment or discharge (whichever comes first) for safety and will be summarized separately in the clinical report.

10.6.2 Modified Intent to Treat Sample

In addition to the ITT sample, a modified Intent-to-Treat (mITT) sample is defined as a subset of the ITT sample. The mITT sample will include enrolled participants that met all eligibility including angiographic criteria with attempted use of the Penumbra System catheter including Thunderbolt (prepped for intervention) regardless of whether the device contacted the subject or not. This population is the primary population for all efficacy and safety parameters.

10.6.3 Per Protocol Sample

In addition to the defined mITT analysis sample, a per-protocol (PP) sample is defined as a subset of the mITT sample. The per-protocol sample will include all mITT participants that received intervention and do not have significant protocol deviations (e.g. major eligibility violation).

10.7 Interim Analysis

Interim analysis will not be performed in the study.

10.8 Statistical Analysis of Primary Efficacy Endpoint

The primary efficacy variable is the proportion of participants with post procedure mTICI 2b or greater. Revascularization is defined by a mTICI score of 2b to 3 following use of the Penumbra System and prior to the use of any additional therapies or adjunctive devices. Subjects with intracranial stenosis/atherosclerosis (ICAD) treated with stenting or angioplasty at primary target vessel occlusion location prior to achieving mTICI 2b or greater will be analyzed as efficacy endpoint failures. The proportion of participants who were successful based on this criterion will be calculated along with the corresponding 95% confidence interval.

A binomial comparison will be used to test the null hypothesis that the efficacy rate is less than or equal to the acceptance criteria vs. the efficacy rate is greater than the acceptance criteria.

$$H_0: P_{TICI} \leq 71.5\%$$
$$H_A: P_{TICI} > 71.5\%$$

The rate of participants with mTICI 2b-3 will be compared to the prespecified acceptance criteria (71.5%) using a one-sided binomial distribution significance test. Statistical significance is achieved if the efficacy rate is significantly greater than 71.5%.Only Core Laboratory data will be used in the primary efficacy endpoint analysis of mTICI. The Core Laboratory data supersede the investigator-reported data in all analyses of post procedure mTICI.

10.9 Secondary Statistical Analysis

The secondary endpoints will be assessed with descriptive statistics and the associated 95% confidence bound. The additional secondary analyses include the following:

- Angiographic revascularization of the occluded target vessel after first pass as defined by mTICI 2b or higher
- Angiographic revascularization of the occluded target vessel at immediate post-procedure as defined by mTICI 2c or higher.
- Time to revascularization
- Occurrence of symptomatic intracranial hemorrhages (sICH) at 24 hours
- All-cause mortality at 90 days
- Occurrence of device or procedure related SAE at 24 hours.
- Modified Rankin Scale (mRS) 0-2 at 90 days

The Core Laboratory data will supersede the Investigator-reported data in analyses of post procedure mTICI. The CEC/DSMB data will supersede the Investigator-reported data in analyses.
Other pre-specified analyses will be performed as outlined in the statistical plan.

10.10 Analysis of Adverse Events

All adverse events will be summarized by showing the number and percent of participants reporting the event. Events will also be reported by relationship to the procedure or device. Adverse events with a probable or definite relationship to the Penumbra System including Thunderbolt will be analyzed as device related. Adverse events with a probable or definite relationship to the procedure will be analyzed as procedure related. The CEC/DSMB data will supersede the Investigator-reported data in all analyses of adverse events.

The secondary endpoint will include the following device related and/or procedural related SAEs within 24 hours post-procedure: symptomatic intracerebral hemorrhage (sICH), embolization to a new territory (ENT), and intracranial vascular injury (e.g. dissection or perforation).

All adverse events (AEs) will be analyzed with specific attention to the rate of all intracranial hemorrhage (ICH), including sICH, subarachnoid hemorrhage (SAH), and death.

10.11 Baseline Characteristics

Participant demographics, medical history, clinical characteristics, and procedure data will be summarized using descriptive statistics.

10.12 Pooling Across Centers

Analyses will be presented using data pooled across centers. Key baseline and study endpoint variables will be presented by study site to assess any potential site effects.

10.13 Final Report

A final report will be completed, even if the study is prematurely terminated. At the conclusion of the study, a multi-center abstract reporting the results will be prepared and may be presented at a major meeting(s). The final report will be submitted to applicable IRB(s)/EC(s) and regulatory authorities, if required. A multi-center publication may also be prepared for publication in a reputable scientific journal. The publication of results from any single center experience within the trial is not allowed until the aggregate study results have been published, unless there is written consent from the Sponsor. All ethical principles and legal requirements will be applied.

11 Study Committees and Core Labs

11.1 CEC/DSMB Joint Committee

The CEC/DSMB is made up of independent medical doctors and statistician who are not participants in the study. The CEC/DSMB is responsible for assisting in the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study as well as review of the overall safety of the study, and make recommendations to adjustments in the study protocol, should any be considered necessary for safety or other related reasons. Additional details will be specified in the CEC/DSMB charter. Statistician will be involved in periodic aggregate safety events review against stopping rules.

The CEC/DSMB will review and adjudicate appropriate clinical events, mainly for relationship to the device and procedure and to the study endpoints. A web-based electronic database will be provided to members for case review and adjudication. The designated Sponsor staff who are responsible for reviewing safety data on an ongoing basis will coordinate collection of information for the event dossier. Additional details are specified in the CEC/DSMB Charter.
If at any point, these reviews raise any safety concerns, the CEC/DSMB will be empowered to suggest that the study be placed on hold and request additional analyses of the study dataset. At the end of each CEC/DSMB meeting, this board shall recommend study (i) continuance according to protocol, (ii) modification of the protocol, or (iii) early study termination. The CEC/DSMB shall base their recommendations on all available evidence and their collective expertise and judgement. Safety stopping rules will be developed and used to help the CEC/DSMB make its safety assessments. Additional details regarding the CEC/DSMB structure, frequency of meetings and stopping rules will be included in the CEC/DSMB charter.

11.2 Imaging Core Lab

The Imaging Core Lab is composed of independent medical doctor(s) who are not participants in the study and have no significant conflict of interest. Significant conflict of interest is defined as the financial interests and arrangements outlined in 21 CFR 54. The Core Lab is responsible for assisting in the development of specific criteria used for the categorization of clinical endpoints in the study. A web-based electronic database will be provided for Core Lab to review and adjudicate images. Additional details related to the Core Lab are specified in the Core Lab Charter.

The independent imaging core lab will review pre-procedure and procedural images to determine at minimum mTICI and 24-hour CT for ECASS defined ICH. An imaging core lab charter will provide procedure for core lab review. Penumbra Inc. is responsible for tracking images received and basic quality review.

12 Study Administration

12.1 Control Measures for Disruption of Study

In case of an unforeseen disruption of the study (e.g., COVID-19) the Sponsor will conduct an impact assessment and take the following into consideration to protect study participants and manage study conduct.

- Electronic informed consent
- Remote and/or telehealth visits, when feasible
- Remote, centralized monitoring

If product shipment is affected, the risk of product availability to study participant safety is low as Thunderbolt is a single use device and the protocol does not require serial treatments.

If the disruption poses significant risk to study participants, the Sponsor will evaluate the need for study suspension or early termination.

12.2 Early Termination/ Study Suspension

The completion of the study will coincide to the last visit of the last participant and when follow up is complete for the clinical investigation.

The Sponsor may temporarily suspend or prematurely terminate the study, site or Investigator at any time for the following reasons:

- Suspicion of unacceptable risk to participants or to public health
- Recommendation by CEC/DSMB
- If no positive IRB/EC decision is obtained or if the judgement of the IRB/EC is revoked
- If the applicable regulatory body has made an irrevocable objection
- If it transpires that continuation of study cannot serve any scientific purpose, and this is confirmed by the IRB/EC

- If monitoring or auditing identifies serious or repeated deviations on the part of an investigator
- Business reasons

In the case of study suspension or premature termination:

- Sponsor will document reasons for study suspension or premature termination
- Sponsor will notify all PIs
- Sponsor will ensure that the IRB/ECs and regulatory authorities are notified in a timely manner
- The Sponsor will continue to provide resources to fulfil the obligations from the study protocol and existing agreements for following up the participants enrolled in the study.
- The Principal Investigator(s), or designee, will promptly inform the enrolled participants at his/her site, if appropriate.

If the Sponsor temporarily suspends the study and wishes to resume it:

- The Sponsor will provide and document a rationale for resuming the study, including corrective actions, if applicable
- Sponsor will inform the PIs
- Sponsor will ensure IRB/ECs are notified. IRB/ECs must provide written approval before the study is resumed.
- Sponsor will notify regulatory authorities (if appropriate)
- The Principal Investigators, or designee, will inform study participants as to the reason for resumption.

12.3 Stopping the Trial Based on Interim Safety Data

The Sponsor Medical Monitor and CEC/DSMB will review periodic safety reports of all AEs and SAEs. Study can be temporarily suspended to evaluate any negative safety trends.

12.4 Clinical Study Termination/Withdrawal

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

- **Voluntary withdrawal of consent:** meaning that a participant voluntarily chooses not to participate further in the study. All data collected up to the withdrawal of consent will be maintained in the study database. Withdrawn participants will not have any additional follow-up and will not be replaced.
- **Lost to follow-up**: a participant will be considered lost-to-follow-up when contact is not achieved at the last required follow-up visit window. At a minimum, the effort to obtain follow-up information will include three (3) attempts to make contact via telephone or e-mail and if unsuccessful, then a letter from the Investigator sent via courier or other traceable method will be sent to the participant's last known address. These efforts to obtain follow-up will be recorded in the participant's study files.

- **Withdrawn by Investigator:** A participant's enrollment in the clinical study will be terminated if the investigator believes that this is in the participant's best medical interest or if the participant no longer complies with the clinical study requirements.

12.5 Missing Visits

Every effort should be made to contact the participant for scheduled follow-up visits. Any study participant who does not attend a scheduled follow-up visit should be contacted by site personnel to reschedule. If the missed visit was due to an adverse event, an AE CRF must be completed, and any reporting requirements met.

12.6 Protocol Adherence and Amendments

The Principal Investigator must sign the protocol signature page documenting his/her agreement to conduct the study in accordance with this protocol and subsequent amendments. Deviations outlined in section 7.6.5 from the protocol must be documented and reported to Penumbra as soon as possible, and to the IRB/EC per local guidelines and government regulations.

12.7 Study Registration

The study will be registered in a publicly accessible trial database (e.g., clinical trials.gov, EUDAMED as applicable) prior to study initiation.

13 Publication of Information

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

The results of this study may be offered for publication. The investigators and the Sponsor shall collaborate in the writing of the study to ensure accuracy. All information not previously published concerning the test device and research, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and should remain the sole property of Penumbra Inc. The investigator agrees to use this information only in connection with this study and will not use it for other purposes without written permission from the Sponsor.

14 Contact Information

The address of Penumbra Incorporated, who is funding this research is:

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16 Appendix I: Acronyms and Abbreviations

Acronyms	Definition

ADAPT		A Direct Aspiration First Pass Technique
ADE		Adverse Device Effect
AE		Adverse Event
AHA		American Heart Association
AIS		Acute Ischemic Stroke
ASA		American Stroke Association
ASPECT Score		Alberta Stroke Program Early CT Score
ASPECTS	M1	Anterior MCA cortex
	M2	MCA cortex lateral to the insular ribbon
	M3	Posterior MCA cortex
	M4	Anterior cortex immediately rostal to M1
	M5	Lateral cortex immediately rostal to M3
	M6	Posterior cortex immediately rostal to M3
CE		European Conformity
CEC		Clinical Events Committee
CFR		Code of Federal Regulations
CRF		Case Report Form
CTA		Computed Tomography Angiography
CT		Computed Tomography
CTP		Computed Tomography Perfusion
CV		Curriculum Vitae
DSA		Digital Subtraction Angiography
DSMB		Data Safety Monitoring Board
EC		Ethics Committee
ECASS		European Cooperative Acute Stroke Study
EDC		Electronic Data Capture
ENT		Embolization to Uninvolved or New Territories
eTMF		Electronic File Master File
FDA		Food and Drug Administration
GCP		Good Clinical Practices
HI		Hemorrhagic infarction
HI 1		small petechiae along the margins of the infarcted area without space
HI 2		more confluent petechiae within the infarcted area but without space-occupying effect
IA		Intra-Arterial
ICA		Intracranial Carotid Artery
ICH		Intracranial Hemorrhage
ID		Inner Diameter
IFU		Instructions for Use
IRB		Institutional Review Board
ISO		International Organization for Standardization
ITT		Intent To Treat

LVO	Large Vessel Occlusion
MCA	Middle Cerebral Artery
MR	Magnetic Resonance
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
MT	Mechanical thrombectomy
mTICI	modified treatment in cerebral ischemia
NCCT	Non-Contrast Computed Tomography
NIHSS	National Institute of Health Stroke Scale
PH	Parenchymal Hematoma
PH 1	Hematoma in ≤ 30% of the infarcted area with some slight space-occupying effect
PH 2	Hematoma in > 30% of infarcted area with substantial space-occupying effect
PP	Per Protocol
RCT	Randomized Control Trial
rtPA	Recombinant Human Tissue Plasminogen Activator
SAE	Serious Adverse Event
sICH	Symptomatic Intracerebral Hemorrhage
SNIS	Society of NeuroInterventional Surgery
SVIN	Society of Vascular and Interventional Neurology
TICI	Thrombolysis in Cerebral Infarction
TIMI	Thrombolysis in Myocardial Infarction
TLSW	Time Last Seen Well
US	United States
UADE	Unanticipated Adverse Device Effect

17 Appendix II: Definitions

17.1 Adverse Events

- **Adverse Event (AE):** any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the study device and whether anticipated or unanticipated.
- **Adverse Device Effect (ADE):** An adverse event related to the use of the study medical device(s).
- **Serious Adverse Event (SAE)** An adverse event is serious if the event led to the following:
    - Death
    - Serious deterioration in the health of the participant that resulted in any of the following:
        - Life-threatening illness or injury
        - Permanent impairment of a body structure or a body function
        - Hospitalization or prolongation of patient hospitalization
        - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
    - Fetal distress, fetal death or a congenital physical or mental impairment or birth defect
- **Unanticipated Adverse Device Event (UADE):** An unanticipated adverse device effect is 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 protocol, IFU, or risk analysis. Unanticipated adverse device effect also includes any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

17.2 Relationship to the Device

- **Definite:** The temporal sequence is relevant and the event abates upon study device application completion/removal, or reappearance of the event on repeat study device application.
- **Probable:** The temporal sequence is relevant or the AE abates upon study device application completion/removal or the AE cannot be reasonably explained by the participant's condition or comorbidities. The AE is related or most likely associated with the study device.
- **Possible:** The temporal sequence between the study device and the AE is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the participant's condition. There is a possibility of a relationship between the AE and the study device.
- **Unrelated:** The AE is not associated with the device. There is no relation between the AE and the study device.

Similar grading will be used for assessing the relationship to index procedure.

17.3 ASPECT Score

- In the anterior circulation ASPECT score is calculated by evidence of early ischemic change for each of the defined regions:
    - Caudate
    - Putamen
    - Internal capsule
    - Insular cortex
    - M1: "anterior MCA cortex," corresponding to the frontal operculum
    - M2: "MCA cortex lateral to insular ribbon" corresponding to the anterior temporal lobe
    - M3: "posterior MCA cortex" corresponding to the posterior temporal lobe
    - M4: "anterior MCA territory immediately superior to M1"
    - M5: "lateral MCA territory immediately superior to M2"
    - M6: "posterior MCA territory immediately superior to M3"

When calculating score 1 point is deducted from the initial score of 10 for every region involved

- In the posterior circulation, ASPECT score (pc-ASPECTS) is calculated by evidence of early ischemic change for each of the defined regions:
    - Midbrain (2 points)
    - Pons (2 points)
    - Thalami (1 point each)
    - Occipital lobes (1 point each)
    - Cerebellar hemispheres (1 point each)

When calculating deduct points indicated from the initial score of 10 for every region involved

17.4 Procedural Pass

When performing mechanical thrombectomy, an attempt is defined as re-inserting the reperfusion catheter into the body after removal and/or anytime a DSA run is completed to assess vessel reperfusion. The use of an adjunctive device is considered an additional attempt.

17.5 Embolization in New Territory (ENT)

Emboli observed on post thrombectomy angiography within previously unaffected territories.

17.6 Symptomatic Intracerebral Hemorrhage (sICH)

24-hour CT evidence of an ECASS defined ICH and a 4-point or more worsening of the NIHSS score

17.7 Perforation

The piercing or rupturing of a blood vessel; perforations can be detected or observed angiographically.

17.8 Dissection

Angiographic evidence of a tear in the arterial wall as defined by the occurrence of intramural hematoma.

17.9 Vasospasm

Spasm of a blood vessel as seen in angiogram, resulting in prolonged decrease in lumen diameter requiring treatment

17.10 Severe Vasospasm

Cerebral vasospasm as seen in the final angiogram is defined as spasm of intracranial arteries resulting in decrease in lumen size by >50% and a decrease in distal territory perfusion.

18 Appendix III: Standard Assessments

18.1 Modified Rankin Scale[37]

0	No Symptoms at all
1	No significant disability, despite symptoms; able to perform all usual duties and activities
2	Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability; requires some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden; incontinent, and requires constant nursing care and attention
6	Death

18.2 National Institute of Health Stroke Scale[38]

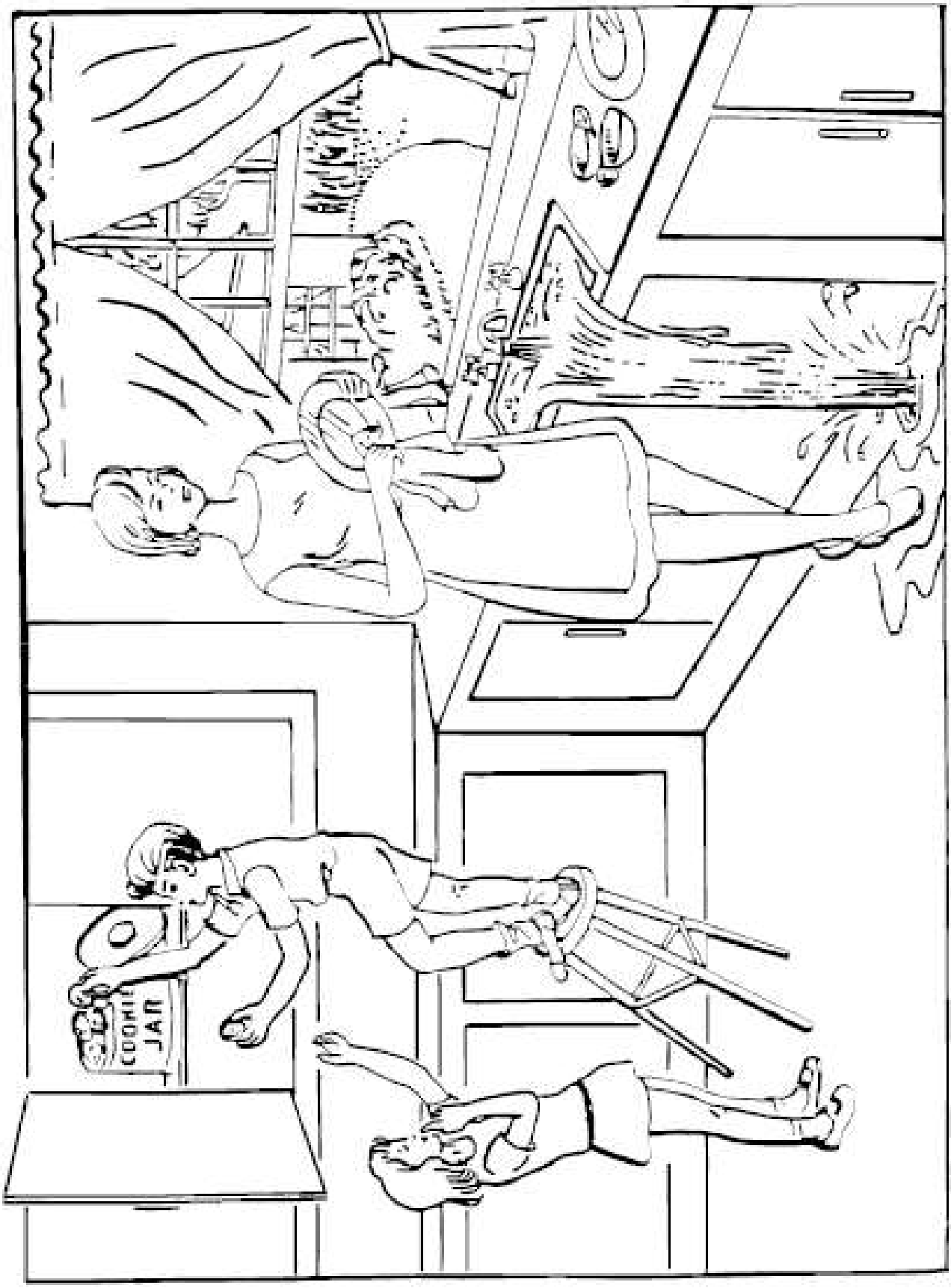
NIH STROKE SCALE		
Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert;** but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert;** requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate	0 = **Normal**. 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but	

NIH STROKE SCALE		
deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movement. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = D**rift**; Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds: does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down	

NIH STROKE SCALE		
the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 **= No movement.** UN = **Amputation** or joint fusion, explain: _____	
	5a. Left Arm	
	5b. Right Arm	
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30 degrees position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5 second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 **= No effort against gravity;** leg falls to bed immediately. 4 = **No movement**. UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg**	
	6b. Right Leg	
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent**. 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, “severe or	0 = **Normal**; no sensory loss. 1 = **Mild to moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched.	

NIH STROKE SCALE		
total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an	0 = **Normal.** 1 = **Mild to moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 **= Severe;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.	

NIH STROKE SCALE		
explanation for this choice. Do not tell the patient why he or she is being tested.	UN = **Intubated** or other physical barrier, explain: _____ __	
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	


COOKIE
JAR

You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

18.3 mTICI Classification[39]

Grade 0:	No perfusion or anterograde flow beyond site of occlusion
Grade 1:	Penetration but not perfusion. Contrast penetration exists past the initial obstruction but with minimal filling of the normal territory
Grade 2:	Incomplete perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but rate of entry or clearance from the bed is slower or incomplete when compared with non-involved territories
Grade 2a:	Some perfusion with distal branch filling of <50% of territory visualized
Grade 2b:	Substantial perfusion with distal branch filling of ≥50% of territory visualized
Grade 2c:	Near-complete perfusion except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli
Grade 3:	Complete perfusion with normal filling of all distal branches