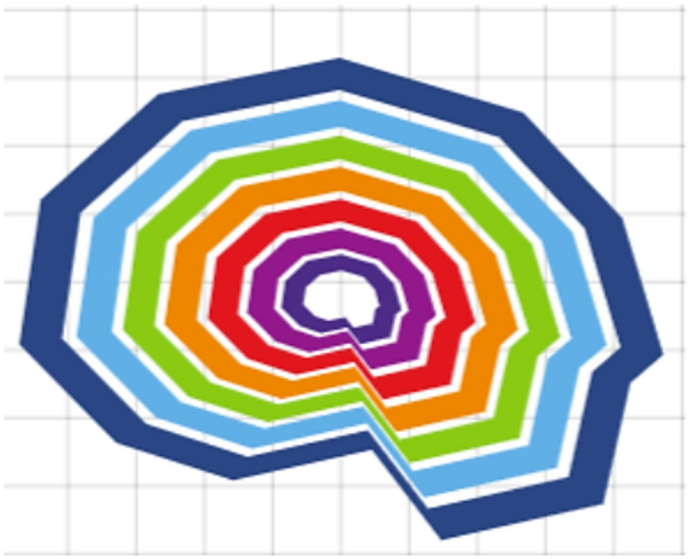

STEP **StrokeNet Thrombectomy Endovascular Platform**

Domain Specific Appendix:

DOMAIN A

EVT INDICATION EXPANSION

StrokeNet Thrombectomy Endovascular Platform (STEP)

Investigator Agreement Domain A EVT Indication Expansion Protocol

I have read the following STEP Domain A EVT Indication Expansion Protocol and agree to conduct the study as described herein. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational plan and the conduct of the study according to 21 CFR parts 50, 54, 56 and 812, International Council for Harmonisation Good Clinical Practices Guidelines and Institutional Review Board requirements.

NOTE: By signing the protocol, the investigator agrees to keep all study related documents in strict confidence and to request the same from his/her staff and the Institutional Review Board. Study-related documents will be stored appropriately to ensure their confidentiality. The investigator should not disclose such information to others without authorization, except to the extent necessary to conduct the study.

_____ _____

Principal Investigator's Signature **Date**

_____

Principal Investigator's Printed Name

_____

Clinical Performance Site Name

Summary
In this domain of the STEP trial, the study population will consist of the subsets of adult acute cerebral ischemia patients who present to the enrolling hospital within 24 hours of last known well/stroke onset, currently not treated with EVT according to guidelines. Participants will be randomized to receive one of two strategies:
- Endovascular Therapy (EVT)
- Medical Management (MM)

At domain inception, the following populations are being enrolled within this domain:
☐ LVO patients with mild deficits/low NIHSS
☐ MVO patients with Non-dominant/Co-dominant M2 occlusion
☐ DMVO patients with M3,4 or A1,2,3 or P1,2,3 occlusion.

This DSA applies to the following states and/or stratum:

EVT Indications Domain Summary	
Interventions	• Endovascular Therapy (EVT) • Medical Management (MM)
Unit-of-analysis, Strata	There are 3 strata within this domain. Unit-of-analysis (the group of patients who are analyzed together within a model): 1. LVO patients with mild deficits/low NIHSS 2. MVO patients with Non-dominant/Co-dominant M2 occlusion 3. DMVO patients with M3,4 or A1,2,3 or P1,2,3 occlusion. **Strata** comprise a set of mutually exclusive and exhaustive categories (stratum), defined by baseline characteristics of a patient within the Platform, in which the relative effects of interventions may be differential. The treatment effect of EVT versus MM is estimated within vessel stratum for every incremental point of the baseline NIHSS score.
Evaluable Treatment-by-Treatment Interactions	None
Nesting	None
Timing of Reveal	Randomization with Immediate Reveal and Initiation.
Domain-Specific Inclusions	1. Age 18 years or older 2. Pre-stroke modified Rankin Scale score 0-2 3. Presentation to enrolling hospital within 24 hours of last known well/stroke onset 4. Has any one or more of the following presentations:

	a) LVO patients with mild deficits/low NIHSS *(must have both):* 1. Mild presenting neurologic deficits - NIHSS 0-5 2. Occlusion of the intracranial ICA or M1 MCA b) *Medium/Distal Vessel Occlusion (must have all 4):* 1. Visualized occlusion or perfusion deficit supportive of a cortical branch occlusion (10 cc volume of Tmax >4s) in one of the following vessels i) Non-dominant/Co-dominant M2 (defined as serving ≤ 50% of entire overall MCA territory) ii) M3 iii) M4 iv) A1 v) A2 vi) A3 vii) P1 viii) P2 ix) P3 2. Less than 50% core in the territory supplied by the occluded vessel as evident by hypodensity and loss of grey-white border on NCCT or ADC <620 mm^2/s on diffusion MRI or rCBF<30% on CTP after 6h of symptom onset. 3. NIHSS ≥ 4 or NIHSS 2-3 with clearly disabling deficits at presentation to enrolling hospital 4. Able to initiate arterial puncture within 2 hours from qualifying CTA/MRA or CTP/MRP imaging. *CT/MR and qualifying CTA/MRA or CTP/MRP should be repeated if more than 120 minutes have elapsed since the imaging and randomization has not been performed.[1]
Domain-Specific Exclusions	1. Clinical a. Presumed septic embolus; suspicion of bacterial endocarditis b. Seizure at stroke onset or between onset and enrollment c. Known anaphylactic reaction to contrast material that precludes endovascular reperfusion therapy d. Intracranial occlusion suspected to be chronic, based on history and/or imaging e. Intracranial dissection, based on history and/or imaging f. Cerebral vasculitis, based on history and/or imaging g. Known pregnancy h. Known pre-existing medical, neurological or psychiatric disease that would confound the neurological or functional evaluations i. Known serious, advanced, or terminal illness or life expectancy less than 6 months in the investigator judgment. 2. Laboratory a. Known platelet count < 100,000/uL 3. Imaging a. CT ASPECT score <6 (MRI ASPECT score <7) b. Unfavorable vascular anatomy that limits access to the occluded artery precluding endovascular reperfusion therapy. c. Acute occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation)

	d. Significant mass effect with midline shift (>5mm) e. Evidence of intra-axial tumor (except small meningioma) f. Evidence of acute intracranial hemorrhage
Intervention-Specific Exclusions	None
Outcome Measures	**Primary Endpoints** **Efficacy** • 90-day global disability assessed with the modified Rankin Scale **Safety** • Symptomatic intracranial hemorrhage (sICH) (per modified Heidelberg criteria) **Secondary Endpoints** <u>Clinical Efficacy</u> For all EVT INDICATION EXPANSION DOMAIN patients, secondary clinical efficacy endpoints will be: • mRS 0-2 (functional independence) at 90 days • Level of disability [mRS 6-level (0,1,2,3,4,5/6) ordinal distribution] • NIHSS (neurologic deficit) at 24 hours In addition, for the subsets of patients with low NIHSS and/or target MVO occlusion site, secondary clinical efficacy endpoints will also include: • mRS 0-1 (freedom from disability) at 90 days <u>Technical Efficacy</u> Technical efficacy endpoints (analyzed only in EVT patients) will be: • eTICI 2b50-3 (substantial reperfusion) at end of procedure • eTICI 2c-3 (excellent reperfusion) at end of procedure • eTICI 2c-3 (excellent reperfusion) on first device pass **Safety** Secondary safety endpoints analyzed in both EVT and MM patients will be: • Any radiologic intracranial hemorrhage within 36 hours after randomization • Mortality by 90 days • Serious adverse events (SAEs) • Early Clinical Deterioration within 36 hours of randomization An additional secondary safety endpoint analyzed in the EVT group will be: • Unanticipated adverse device effects (UADEs) before hospital discharge • Arterial access complications requiring surgical intervention • Intracranial vessel perforation or dissection • Embolization to previously uninvolved territory before the end of EVT procedure

Affected Section(s)	Summary of Revisions Made	Rationale
V 1.0 to V 2.0		
Header Footer Title page	Added "Domain A"	Added the label Domain A to easily distinguish this appendix from future Domains
Page 17	Added Signature Page	For Investigator sign off of the Domain Appendix
Synopsis and 5.2.1	Removed "or Dominant M2 MCA"	Patients with mild deficit and Dominant M2 MCA will no longer be enrolled
Synopsis and 5.2.1	Removed "….. must confirm presence of occlusion with angiogram prior to randomization. ….must confirm presence of occlusion with catheter angiogram prior to randomization"	Repeat angiograms are not required to be enrolled
2.1	Removed names	In the event that member of the Working Groups/Chairs are replaced
7.2	ENDOLOW trial to merge with STEP	Due to overlapping participant eligibility criteria, the ENDOLOW trial will contribute all data to the STEP analysis.
Changes in V 3.0		
Summary 5.1.2	Unit of analysis includes a consideration of the baseline NIHSS score Change Inclusion criteria #3	Clarification that different treatment effects may be estimated for different NIHSS levels within vessel stratum Clarification
Synopsis and 5.2.1 5.1.2	"Within 24 hours of last known well" revised to "*Presentation to <u>enrolling</u> hospital* within 24 hours of last known well/*stroke onset"* 4 a) Changed "Low NIHSS" to "LVO patients with mild deficits/low NIHSS" Descriptions of Domain-Specific strata reworded for clarification	Clarification
Synopsis and 5.2.1	4 b) Inclusion criteria of "Lumen diameter >/= 0.75" revised to "Visualized occlusion or perfusion deficit supportive of a cortical branch occlusion (10 cc volume of Tmax >4s)…" Inclusion criteria of "Non-dominant/Co-dominant M2 or M3,4 or A1,2,3 or P1,2,3" was restated. Wording "Non-dominant/Co-dominant" only applies to M2. Added an NIHSS criteria for MVO/DVO-NIHSS <u>> 4 and NIHSS 2-3 with clearly disabling deficit</u>	4 b 1-Impracticality of measurements in medical management arm 4 b 1 i- clarification 4 b 3-minimize potential risk based on evolution of literature and external data.

Synopsis and 5.2.1	4 b) Time from qualifying CTA/MRA or CTP/MRP imaging	Qualifying image may be a CTP/MRP
Synopsis and 5.2.2	Added Exclusion Criteria of CT ASPECT score <6 (MRI ASPECT score <7)	New Exclusion Criteria
Synopsis and 5.2.2	Exclusion of allergy to contrast changed to known anaphylactic reaction to contrast	Clarification
5.2.1	*Operational definition of a non/co-dominant subsegment of the M2 MCA*: 45% and 55% changed to 50%	Easier to ascertain
5.3 & 5.4.1 5.3.1	Restated the wording "…devices legally marketed in the US" Added Section on Rescue Therapy	Canadian sites are participating Requested by DSMB
5.5.1 5.5.2 5.6.1.1 5.6.1.2	(+/- 15) (+/- 12) windows removed from outcome definitions	Clarification. Data outside of the protocol defined visit window may still be included in the analysis.
5.6.1.2	Safety endpoints in EVT patients are defined as those that occur during the during procedure	Clarification
6.1.1	Added Domain Specific Schedule of Assessments	Clarification
6.1.3	At the 24 hour visit ASPECT score will be collected Removed some EVT data items which were already a part of the Master protocol Neuroimaging collection CRF is to be completed at Hospital Discharge.	ASPECT moved from Master protocol to domain only to reduce burden
6.1.4	Clarified type of scan and time period of neuroimaging scans to be uploaded for central reading	Clarification
Signature Page	Signature Page moved to the top of the document	To make this easier to locate.

TABLE OF CONTENTS

1 PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While, all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Section 1.2 Master Protocol for definitions of these terms).

The protocol has multiple modules, in brief, comprising a Master Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and Simulations Appendix (details of the current simulations of STEP), and Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain).

The Master Protocol contains all information that is generic to the trial, irrespective of the site in which the trial is conducted and the domains or interventions that are being tested. The Master Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Master Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject to a separate ethics application for approval.

The Master Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations, but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the STEP Executive Committee in conjunction with NINDS and the Data Safety and Monitoring Board (DSMB).

2 DOMAIN GOVERNANCE

Each Domain is assigned a Chair and will have a multiple PI liaison from the STEP Executive Committee (see MOP).

3 BACKGROUND AND RATIONALE

3.1 DOMAIN DEFINITION

This is a domain within the STEP platform to compare EVT versus medical management (MM).

3.2 Domain Specific Background

Stroke is the fifth leading cause of death in the United States, and a leading cause of major disability. The recent advent of endovascular therapy as a treatment of proven benefit has revolutionized acute ischemic stroke care, specifically for some patients with large vessel occlusions, by restoring blood flow before stroke completion and reducing 3-month disability in one of every 2.5 patients treated. Initial trials established EVT benefit for select anterior circulation LVO-AIS patients within 6 hours of last known well, and subsequent trials expanded the demonstration of benefit to: 1) additional anterior circulation LVO-AIS patients 6-24 hours from last known well with advanced imaging evidence of small ischemic core size; 2) posterior circulation LVO-AIS patients; and 3) anterior circulation AIS-LVO patients with large ischemic core size. Given the large benefit magnitude of EVT for patients with established indications, a widely-shared, and physiologically well-founded hypothesis is that EVT would be beneficial for additional patient subgroups.

Epidemiologic studies indicate that, among the 680,000 acute ischemic strokes that occur in the United States each year, 25-35% are due to LVOs and 25-35% MVOs, with the remainder due to small, penetrator vessel occlusions (25%), isolated extracranial occlusions (5%), and other causes (5%).[2-15] Accordingly, ~400,000 are due to intracranial large and medium vessel occlusions potentially amenable to EVT therapy. Best estimates are that currently only between 18,000-32,000 AIS patients nationwide are treated with EVT annually – just 5-8% of the combined AIS-LVO/MVO population.[16-18] The leading reason for this low rate of EVT use is that clinical trials have not yet fully mapped the extensive "response space" of AIS-LVO/MVO patients lacking baseline clinical characteristics placing them within the relatively narrow population for whom EVT is definitively proven. The EVT Indication Expansion Domain will identify additional LVO and MVO patients who do and do not benefit from EVT, an issue of pressing major public health urgency.

3.2.1 Completed Trials of Endovascular Therapy for Select Subgroups of AIS -LVO/MVO Patients

In 2013, three multicenter prospective randomized clinical trials (RCTs) failed to show a benefit from endovascular intervention for acute ischemic stroke, including two for intravenous (IV) alteplase-eligible patients (IMS III[19] and SYNTHESIS-Expansion[20]) and one for under 8 hour patients (MR RESCUE[21]). These trials raised concerns about the efficacy of endovascular therapy in large vessel occlusion. However, the design and conduct of these studies had substantial limitations. Only one of the three trials, MR RESCUE, routinely identified large vessel occlusion with either CTA or MRA prior to randomization, likely diluting treatment effect; all used mainly first-generation EVT devices with low recanalization rates; and treatment times were often delayed, again diluting treatment effect.[22]

In 2014-15, five multicenter prospective RCTs all addressed these limitations by requiring evidence of LVO for entry, using second generation, highly effective EVT devices, and achieving faster treatment workflows, and all provided evidence of substantial benefit from endovascular stroke therapy (MR CLEAN[23],ESCAPE[24], SWIFT PRIME[25], EXTEND-IA[26], and REVASCAT[27]).

The HERMES collaboration pooled patient-level data from these first five trials and showed that endovascular thrombectomy reduced disability from acute ischemic stroke due to anterior circulation LVO in patients who were predominantly treated within 6h of last known well, had ICA or M1 MCA target occlusions, had NIHSS ≥ 6, ASPECTS ≥ 6, and no major pre-stroke disability.[28] The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on the mRS for one patient was 2.6.

In 2018, two multicenter RCTs expanded the indications for thrombectomy by demonstrating that anterior circulation AIS-LVO patients in the 6-16 hour (DEFUSE 3[29]) and 6-24 hour (DAWN[30]) time window after last known well, who had multimodal CT or MR imaging evidence of small ischemic cores, also benefitted substantially from EVT. In 2022, two multicenter RCTs (ATTENTION and BAOCHE) further expanded the indications for thrombectomy by demonstrating that posterior circulation AIS-LVO patients also benefitted substantially from EVT.[31] In 2022-23, three multicenter RCTS (RESCUE-Japan LIMIT, SELECT-2, and ANGEL-ASPECT) further expanded the indications for thrombectomy by demonstrating that anterior circulation AIS-LVO patients with large ischemic cores also benefitted substantially from EVT.[32-34]

3.2.2 Endovascular Therapy –Types of Additional Patients Who May Benefit from EVT

3.2.2.1 Patients with Mild Deficits (Low NIHSS)

Current randomized and observational trial data raise the possibility that AIS-LVO/MVO patients with mild presenting deficits (NIHSS 0-5) may benefit from EVT, but substantially more randomized data are needed to confirm this supposition, as well as to distinguish subsets of NIHSS 0-5 patients who may not benefit. Among all 1766 patients entered in randomized trials of EVT to date, only 14 patients had baseline NIHSS 0 to 5.[35] However, pooled individual patient level trial data of patients with NIHSS scores from 6 to 41 did not suggest effect modification by NIHSS.[28](see Figure 2.2.2.2) In addition, two multicenter, non-randomized, matched-patient analyses suggested better outcomes with immediate mechanical thrombectomy rather than initial medical therapy with potential rescue mechanical thrombectomy for neurologic deterioration (which occurs in 20-40% of patients).[35,36]

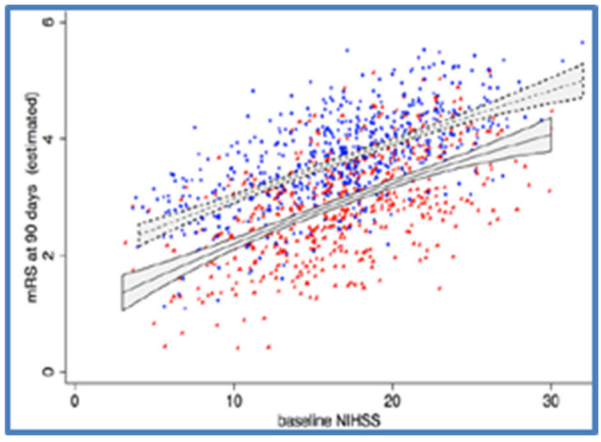

Figure 2.2.2.2 mRS Scores at 3m (y-axis) in EVT group (lower line) compared to MM group (upper line) according to baseline NIHSS score (x-axis) in the HERMES pooled analysis. Note the absence of data for patients with NIHSS 0-5.

3.2.2.2 Patients with Medium/Distal Vessel occlusions

With iterative advances in catheter technology, distal/medium vessel occlusions (DMVOs) have recently become accessible for potential thrombectomy. DMVOs account for 25-40% of cases of acute ischemic stroke.[37] DMVOs in the cerebral hemispheres produce clinical syndromes that are heterogenous but frequently disabling. Distal medium arterial segments that supply particularly critical brain regions are the co-/non-dominant M2 MCA, M3-M4 MCA, A1-A3 ACA, and P1-P3 PCA. In a pooled analysis of two multicenter studies of medical therapy (intravenous thrombolysis or antithrombotic treatment) of DMVOs, among 184 patients with occlusions in these

segments, 44% had a disabled (mRS 2-6) outcome, 26% a dependent (mRS 3-6) outcome, and 7% a fatal outcome.[38]

While intravenous thrombolytics are more effective for distal than proximal occlusions, they fail to recanalize one-half to two-thirds of DVOs[10, 40]. Early clinical series using recently available, smaller, more navigable stent retriever and thromboaspiration devices suggest EVT for DVOs is safe, technically efficacious, and potentially clinically beneficial.[37,39,40] However, the distal cerebral arteries have 2 characteristics that potentially could increase the risk of EVT[37]: 1) Tortuosity/vessel distance: Distal arteries have ≥1 additional branch steps than proximal arteries, producing more tortuous and longer cumulative travel pathways from the arterial puncture site. This tortuosity increases the difficulty of successful navigation to target occlusions and constrains the physical forces deliverable by a retrieval device separated from its manipulable end by multiple turns. 2) Medium size lumens: Medium size cerebral arteries have lumen diameters between 0.75 and 2.0 mm. In contrast, large size intracranial cerebral arteries have lumen diameters > 2.0 mm and typically between 2.7-3.8 mm. The smaller size of medium cerebral vessels increases the risk of vessel injury when they are traversed by catheters and retrieval devices.

STEP DMVO are further divided into MVO1 (Non-dominant/Co-dominant M2) and MVO2 (M3,4 or A1,2,3 or P1,2,3).

3.3 Risk/Benefit Assessment

3.3.1 Known Potential Risks of EVT

Intracranial arterial perforation and subsequent symptomatic intracranial hemorrhage (intracerebral and/or subarachnoid) may occur. Complications associated with the arterial access site can include peripheral arterial injury resulting in retroperitoneal hemorrhage, groin hematoma, pseudoaneurysm, or infection. Complications arising from catheter navigation can include arterial dissection and dislodging of atherosclerosis. If there is a proximal stenosis or occlusion of the cervical carotid bifurcation, thrombus or atherosclerotic debris at the bifurcation may embolize during the procedure into new territories or re-occlude the originally occluded intracranial artery. Complications from fragmentation of the target thrombus can include emboli in new territories and emboli in distal territories. These risks are all relatively low (<4%).[28,41-43] Complication rates may be increased in patients with more tortuous vessels, which are more common in individuals with more comorbidities. Treatment of more distal occlusions, such as M2 MCA occlusions, may be associated with higher rates of hemorrhage due to the need to traverse more artery length, negotiate more arterial turns, and instrument narrow, more thin-walled vessels. For patients with low NIHSS, the risks must be considered in the context of smaller potential benefits. Patients with low NIHSS have an increased frequency of underlying atherosclerotic intracranial stenosis, allowing compensation through collateralization; this stenosis can lead to greater likelihood of vessel wall disruption including perforation and distal embolization.

3.3.2 Known Potential Benefits

For individual participants in the trial, the potential benefits of EVT may include smaller final brain infarct size, increased functional independence, and reduced disability 3 months after stroke. For society, the benefits include providing future patients and health system planners with improved knowledge regarding when and when not to pursue EVT therapy.

3.3.3 Assessment of Potential Risks and Benefits

There is potential benefit to the individual participant (improved outcome) and substantial benefit to society (more informed treatment of future patients). In contrast, the risks of EVT are relatively low and are being further minimized by adherence to national guidelines regarding best techniques for EVT deployment and by monitoring of patient outcomes by Medical Monitors, the STEP Platform Endovascular Core, and an independent DSMB. Accordingly, the risk of participation in the study is outweighed by the benefit to be gained.

4 Domain Objectives

To determine subsets of AIS patients within 24 hours of last known well, currently not treated with EVT according to guidelines, who do or do not benefit from EVT compared to Medical Management by having better functional outcome.

5 Trial Design

5.1 Population

This domain is available for the subsets of adult acute cerebral ischemia patients who present to the enrolling hospital within 24 hours of last known well/stroke onset, currently not treated with EVT according to guidelines.

5.1.1 State

Hyper-acute state defined as within first 90 minutes of hospital arrival for out-of-hospital strokes or within 90 minutes of stroke alert for in-hospital onset strokes.

5.1.2 Domain-specific Strata

There are 3 distinct populations being evaluated:

1) LVO patients with mild deficits/Low NIHSS
2) MVO patients with Non-dominant/Co-dominant M2 occlusion
3) DMVO patients with M3,4 or A1,2,3 or P1,2,3 occlusion.

The strata are defined in detail in the statistical analysis plan. The treatment effect of EVT versus MM is estimated within vessel stratum and baseline NIHSS score.

5.2 Eligibility Criteria

5.2.1 Domain Inclusion Criteria

1. Age 18 years or older
2. Pre-stroke modified Rankin Scale score 0-2
3. Presentation to enrolling hospital within 24 hours of last known well/stroke onset
4. Has one of the following presentations:

a) *Low NIHSS, LVO Patient (must have both):*
   1. Mild presenting neurologic deficits - NIHSS 0-5
   2. Occlusion of the intracranial ICA or M1 MCA

b) *Medium/Distal Vessel Occlusion (must have all 4):*
   1. Visualized occlusion or perfusion deficit supportive of a cortical branch occlusion (10 cc volume of Tmax >4s) in one of the following vessels
      i) Non-dominant/Co-dominant M2 (defined as serving ≤ 50% of entire overall MCA territory)
      ii) M3
      iii) M4
      iv) A1
      v) A2
      vi) A3
      vii) P1
      viii) P2
      ix) P3
   2. Less than 50% core in the territory supplied by the occluded vessel as evident by hypodensity and loss of grey-white border on NCCT or ADC <620 mm^2/s on diffusion MRI or rCBF<30% on CTP after 6h of symptom onset.
   3. NIHSS ≥ 4 or NIHSS 2-3 with clearly disabling deficits at presentation to enrolling hospital
   4. Able to initiate arterial puncture within 2 hours from qualifying CTA/MRA or CTP/MRP imaging.
      *CT/MR and qualifying CTA/MRA or CTP/MRP should be repeated if more than 120 minutes have elapsed since the imaging and randomization has not been performed.[1]

*Operational criteria for identifying "Occlusions of a non/co-dominant M2 middle cerebral artery segment":

a) *Operational definition of the M2 MCA segment*: For this domain, the M2 MCA segment will be defined as recommended in a consensus EVT trialist paper.[44] This definition uses a mixed branch-and-stem and Sylvian approach that is a formally operationalized approach and is convenient to employ in real-time reading of CTAs, MRAs, and catheter angiograms. The approach recognizes the M1 segment as the initial stem of the MCA including small penetrating branches and the anterior temporal artery branch. The M2 segment starts with first non-penetrator branching that occurs after take-off the anterior temporal artery branch. The anterior temporal artery branch of the M1 may be identified by the confinement of its course to the anterior temporal lobe. If a branch artery exits the Sylvian fissure and supplies territory beyond the anterior temporal lobe (including the posterior temporal or low parietal regions), it is

considered an M2 MCA segment rather an anterior temporal artery branch. The M2 MCA continues through the entire vertical course of branches up the Sylvian fissure. The M3 MCA starts with the turn of these branches to run horizontally under the temporal lobe.

b) *Operational definition of a non/co-dominant subsegment of the M2 MCA*: For STEP, the size (dominant vs co-dominant vs non-dominant) of the occluded M2 MCA segment will be characterized based on a modification of the method of the HERMES EVT trialists consortium.[45] Based on pre-randomization CTA or MRA, plus information from CTP or PWI MRI if performed, the subsegment of the M2 MCA that is occluded is classified as: dominant if it supplies >50% of the MCA territory; co-dominant if it supplies ~50% of the MCA; and non-dominant if it supplies <50% of the MCA territory.

5.2.2 DOMAIN EXCLUSION CRITERIA

1. Clinical
    i. Presumed septic embolus; suspicion of bacterial endocarditis
    ii. Seizure at stroke onset or between onset and enrollment
    iii. Known anaphylactic reaction to contrast material that precludes endovascular reperfusion therapy
    iv. Intracranial occlusion suspected to be chronic, based on history and/or imaging
    v. Intracranial dissection, based on history and/or imaging
    vi. Cerebral vasculitis, based on history and/or imaging
    vii. Known pregnancy
    viii. Known pre-existing medical, neurological or psychiatric disease that would confound the neurological or functional evaluations
    ix. Known serious, advanced, or terminal illness or life expectancy less than 6 months in the investigator judgment.

2. Laboratory
    i. Known platelet count < 100,000/uL

3. Imaging
    i. CT ASPECT score <6 (MRI ASPECT score <7)
    ii. Unfavorable vascular anatomy that limits access to the occluded artery precluding endovascular reperfusion therapy.
    iii. Acute occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation)
    iv. Significant mass effect with midline shift (>5mm)
    v. Evidence of intraaxial tumor (except small meningioma)
    vi. Evidence of acute intracranial hemorrhage

5.3 INTERVENTIONS

Patients randomized to EVT treatment will undergo endovascular recanalization therapy using legally marketed devices. Choice of device(s) deployed will be at the discretion of the expert neurointerventionalist performing the procedure. Endovascular procedure conduct will adhere to protocol aspects delineated in the endovascular procedure conduct section of the STEP Platform Master Protocol.

Medical management will adhere to protocol aspects delineated in the medical management section of the STEP-Trial Conduct Module of the STEP Platform Master Protocol, including intravenous thrombolysis for participants who are determined to be eligible by the local clinical team.

5.3.1 RESCUE THERAPY

For participants in the mild neurological deficit strata (NIHSS 0-5) and randomized to MM, rescue EVT is allowed if there is sustained neurological worsening to a total NIHSS score of ≥ 6 points and the participant is still within 24 hours of stroke onset or last known well.

For the DMVO strata, rescue therapy is not allowed.

5.4 CONCOMITANT CARE AND BEST PRACTICE RECOMMENDATIONS

5.4.1 Preparation/Handling/Storage/Accountability

All EVT devices used in STEP patients will be devices legally marketed and approved for clinical use at each participating center. Device accountability will not be tracked for STEP.

5.5 ENDPOINTS

5.5.1 PRIMARY EFFICACY ENDPOINT

90-day global disability assessed with the modified Rankin Scale

5.5.2 SECONDARY EFFICACY ENDPOINTS

Secondary Endpoints

Clinical Efficacy

For this domain, secondary clinical efficacy endpoints will be:

1) mRS 0-2 (functional independence) at 90 days
2) Level of disability at 90 days [mRS 6-level (0,1,2,3,4,5/6) ordinal distribution]
3) NIHSS (neurologic deficit) at 24 hours

These additional clinical efficacy endpoints were selected as they assess important aspects of health state that are complementary to the primary endpoint. The mRS 0-2 (functional independence) dichotomy assesses patient ability to return to independent living in the community. The ordinal mRS indexes level of disability unmodified by qualitative patient ratings. The NIHSS at 24 (+/-12) hours indicates early therapeutic effects on neurologic deficits in a manner highly predictive of subsequent course.

In the EVT Indication Expansion Domain study population, additional secondary clinical endpoints of distinctive clinical interest and informativeness for those populations will be obtained:

Patients with Low NIHSS and patients with Medium/Distal Vessel Occlusion at study entry generally have more favorable prognosis under any treatment strategy. Accordingly, it is desirable to assess additionally the effect of study treatment upon health state transitions important in less severely affected acute ischemic stroke patients. The additional secondary clinical efficacy endpoint will be:

- mRS 0-1 (freedom from disability) at 90 days

5.5.3 Technical Treatment Characteristics

To describe the technical performance of EVT in restoring perfusion to the target cerebral, the following will be measured in EVT patients:

- eTICI 2b-3 (substantial reperfusion) at end of procedure
- eTICI 2c-3 (excellent reperfusion) at end of procedure
- eTICI 2c-3 (excellent reperfusion) on first device pass

5.6 Safety and Other Assessments

5.6.1 Safety Outcomes

5.6.1.1 Primary Safety Endpoint

The primary safety endpoint for the EVT Indication Expansion Domain will be:

Symptomatic intracranial hemorrhage (sICH) w*ithin (≤) 36 hours after randomization*, defined as presence of both 1) and 2):

1) *Brain image finding of major parenchymal hematoma (PH2), remote intraparenchymal hemorrhage, subarachnoid hemorrhage, or intraventricular hemorrhage, and*
2) *Clinical Deterioration, evidenced by:*
   i) *In all patients: ≥ 4-point increase on NIHSS, OR*
   ii) *In patients with mild NIHSS 0-5 deficits at entry: ≥ 2-point increase on any single NIHSS subitem*

5.6.1.2 Secondary Safety Endpoints

Secondary safety endpoints will be:

- Any radiologic intracranial hemorrhage within 36 hours after randomization
- Mortality by 90 days
- Serious adverse events within 90 days
- Early Clinical Deterioration, evidenced by within 36 hours of randomization:
  - In all patients: ≥ 4-point increase on NIHSS, OR
  - In patients with mild NIHSS 0-5 deficits at entry: ≥ 2-point increase on any single NIHSS sub-item

The following additional safety endpoints will be analyzed only in EVT patients:

- Unanticipated adverse device effects before hospital discharge
- Arterial access complications requiring surgical intervention
- Intracranial vessel perforation or dissection
- Embolization to new or distal territory before the end of the EVT procedure

5.7 Adverse Events and Serious Adverse Events

EVT Indication Expansion Domain will follow the detailed processes for Adverse Events and Serious Adverse Events specified in the STEP Platform Master Protocol.

6 Trial Conduct

6.1 Domain-Specific Data Collection

6.1.1 Domain-Specific Schedule of Assessments

	Baseline / Randomization	Procedure Visit (EVT patients only)	24h (±12h) after time of randomization	Day of Discharge	Day 90 (±15d)
Randomization- Domain A	X				
Informed Consent -Domain A	X				
EVT Procedure		X			
ASPECTS Score			X		
Neuroimaging Collection				X	
End of Study- Domain A					X

6.1.2 Endovascular Device Data Collection

This STEP Domain will track device utilization and report all identified off-label usages to the FDA annually.

6.1.3 Domain-specific Study Visits and Patient Assessments

At the Post-Procedure Visit that is performed in EVT-allocated patients, the following additional data regarding each pass of a study device will be recorded:

- Intermediate eTICI scores after each pass, including after completion of use of one type of EVT device before use of another type of EVT device

At the 24 hour visit

- ASPECTS score (If only MRI scan is available: Any change in the 'region' is counted as abnormal.)

At Hospital Discharge

- Neuroimaging Collection

6.1.4 NeuroImaging

Deidentified baseline qualifying images (CT and/or MR; CTA and/or MRA; CTP and/or MRP [if available]), catheter angiographic images, and any head CT and/or MR images performed up to 72 hours after randomization will be uploaded for potential central imaging review. If there are significant disagreements between the site and Core Lab regarding imaging findings, then the sites will be retrained.

6.2 Criteria for Discontinuation

As per the STEP Master Protocol.

6.3 Blinding

Day 90 mRS will be performed by site raters blinded to treatment assignment.

7 Statistical Considerations

7.1 Domain-specific stopping rules

See Domain Design Report Appendix for description of domain-specific stopping rules and models.

7.2 ENDOLOW PATIENTS

Participant-level data collected on behalf of the ENDOLOW trial (NCT04167527) (industry-funded, investigator-initiated, randomized trial of EVT versus MM) will be counted towards to the total sample size of STEP. The eligibility criteria of ENDOLOW is a subset of the DOMAIN A EVT Indications Low NIHSS strata. These data will not be analyzed for ENDOLOW as originally planned. Given the overlap with the STEP Domain A EVT Indications Low NIHSS strata, the ENDOLOW investigators have decided to stop their trial and contribute their data to the STEP analysis.

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