StrokeNet Thrombectomy Endovascular Platform Domain A Training (V5.0)

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on behalf of the STEP Executive Committee

Domain A Analysis

Unit of analysis (the group of patients who are analyzed together within a model).

1. **LVO patients with mild deficits/low NIHSS**

2. **MVO/DMVO patients with Non-dominant/Co-dominant M2 and M3 occlusions**

Domain A Secondary Endpoints

Clinical Efficacy

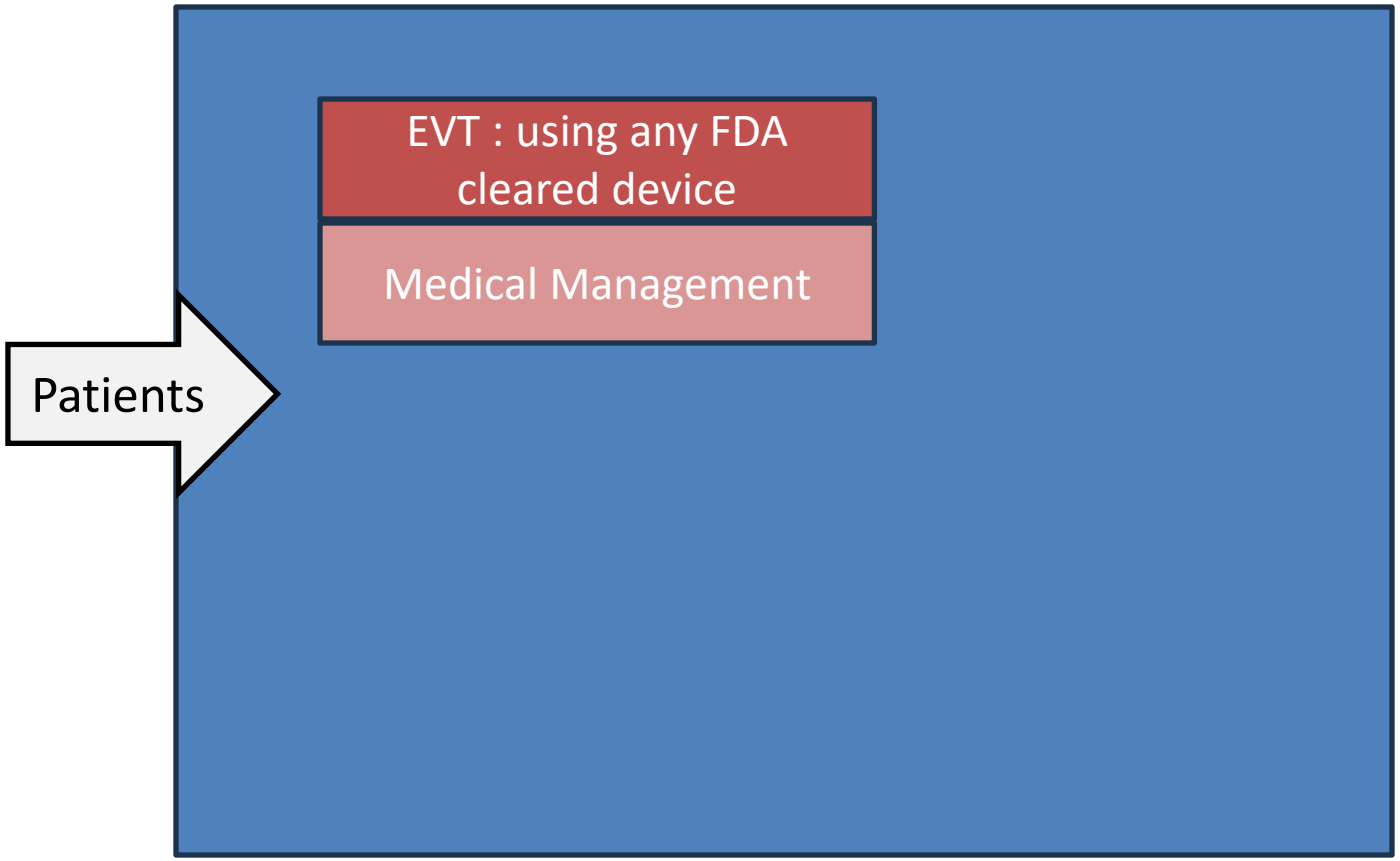
For all EVT INDICATION EXPANSION DOMAIN patients, secondary clinical efficacy endpoints will be:

- **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**
- **Ordinal analysis of the 10-level mRS (0/1A/1B/2A/2B/3A/3B/4/5/6)**
- **AMC (Academic Medical Center) linear disability score (ALDS)**

Domain A Sample size

- **The maximum sample size for this domain :**
  - **1,000 patients with LVO mild deficits/low NIHSS (over 4 years)**
  - **600 patients with MVO/DMVO (over 2.5 years)**

Domain A- Inclusion Criteria



- **Inclusion:**
  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. **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. The exception is for LVO Mild deficit/Low NIHSS 0-5 for which imaging would only need to be repeated if there has been significant improvement in the NIHSS prior to randomization.

Domain A Inclusion criteria- continued…

5. Has any one or more of the following presentations:

a) *Low NIHSS, LVO Patient* *(must have both):*

1. Mild presenting neurologic deficits - NIHSS 0-5

(Must have some focal neurological deficit attributable to the target occlusion if NIHSS 0)

2. Complete occlusion of the intracranial ICA or M1 MCA

b) Medium/Distal Vessel Occlusion

1. Visualized complete occlusion or perfusion deficit (Tmax >4s) supportive of a cortical branch occlusion in one of the following vessels:

   i) Non-dominant/Co-dominant M2 (defined as serving ≤ 50% of entire overall MCA territory)

   ii) M3

2. If symptom onset is >6h, the core must be less than 50% of the territory supplied by the occluded vessel as evident by either

   i) hypodensity and loss of grey-white border on NCCT or

   ii) ADC <620 mm^2/s on diffusion MRI or rCBF<30% on CTP

- NIHSS ≥ 8

Domain A 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 judgement

x) Known or high suspicion for underlying intracranial atherosclerotic disease (ICAD)

2. **Laboratory**

i) Known platelet count < 100,000

Domain A Exclusion criteria

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)

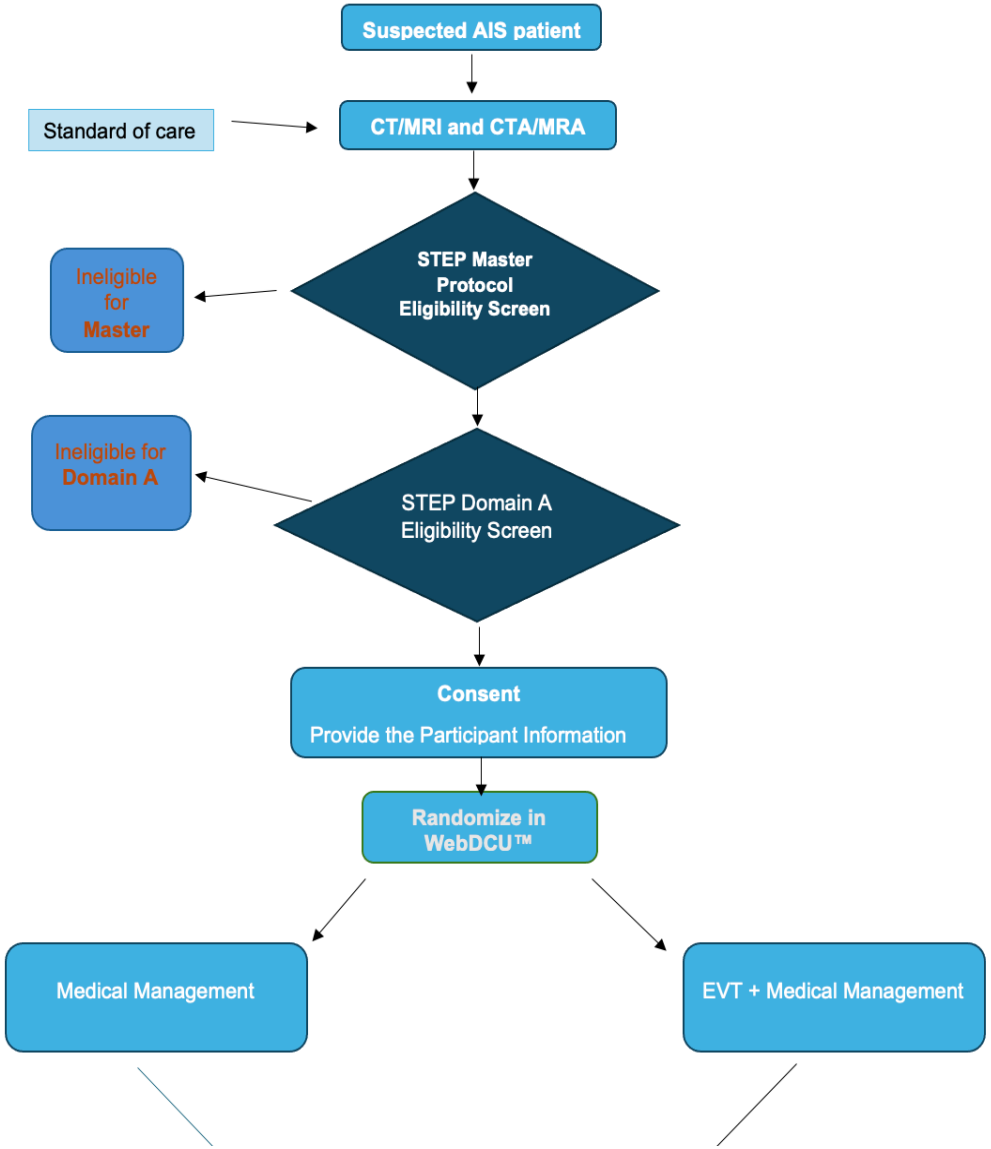
iv) Tandem occlusions

v) Significant mass effect with midline shift (>5mm)

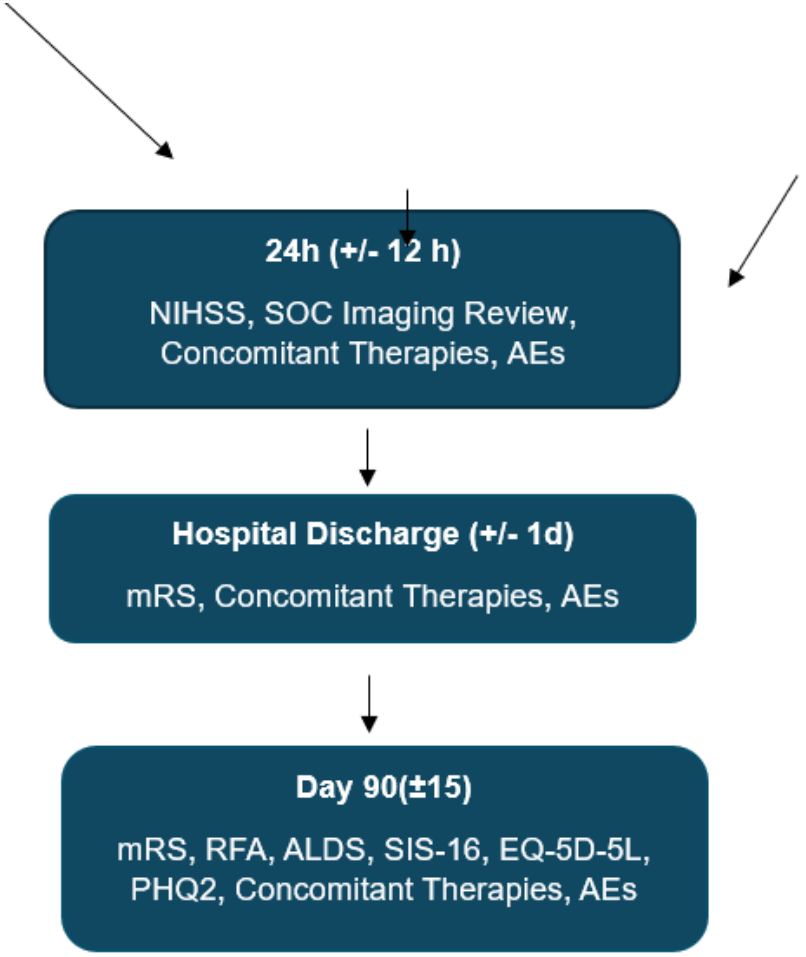
vi) Evidence of intracranial tumor (except small meningioma defined as (1) ≤ 3cm, (2) asymptomatic) as confirmed on CT/MRI

vii) Evidence of acute intracranial hemorrhage

Workflow for Domain A



Workflow for Domain A



Inclusive of Master Protocol Assessments for these visits.

Domain A Interventions

EVT + Medical Management:

- Using legally marketed devices.
- Choice of device(s) deployed will be at the discretion of the expert neurointerventionalist performing the procedure.

For M2/M3 occlusions, EVT should be performed with aspiration catheters or stent retrievers appropriate in size for the target vessel.

STEP Thrombectomy Best Practices training can be found at:
https://dcu.musc.edu/Campus/ProjectTraining/STEPThrombectomyBest%20Practices9_27_24.mp4)

Medical Management Alone:

- As per the national American Heart Association/American Stroke Association clinical practice guidelines
- Administer thrombolysis and antithrombotic (including DAPT) as indicated. Use of DAPT will be tracked.

Domain A Rescue Therapy

- For participants in the LVO/Mild Deficit Low 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 arterial puncture can occur within 24 hours of last known well.**

- For the DMVO strata, **rescue therapy is not allowed for the target occlusion**.

EVT performed outside of these protocol-allowed recue treatment will be considered protocol violation and a crossover.

Domain A Definition of symptomatic ICH

Symptomatic intracranial hemorrhage (sICH) within (≤) 36 hours after randomization, defined as presence of <u>both</u> 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

- *Note relatedness is not part of the definition*

STEP Heidelberg Bleeding Classification Training can be found at:

dcu.musc.edu/campus/ProjectTraining/STEPHeidelbergBleedingClassificationTraining.mp4

Domain A Schedule of Assessments

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

Refer to the STEP Master Protocol section 7.1.1 for the schedule of assessments. The domain-specific schedule of assessments is supplementary to the schedule of assessments in the Master Protocol.

Domain A and ENDOLOW

- ENDOLOW- investigator-initiated, industry-funded RCT of EVT vs Medical Management for LVO patients with low NIHSS. Patients enrolled in ENDOLOW will be considered towards STEP's final sample size.
- ENDOLOW CCC and DCC will hand over the trial data to the STEP NIH StrokeNet NCC and NDMC respectively
- Existing ENDOLOW sites that are selected as STEP sites (8 in US, 4 in Canada) will continue enrollment under the STEP protocol.
- ENDOLOW sites not selected for participation in STEP will close enrollment with the ENDOLOW trial closure