NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

STEP Platform

StrokeNet Thrombectomy Endovascular Platform Master Protocol Training (V7.0)

Eva A. Mistry, MBBS, MSCI - STEP MPI and Protocol PI
on behalf of the STEP Executive Committee

MUSC Medical University of South Carolina

University of CINCINNATI

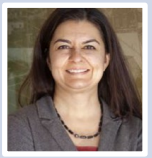
Berry Consultants Statistical Innovation

Leadership Team – MPIs/ Executive Comm

Eva Mistry, MBBS, MSCI
Protocol PI

Colin Derdeyn, MD
IDE Holder

Jordan Elm, PhD
Contact PI and Statistical PI



Pooja Khatri MD,
MSc- MPI

Jeffrey Saver, MD-
MPI

J Mocco, MD-
MPI

David
Fiorella, MD-
MPI

Raul Nogueira, MD –
MPI

Tudor Jovin, MD-
MPI

Adnan Siddiqui, MD –
MPI

Roger Lewis, MD, PhD-
Exec Comm Member

Leadership Team

NIH Leadership Team

Scott Janis, PhD
NINDS Program Officer

Mariam Afzal, BA
NIH StrokeNet and
STEP Program Official

Clinton Wright, MD
Director, NINDS Division
of Clinical Research

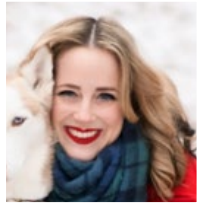
Independent Medical Monitors

Phil Gorelick, MD

Cemal Sozener, MD

Gene Sung, MD

Leadership Team - Managers



Kalli Beasley, MPH
Prime Project Manager

Melissa Hoffman, BS
NCC Project Manager

Caitlin Schaffner, MPH
Site Monitoring Manager

Faria Khattak, MPH
NDMC Data Manager

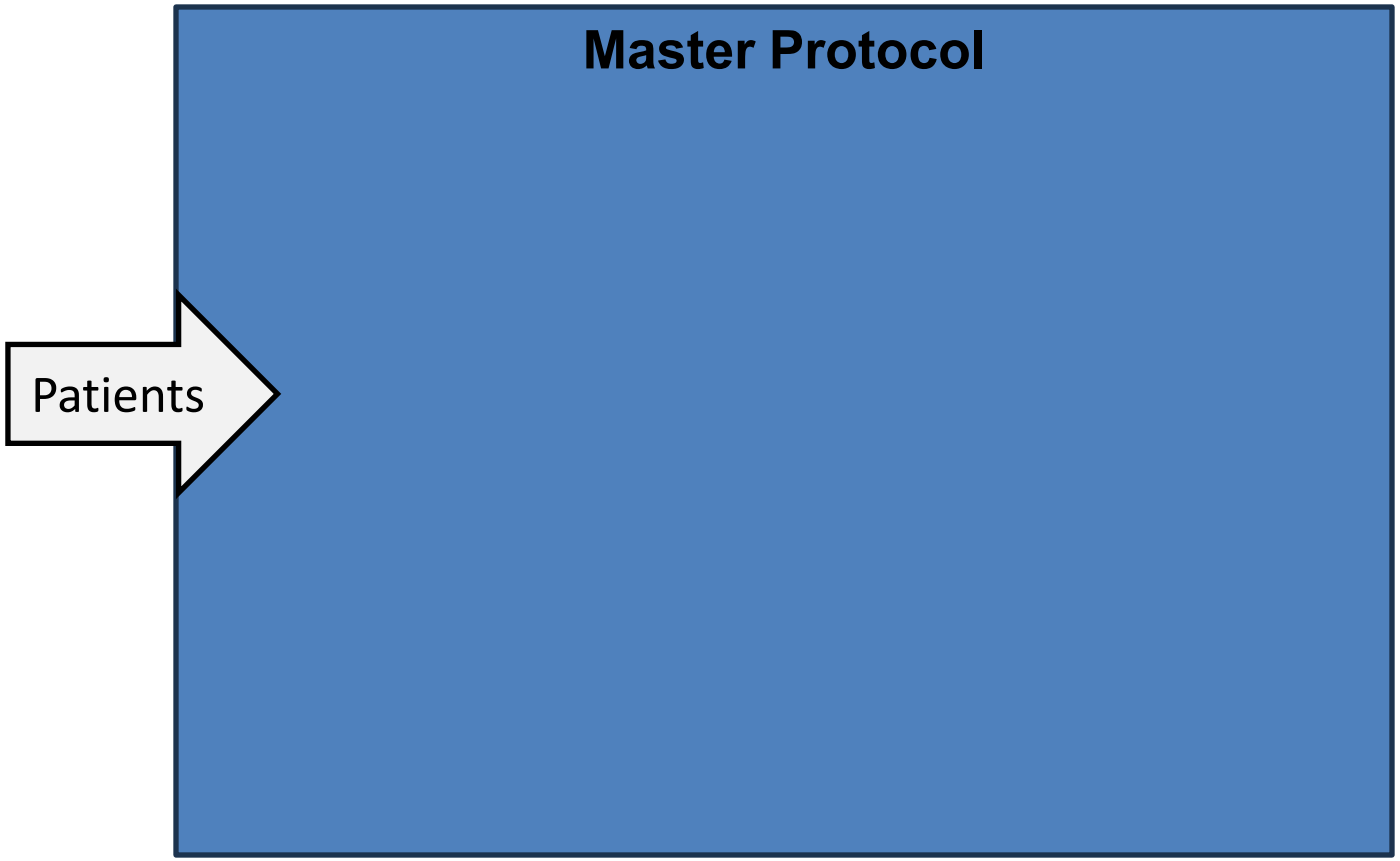
Study Description

- Randomized Multifactorial Adaptive Platform (REMAP design)
- Up to 65 sites across the US + up to 10 Canadian sites
- Leverages existing registries for data collection
  - AHA Get with the Guidelines
  - NVQI-QOD

Primary Objective

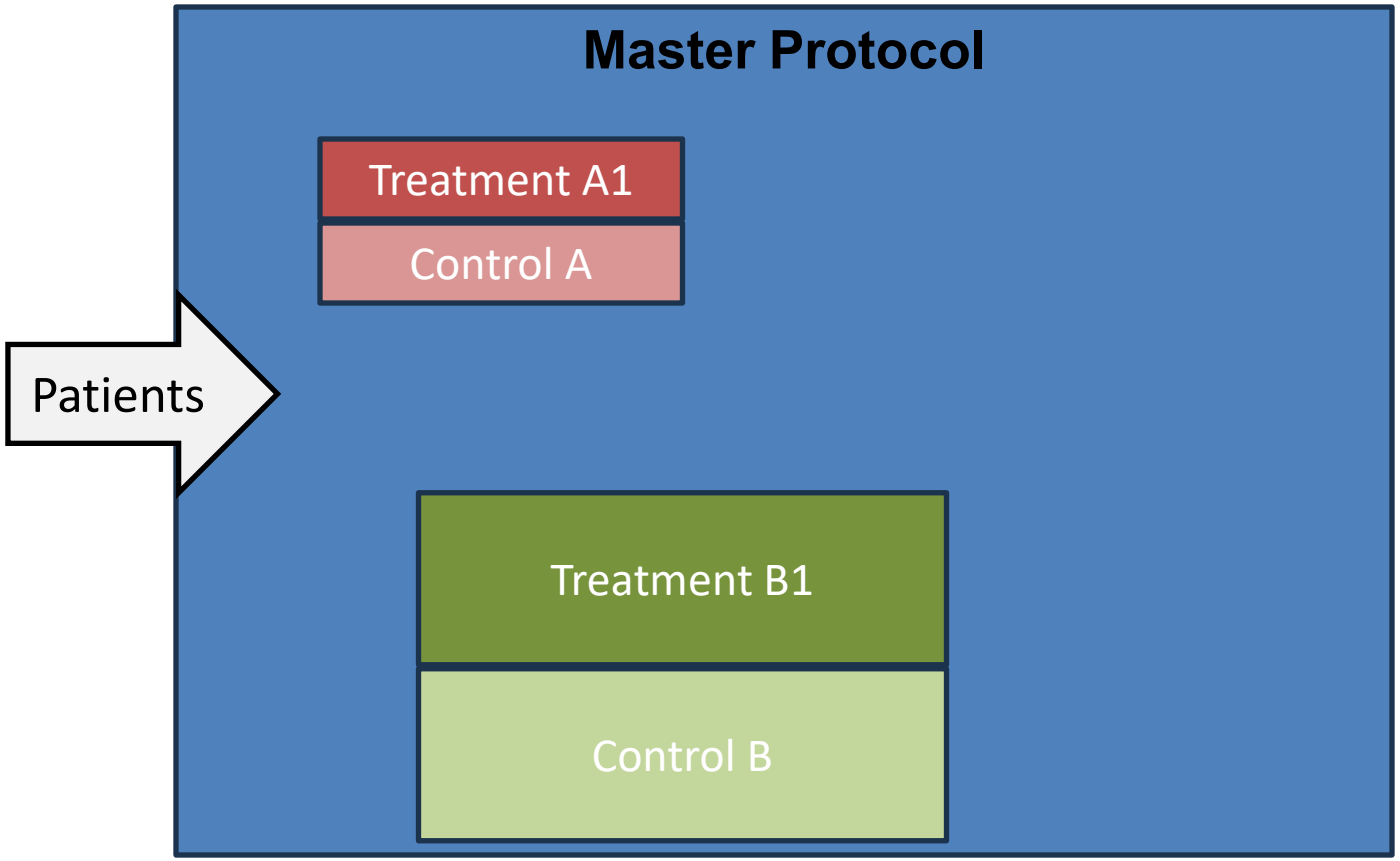
- **To determine the optimal treatment strategy for patients with AIS due to Large or Medium vessel occlusions (LVOs or MVOs)**

Master Protocol



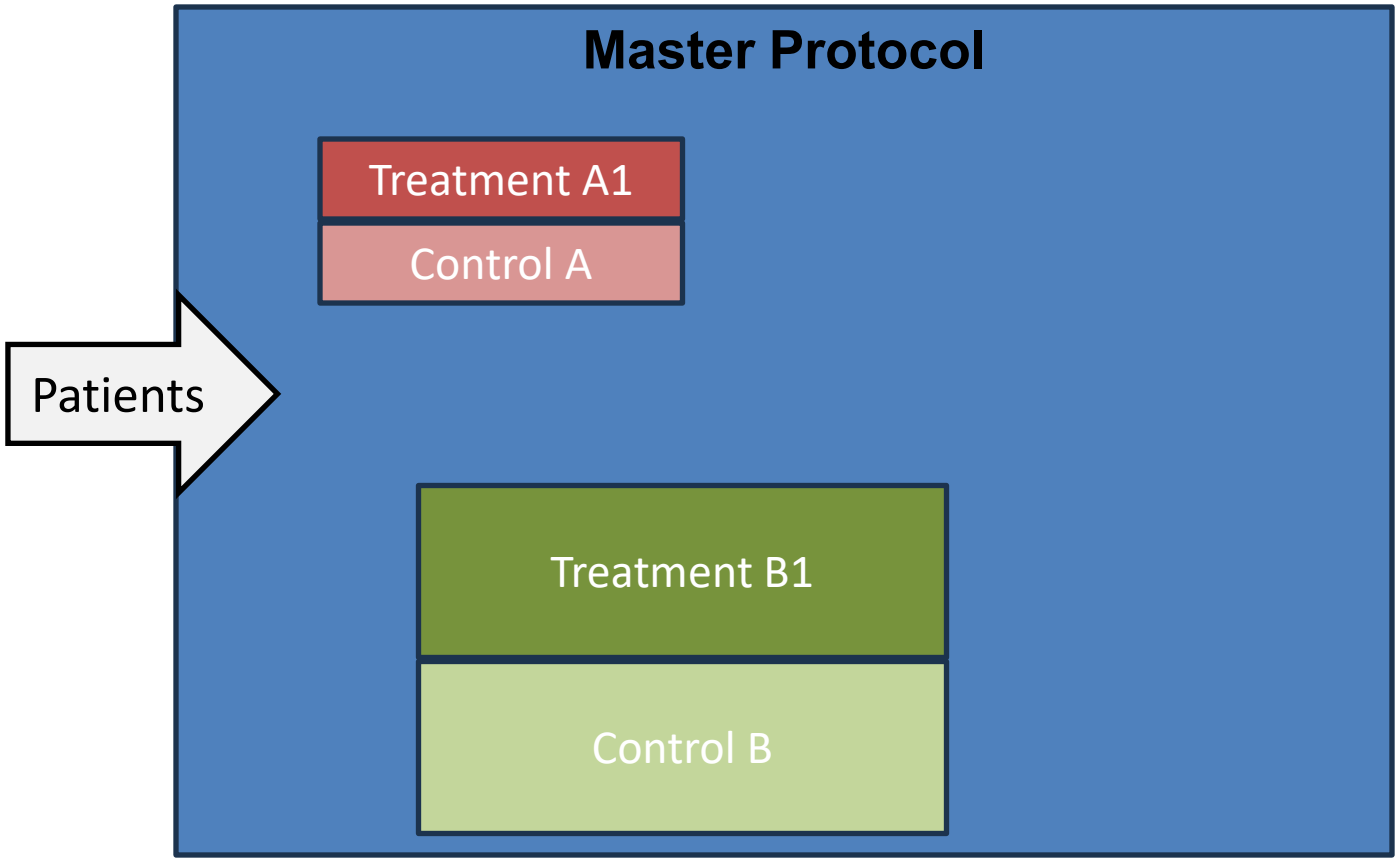
- **Defines the largest set of Inclusion/Exclusion Criteria to be studied**
  - ✓ Suspected acute ischemic stroke patients
  - ✓ Likely causative intracranial large or medium vessel occlusion
  - ✗ Proven contraindication to endovascular thrombectomy
  - ✗ Prisoners/incarcerated
- **Broadly defines overall study terminology and research procedures**
  - ✓ STEP primary outcome is 90-day mRS (using utility weighted approach)
- **Specifies a single underlying statistical model**

Domains (studies of interventions)



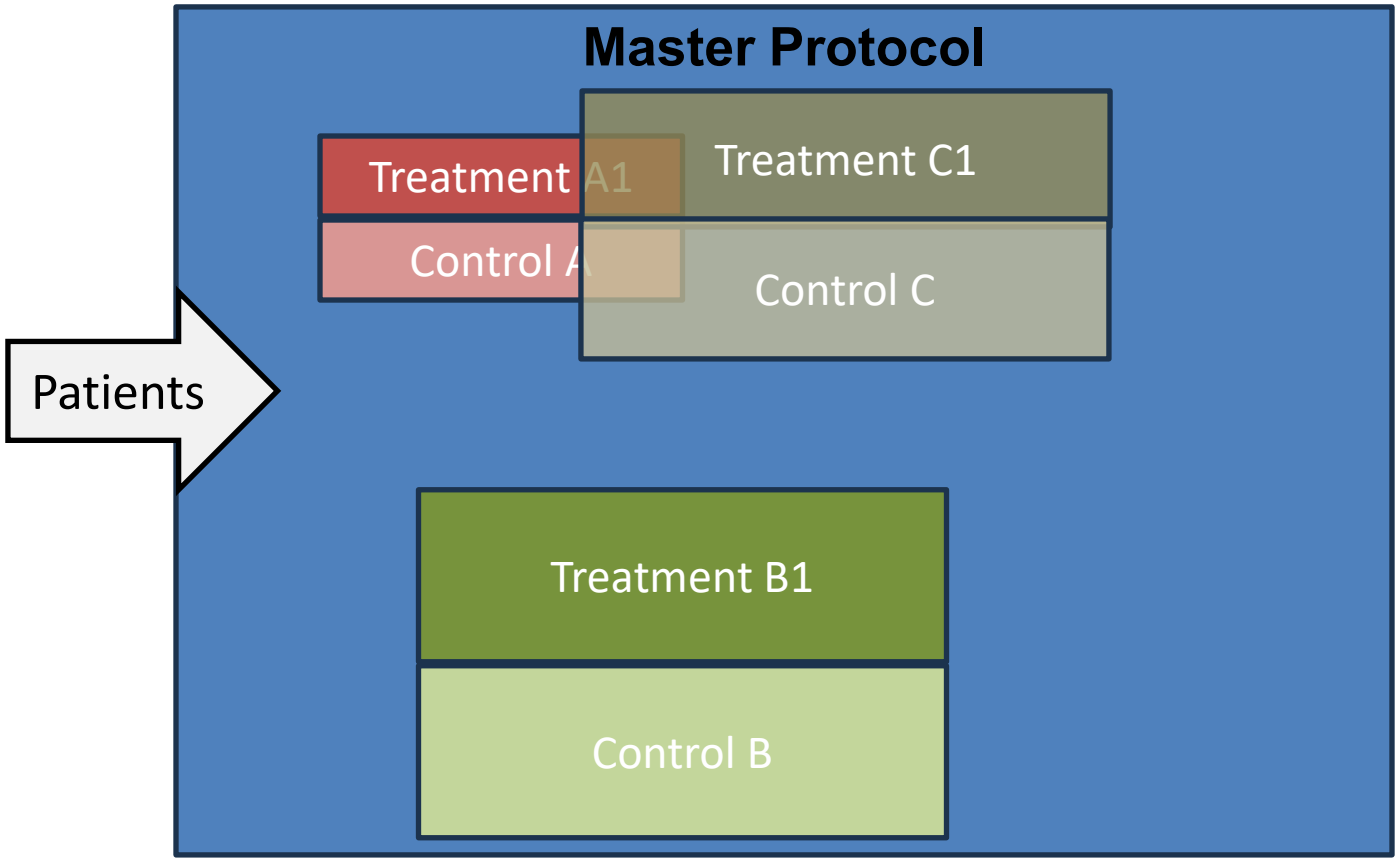
- Studies of **mutually exclusive** interventions
  - ✓ Domain A- EVT vs MM
    - LVO, NIHSS<6
    - Medium/distal vessel occlusions
  - ✓ (Hypothetical) Domain B- Neuroprotectant 1 vs Neuroprotectant 2 vs control
  - ✓ (Hypothetical) Domain C- Adjunctive therapy 1 vs control

Domains specific appendices



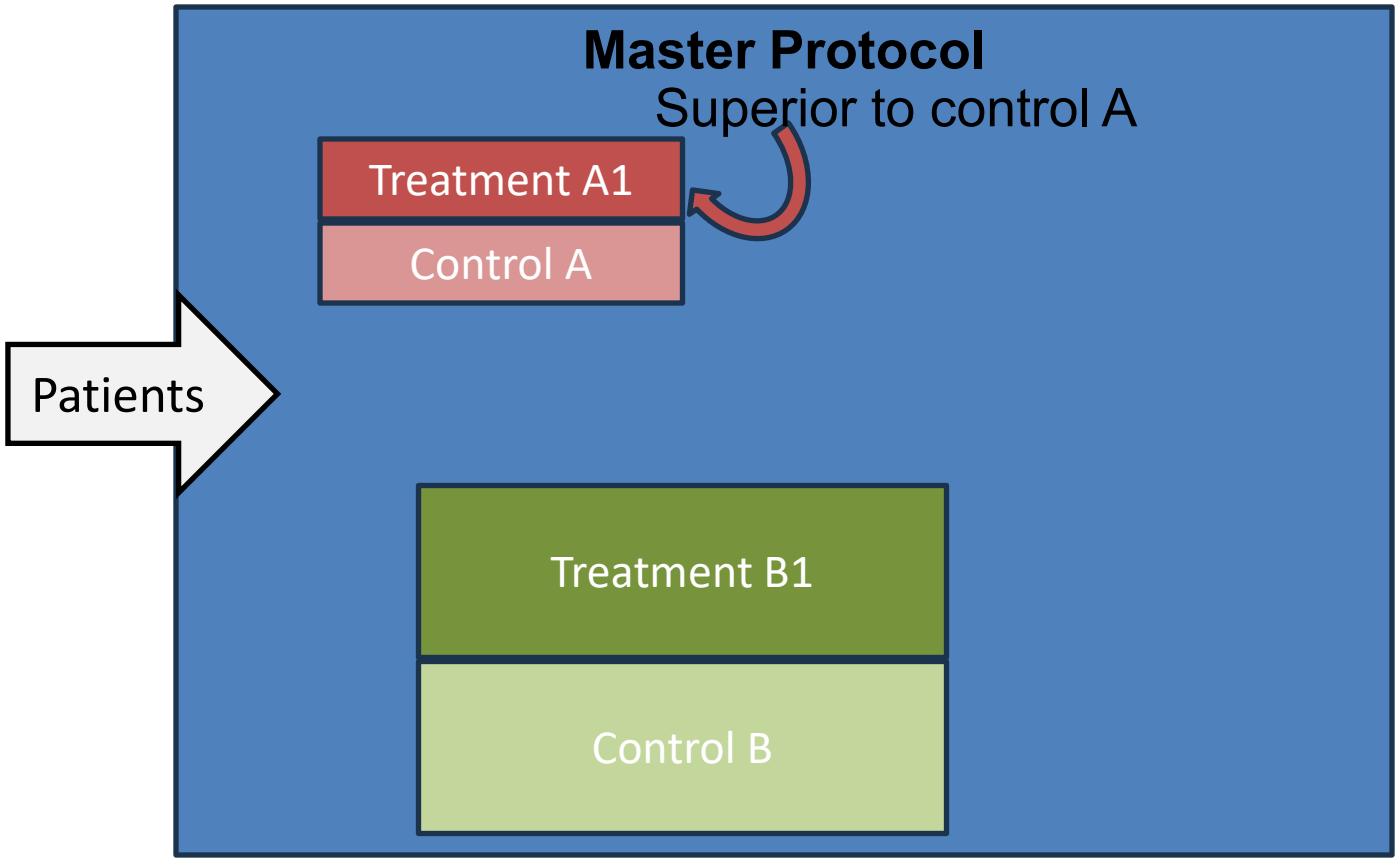
- Defines a I/E criteria for domain-eligible patients
- Details the type/delivery of intervention(s)
- Detailed specifics
  - ✓Randomization/ adaptations
  - ✓Analysis methods
  - ✓Additional research procedures
  - ✓co-enrollment

Domains (studies of interventions)



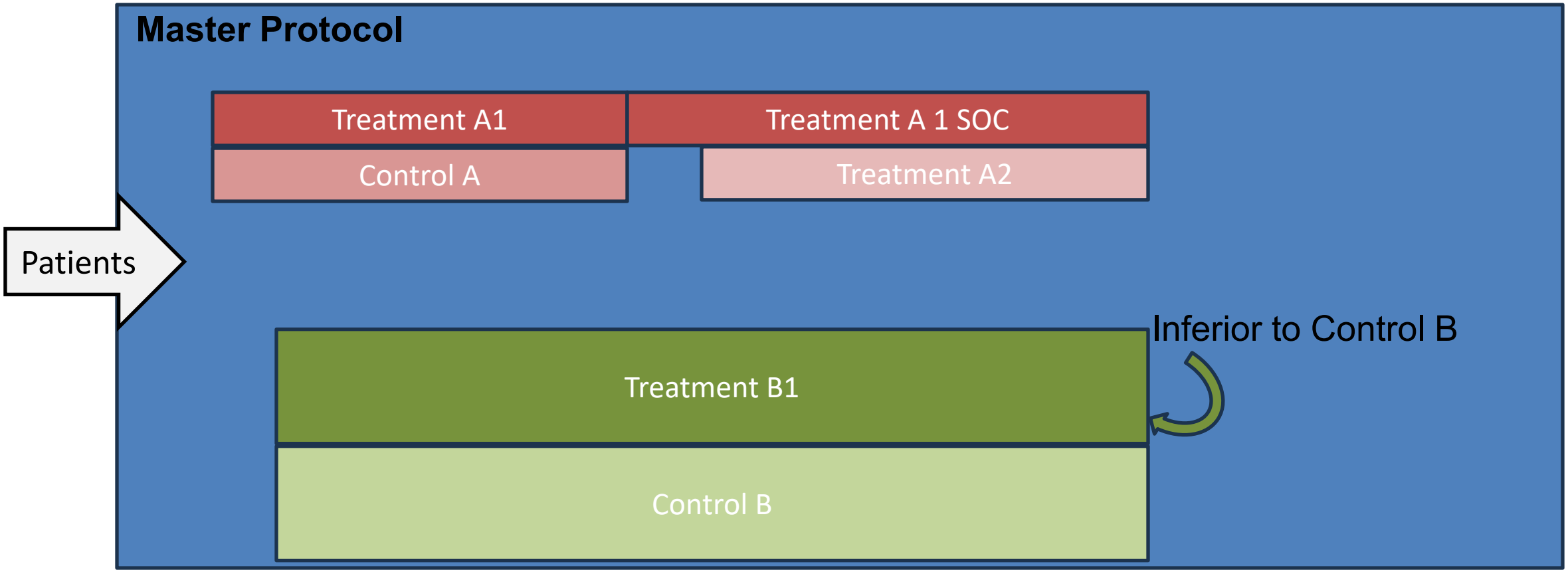
- Treatment within the domains are mutually exclusive but the patient population can overlap between two domains
- Patients can be randomized within multiple domains (**multifactorial**)

Enduring platform- Decisions



- Following types of decisions can be made for an <u>entire domain</u> or <u>particular domain arm (s)</u> or <u>pre-defined subset of patient population (strata)</u>
  - ✓Superior
  - ✓Inferior
  - ✓Futile
  - ✓Equivalent
- Decisions are based on statistical triggers
  - ✓Based on pre-defined analysis frequency
  - ✓Using platform statistical model

Enduring platform- Therapy domains can be perpetually added



Statistical Design - Adaptations

- Interim analyses every quarter
- Domains added and dropped
- Interventions added/dropped within a domain
- Response Adaptive Randomization if more than 2 groups in a domain

Intent-to-Treat Analysis

- All participants in the platform will be analyzed according to their randomly assigned intervention (regardless of whether or not they received the intervention; ITT)

- The primary analysis set: all participants that are randomized to at least one intervention within at least one domain.

- The intent-to-treat group for a domain:
  - Informed only by participants randomized to the respective domain (effect for domain)
  - Covariates can be informed by all participants.
  - A patient not randomized within a domain is not a control for the respective domain.

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STEP Platform

Primary Endpoint : modified Rankin Score (mRS) at 90 days

Ordinal scale 7 points is assigned the following standard utility values.

The mean score for a population or intervention will be modeled as normally distributed.

mRS	0	1	2	3	4	5	6
UW-mRS	1	0.91	0.76	0.65	0.33	0	0

Single Unifying Statistical Model

- **Single inferential model:** model the primary outcome, Y = UW-mRS, as a function of each randomized treatment from each domain

$$Y = [\text{covariates}] + [\text{intervention effects}] + [\text{intervention} * \text{stratum}] + [\text{intervention} * \text{intervention}] + [\text{error}]$$

- Can address across domain interactions (not default)
- Adjusts for time period (year) of randomization
- Domains may have specific analyses.

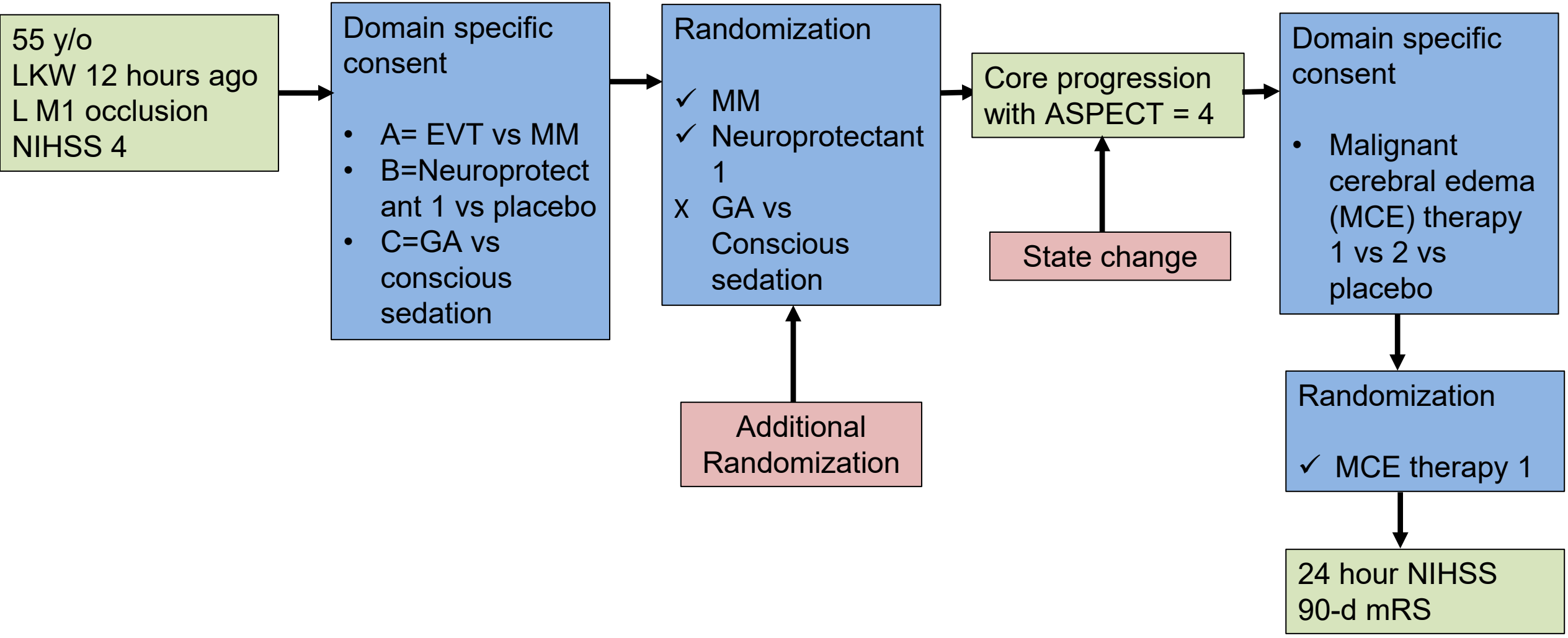
STEP Statistical Model

- The primary analysis within a domain will be based on the posterior distribution for the relative effects of the interventions within that domain.
- Superiority: At any adaptive analysis, if a single intervention has **at least a 0.99 posterior probability** of being the optimal domain therapy, then that intervention will be deemed as being superior to control in that target population.
- Inferiority: If an intervention has **less than a 0.01 posterior probability** of being the optimal domain therapy then that intervention will be deemed as being inferior for that target population.
- There are also rules for futility and equivalence

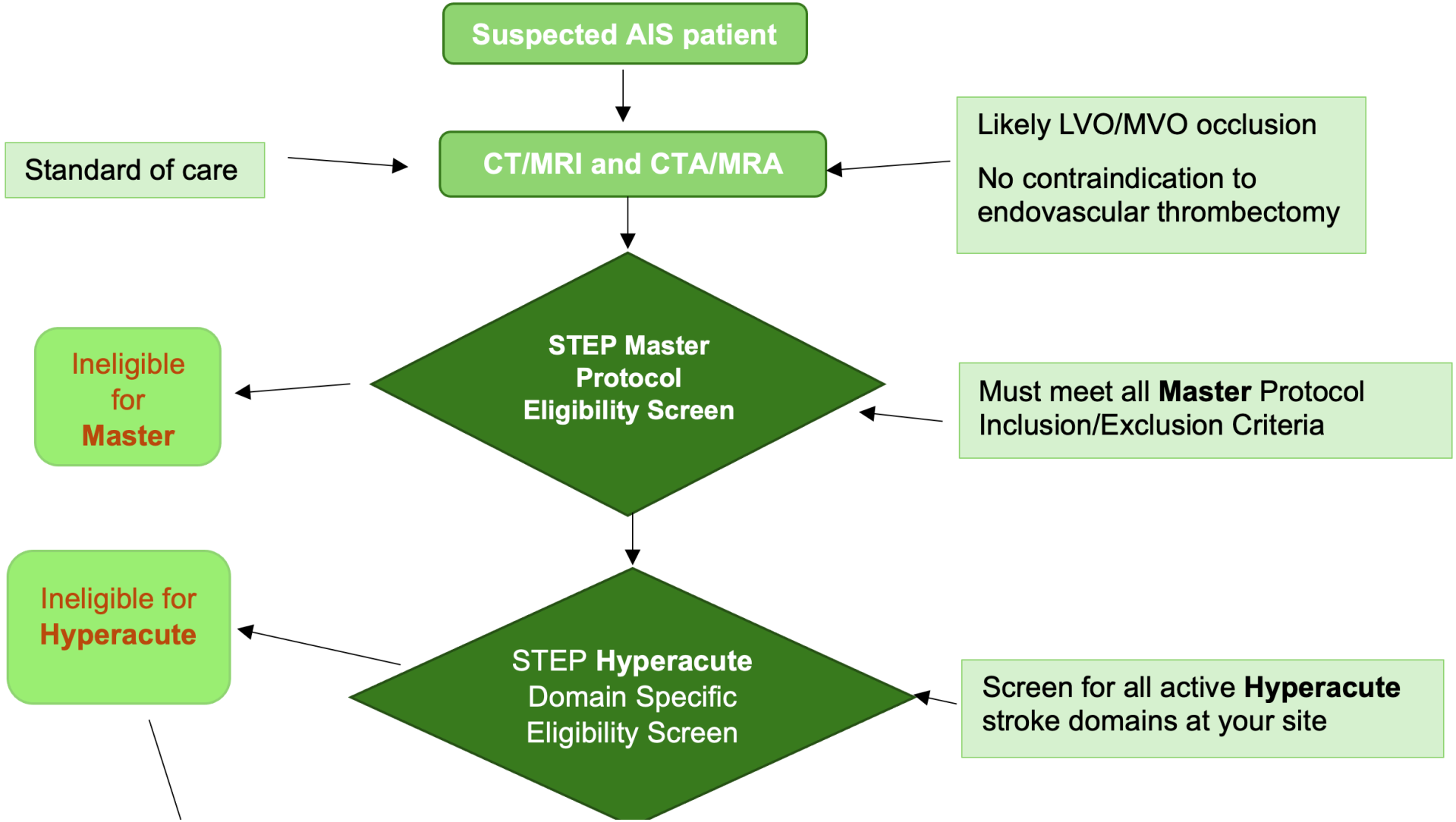
Consent Procedures

- Domain specific consent forms:
  - Electronic consent is strongly encouraged (unless participant or LAR prefers paper consent)
  - Remote consent is encouraged for transfer patients
  - Domain specific consents are shown according to specific inclusion/exclusion criteria for given domains
  - As a participant becomes eligible for more domains, consent forms specific to those can be presented
  - Master protocol participant information sheet
    - One-page sheet explaining the concept of platform in lay language
    - Does not need to be signed

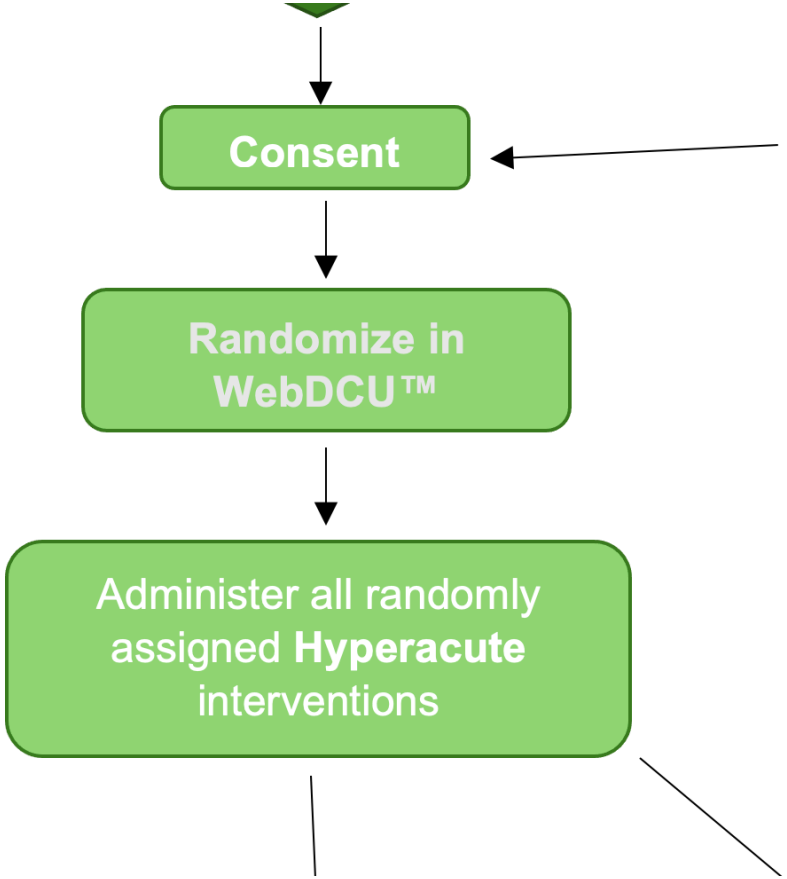
Enrollment Example-1



Study Workflow



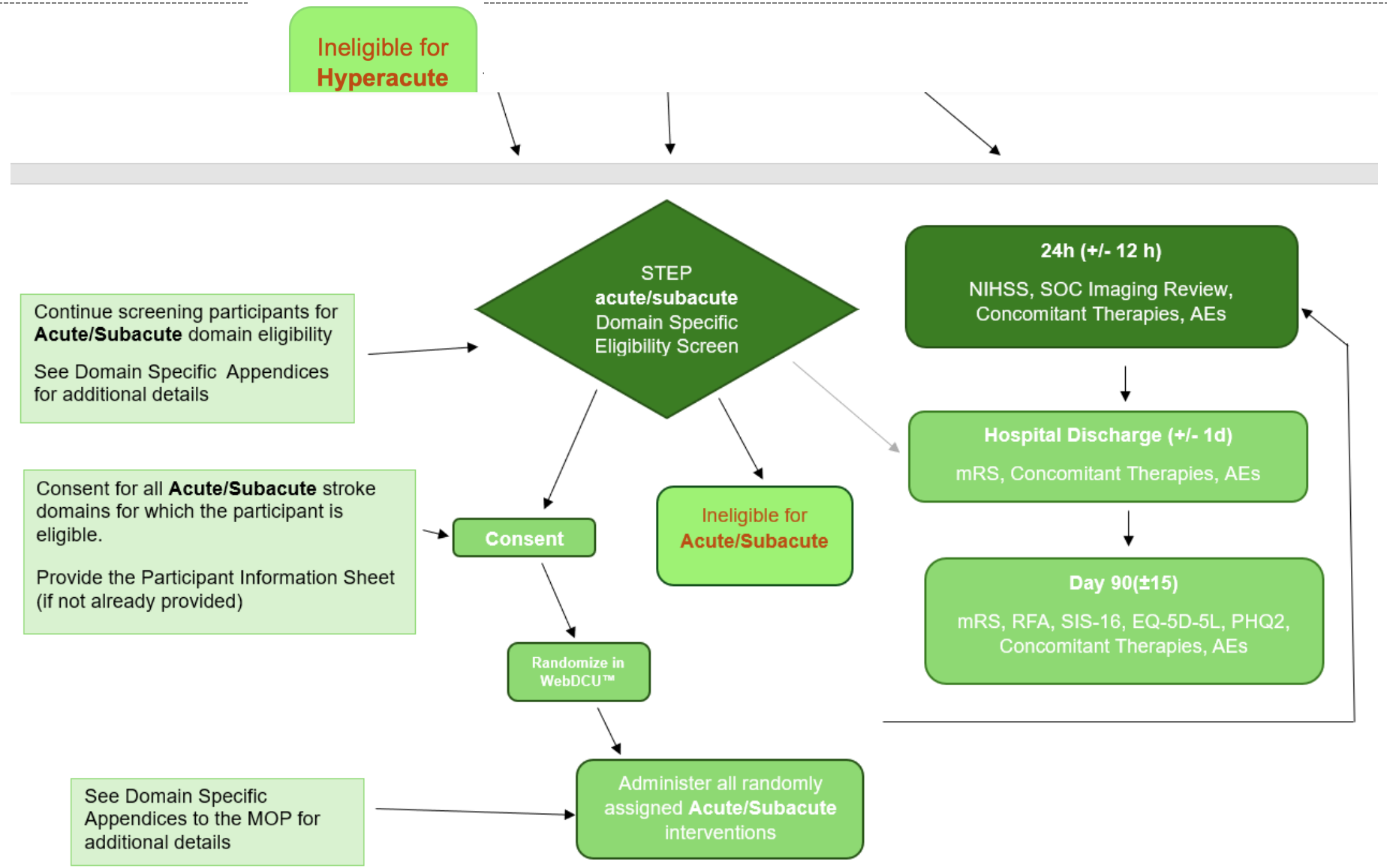
Study Workflow



Consent for all **Hyperacute** stroke domains for which the participant is eligible.

Provide the Participant Information Sheet.

Study Workflow



Schedule of Assessments

	Baseline / Randomization	Procedure Visit (EVT patients only)	24h (±12h) after time of randomization	Hospital Discharge (±1d)	Day 90 (±15d)
Subject Enrollment and Demographics	X				
Inclusion and Exclusion Criteria	X				
Informed Consent	X				
Neuroimaging Findings (including ASPECTS)	X				
Assessment for presence of ICH			X**		
Medical History	X				
Prior Medications	X				
Vital Signs	X				
Labs	X				
NIHSS	X*		X*		
Pre-stroke mRS	X				
Post-stroke mRS				X**	X**
Concomitant Therapies	X		X	X	X
Adverse Events			X	X	X
Hospital Discharge Information				X	
EVT angiogram assessment (EVT Patients Only)		X*			
SIS-16					X**
EuroQOL-5D-5L					X**
Patient Health Questionnaire 2					X**
Biospecimen Collection (Optional)			X		

NOTE: STEP uses a "hybrid" registry-based randomized clinical trial (rRCT) design.[20,22-24,81]
All datapoints are assessed and documented at a minimum with the high rigor methods of the GWTG-Stroke/NVQI-QOD nationwide quality registries. In addition, select datapoints of particularly importance are assessed and documented with intensified rigor, by using only certified raters.

X: Assessment performed by study coordinator/site investigator using information collected as routine clinical care
X*: evaluation by individual with STEP Platform-recognized training and/or certification is strongly encouraged
X**: evaluation by individual with STEP Platform-recognized training and/or certification is required
At least one imaging scan is expected within 36 hours of randomization

Appendix 1 describes biospecimen collection procedures for consented biobank participants

Source for Data Collection

	Baseline / Randomization	Procedure Visit (EVT patients only)	24h (±12h) after time of randomization	Hospital Discharge (±1d)	Day 90 (±15d)
Subject Enrollment and Demographics	T^G /T^W				
Inclusion and Exclusion Criteria	T^W				
Informed Consent	T^W				
Neuroimaging Findings (including ASPECTS)	T^W				
Assessment for presence of ICH			T^W		
Medical History	T^G				
Prior Medications	T^G				
Vital Signs	T^G				
Labs	T^G				
NIHSS	T^W		T^W		
Pre-stroke mRS	T^G				
Post-stroke mRS				T^W	T^W
Concomitant Therapies	T^G		T^W	T^G	T^G
Adverse Events			T^W	T^W	T^W
Hospital Discharge Information				T^G	
EVT angiogram assessment (EVT Patients Only)		T^N /T^W			
SIS-16					T^W
EuroQOL-5D-5L					T^W
Patient Health Questionnaire 2					T^W
Biospecimen Collection (Optional)			T^W		

T^G: Transferred from GWTG-Stroke database (with permission of site hospital and IRB)
T^N: Transferred from NVQI-QOD databases (with permission of site hospital and IRB)
T^W: Data entered directly in the WebDCU

STEP Safety Monitoring

- Safety outcomes (Adverse Events of Special Interest)
- Adverse Events and Serious Adverse Events
- Unanticipated Problems
- Independent Medical Monitor
- Safety Stopping

Adverse Events of Special Interest (AESIs) to be Monitored by DSMB

- **Safety Endpoints (Adverse Events of Special Interest)**
  1. **Symptomatic intracranial hemorrhage within 36 hours after randomization**
  2. **Any radiologic intracranial hemorrhage within 36 hours after randomization**
  3. **Mortality by day 90**
  4. **Serious adverse events (SAEs) within 90 days**

- **EVT Arm-Specific Safety Endpoints**:
  1. **Unanticipated adverse device effects before hospital discharge**
  2. **Arterial access complications requiring treatment, vessel perforation, vasospasm, vessel dissection before hospital discharge**
  3. **Embolization to new territory before the end of the EVT procedure**

Serious Adverse Events and Reporting

Reporting Timelines:

- **SAEs and UADEs <u>not</u> listed as common occurrences in the MOP:** report within **24 hours** of first knowledge.
- **SAEs and UADEs listed as common occurrences in the MOP:** report within **5 days** of first knowledge.
- **AESIs:** report within **5 days** of first knowledge, unless otherwise specified in the Domain-Specific Appendix.
- **Other non-serious adverse events are not reportable.**

Additional Clarifications

Events should be reported upon first awareness and followed until resolution or study exit.

Serious Adverse Events and Reporting

The Independent Medical Monitors (IMM) will monitor the study with regard to safety on an ongoing basis to identify any safety concerns.

- **Review all SAEs**
- **Determine whether they are related to study intervention**
- **Communicate with the investigators for any questions or clarifications regarding an event.**

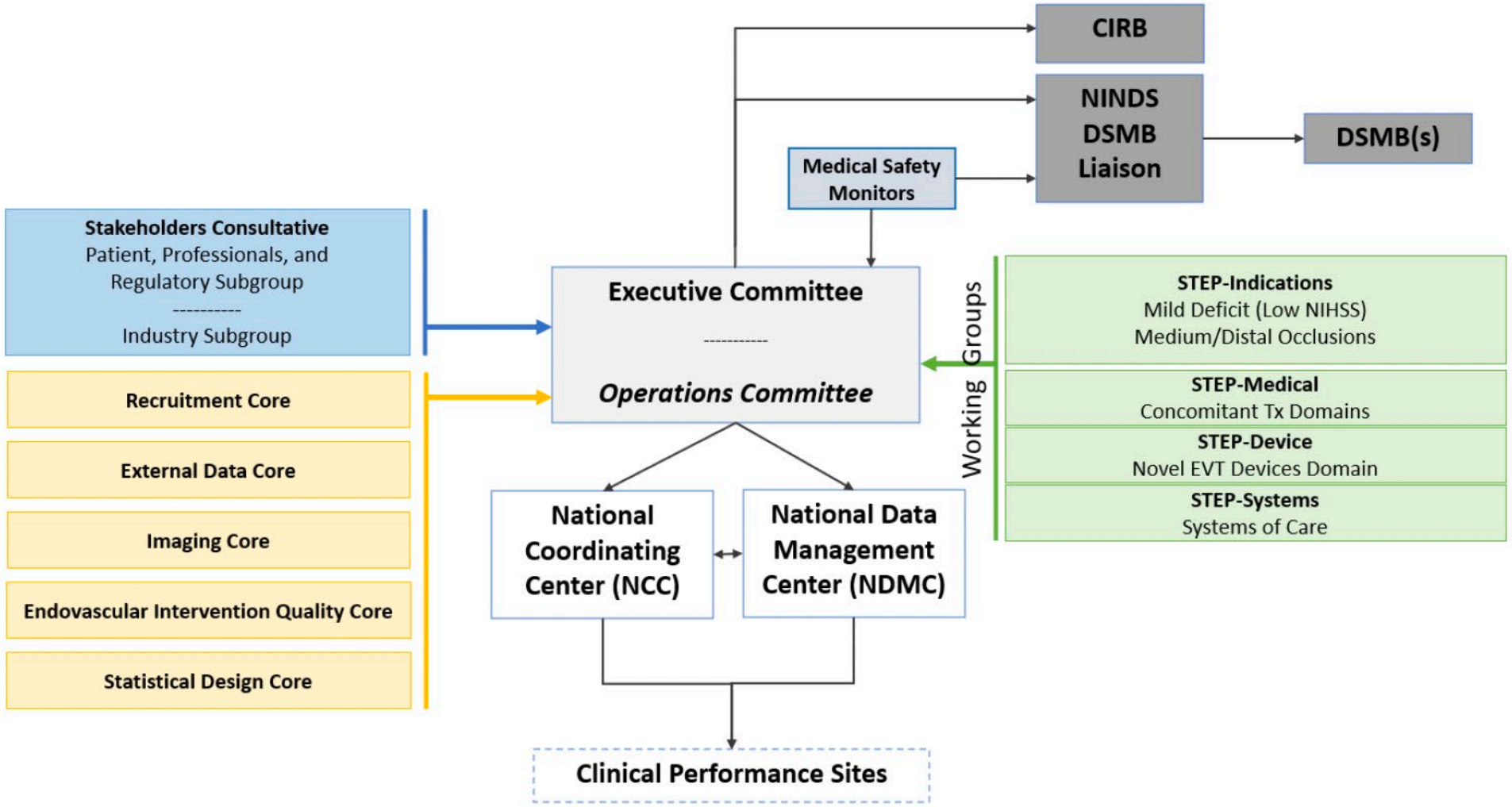
Throughout the study, approximately every six months, the Executive Committee and the IMM will review aggregate reports on the incidence rates of all reported AEs, whether serious or not. Should such monitoring uncover issues that may threaten subject safety (e.g., unexpectedly high rate of AEs), the study statistician and PIs will prepare a report to be submitted to the DSMB for their review proposing further actions to be taken, if any.

Safety Monitoring

Semi-annual DSMB reports

- **Partially unblinded treatment group (Closed Session)**
- **Safety Outcomes (Adverse Events of Special Interest) by domain/strata/treatment group**
- **Subjects with Event**
- **Relative Risk**
- **Expected rates (TBD by Domain) as a guideline (*not formal stopping rule*)**
- **The arm will be paused if there is >90% probability that the sICH rate exceeds expected rate (w/in domain/strata/arm)**

STEP Organization



STEP Participating Sites