National Institute of Neurological Disorders and Stroke

NINDS Perspective: Need for an Endovascular Platform

Clinton Wright

NINDS, Division of Clinical Research

February 8, 2024

NIH StrokeNet
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STEP Platform

Disclosures

None relevant to this talk

How did we get here?

EVT Indication Expansion → *e.g., EVT for low NIHSS, large core, children, etc…*

Novel / Improved Concomitant Therapy to EVT → *e.g., BP control, avoiding tPA, general anesthesia or sedation, novel neuroprotective agents, etc…*

Technol / Systems Improve Access to EVT → *e.g., prehospital identification for EVT routing, etc…*

Deluge of EVT Proposals to NINDS

Guidance Snapshot

U.S. FOOD & DRUG ADMINISTRATION

Master Protocols for Drug and Biological Product Development

Draft Guidance

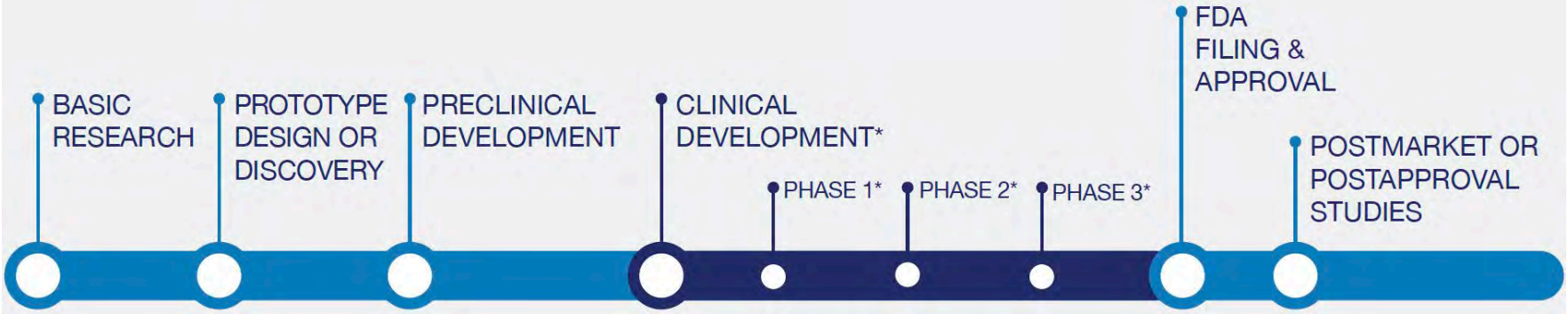
What Is A Master Protocol?

One designed with multiple sub-studies:

- May have different objectives
- Are coordinated within an overall study structure to evaluate one or more medical products
- One or more diseases or conditions

Drug Development Timeline

***When to Apply the Guidance Recommendations**



Umbrella trial

Evaluates multiple medical products at the same time for a single disease or condition

Basket trial

Evaluates a medical product for multiple diseases, conditions, or disease subtypes

Platform trial

Evaluates multiple medical products for a disease or condition and medical products can enter or leave the platform in an ongoing manner

Building off previous and growing experience, the NINDS pursued a clinical trial platform to answer the many questions we have been receiving in the EVT space

	STAMPEDE	GBM AGILE	Healey Center for ALS	HEAL	
Platform	STAMPEDE	GBM AGILE	Healey ALS	EPPIC NET (HEAL)	ACTIV
Condition	Prostate CA	Glioblastoma	ALS	DPN	COVID-19
Year started	2005	2019	2020	2020	2020
Agents/pops tested	10	4	5	>4	27
Centers	>120	>23	>54	>24	>620
Patients	>10,000	>550	>1000	>1000	>20,000

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Funded by a Grant from the National Institutes of Health

Coordinating Center

Renewal RCC

New RCC

Legacy RCC

Overview

- Launched in 2013
- 17 active studies
- 27 regional centers with over 500 satellite stroke hospitals, a coordinating center (Cinn), and a data coordinating center (MUSC)
- Phase 1/2 and phase 3 clinical trials (ancillary studies) and biomarker studies to advance acute stroke **treatment**, **prevention**, and **recovery**

http://nihstrokenet.org/

Next up: **Design and Logistics Overview**

Eva Mistry, M.D.

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STEP Platform

STEP: Design and Logistics Overview

Eva A. Mistry, MBBS, MSCI, FAHA

STEP MPI and Protocol PI, on behalf of the STEP Executive Committee

Associate Professor

Department of Neurology and Rehabilitation Medicine

University of Cincinnati

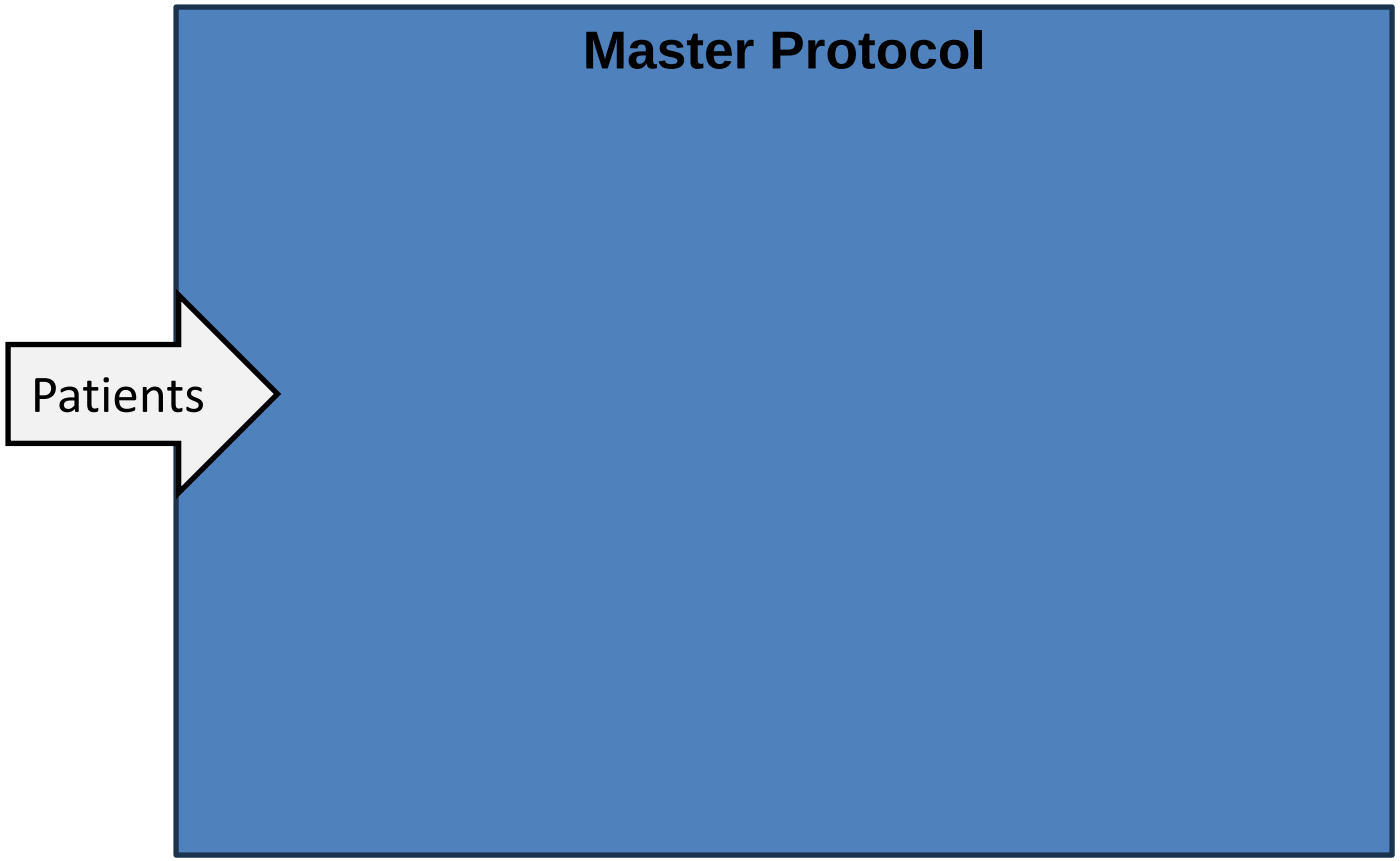
Disclosures

Affiliation/Financial Relationship	Organization/Company
Grant/Research Support	• NIH (UG3/UH3NS125023 , U24NS107241, 1OT2NS129366, K23NS113858) • PCORI (AD-2022C1-25624)
Consulting Fees/Honoraria	• RAPID AI/iSchemiaView, AbbVie, SilverCreek Pharma, AAN
Other Financial Benefit	• American Heart Association (compensation for editorial services)
Other Non-financial Disclosure	• Translational Sciences Inc

STEP Design

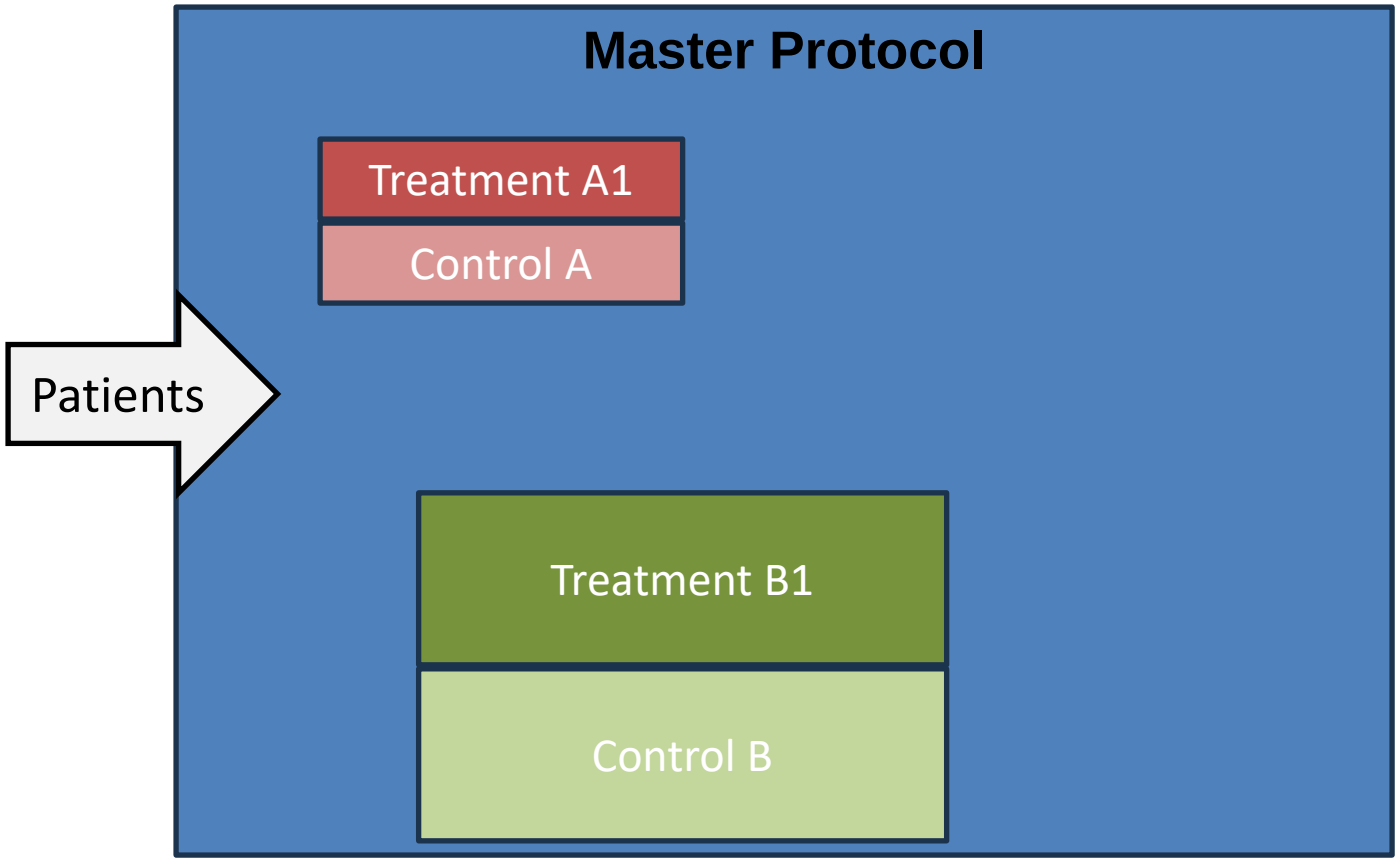
- Randomized Multifactorial Adaptive Platform (REMAP design)
- 38 sites across the US
- Leverages existing registries for data collection
  - AHA Get with the Guidelines
  - NVQI-QOD

STEP- Master Protocol



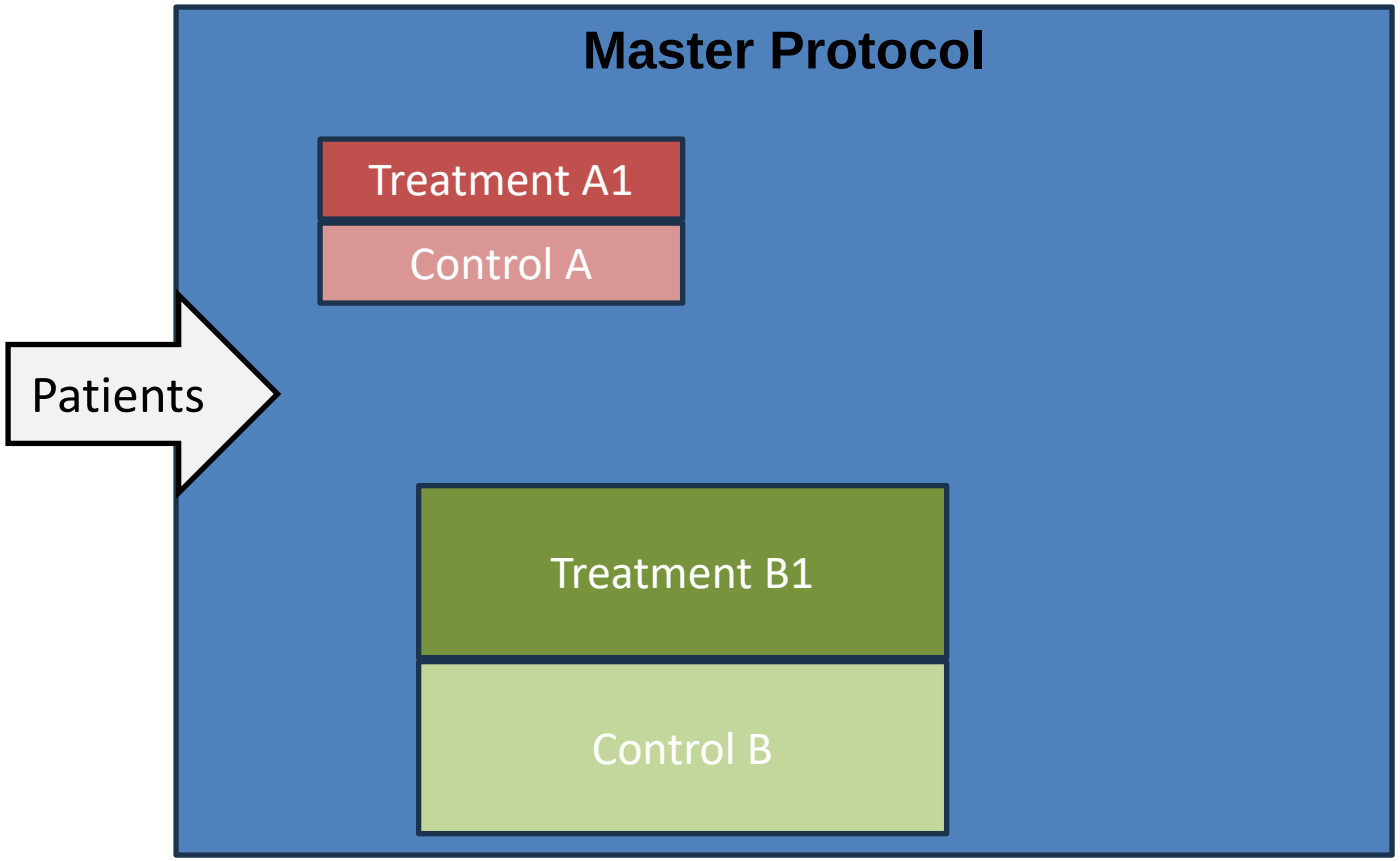
- Defines the largest set of Inclusion/Exclusion Criteria to be studied
  - ✓ Acute ischemic stroke patients
  - ✓ Intracranial large or medium vessel occlusion
- Broadly defines overall study terminology and research procedures
  - ✓ STEP primary outcome is 90-day mRS (using utility weighted approach)
- Specifies a single underlying statistical model

STEP- Domains (studies of interventions)



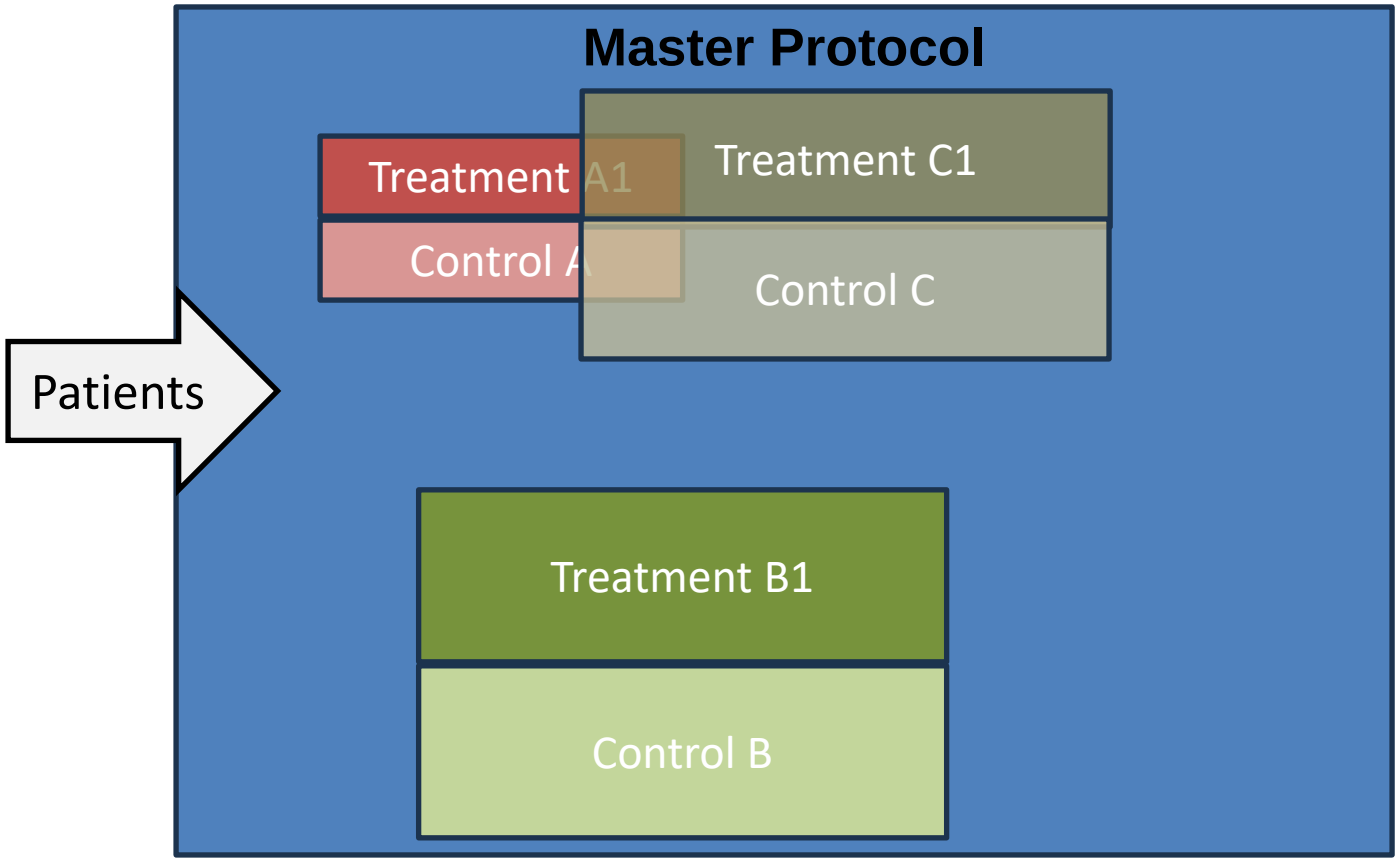
- Studies of **mutually exclusive** interventions
  - ✓ Domain A- EVT vs MM
    - o NIHSS<6
    - o Medium/distal vessel occlusions
  - ✓ (Hypothetical) Domain B- Neuroprotectant 1 vs Neuroprotectant 2 vs control
  - ✓ (Hypothetical) Domain B- Adjunctive therapy 1 vs control
- Patients can be randomized within multiple domains (**multifactorial**)

STEP- Domains specific appendices



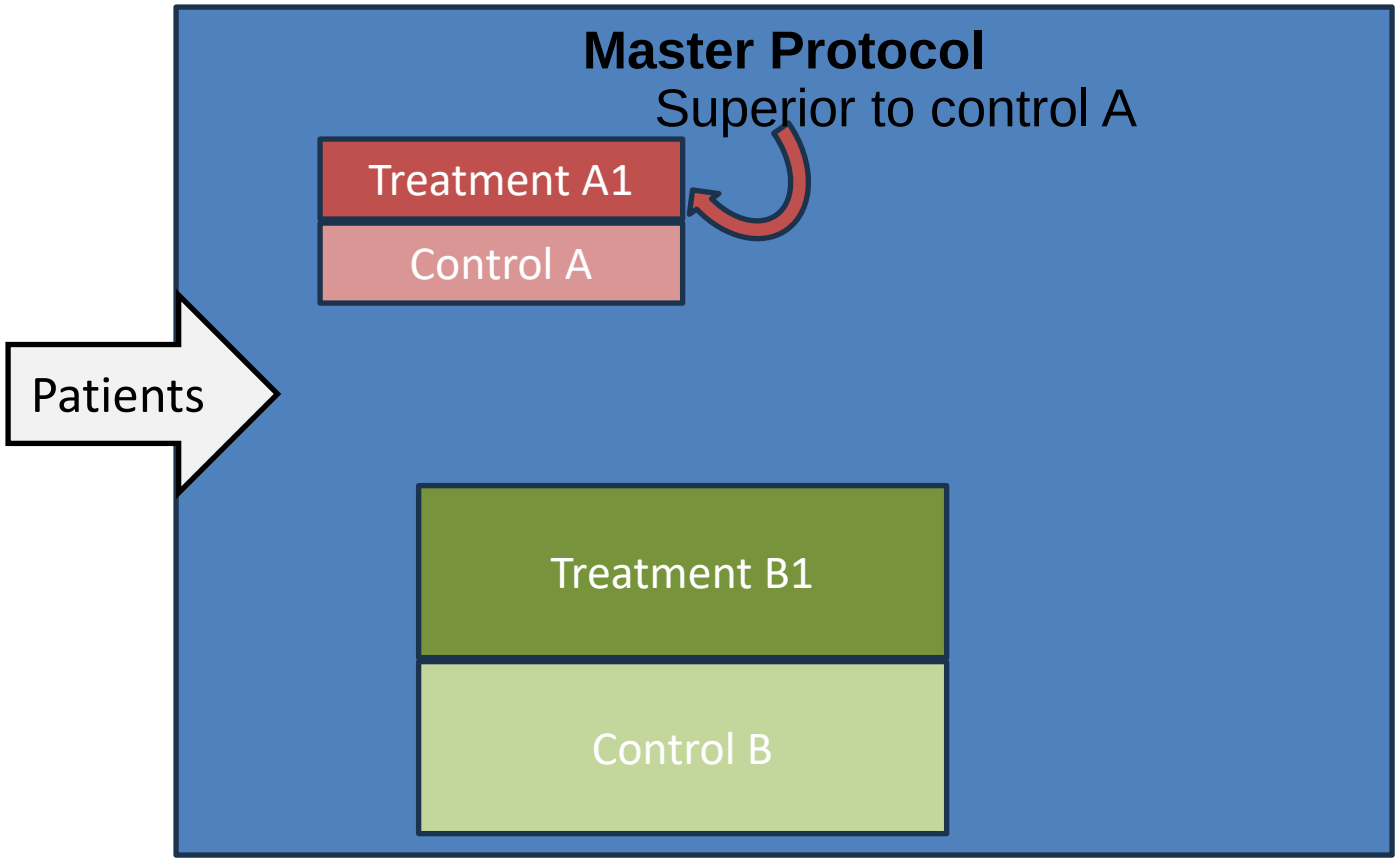
- Defines a I/E criteria for domain-eligible patients
- Details the type/delivery of intervention(s)
- Detailed specifics
  - ✓Randomization/ adaptations
  - ✓Analysis methods
  - ✓Additional research procedures
  - ✓co-enrollment

STEP- Domains (studies of interventions)



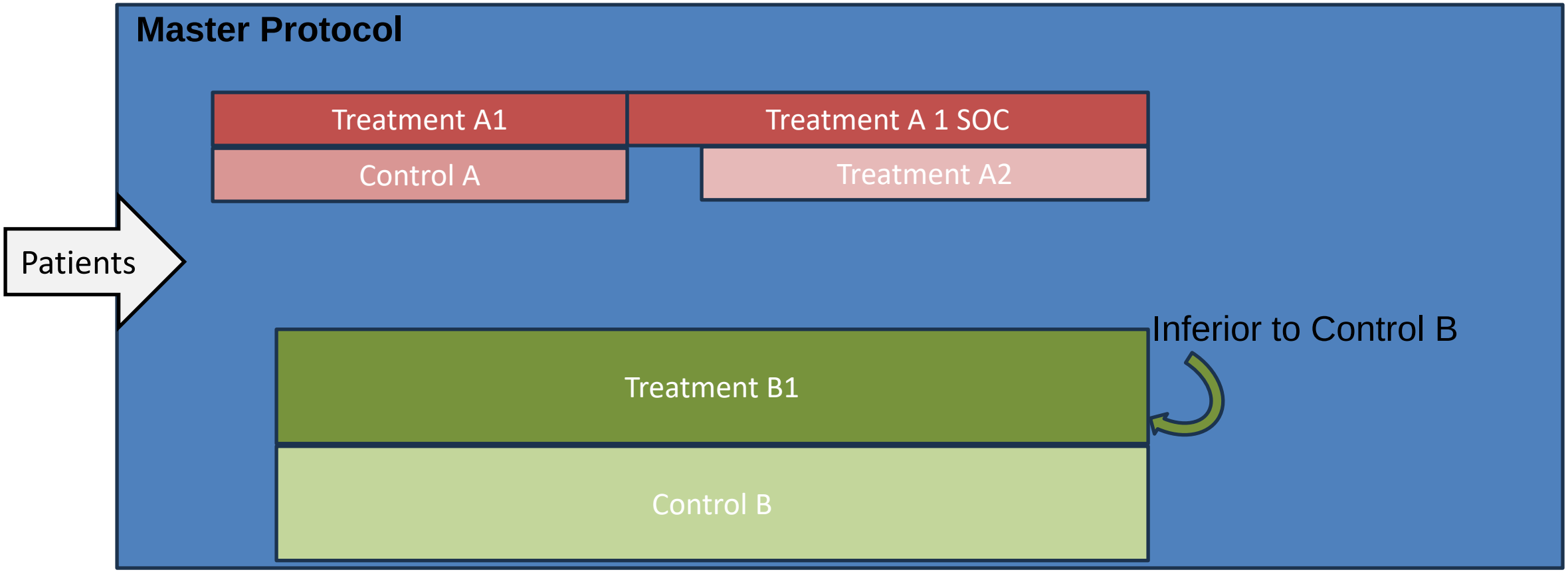
- Treatment within the domains are mutually exclusive but the patient population can overlap between two domains
- Patients can be randomized within multiple domains (**multifactorial**)

STEP enduring platform- Decisions

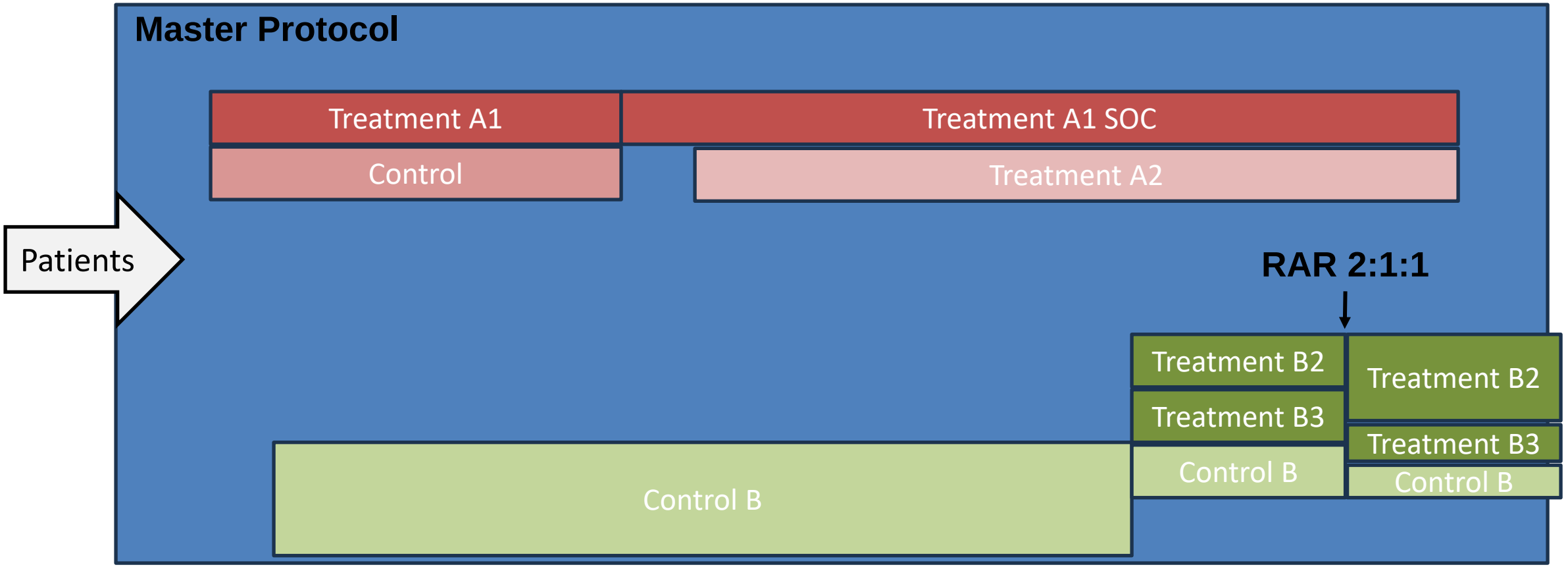


- Following types of decisions can be made for an <u>entire domain</u> or <u>particular domain arm (s)</u> or <u>pre-defined subset of patient population (strata)</u>
  - ✓Superior
  - ✓Inferior
  - ✓Futile
  - ✓Equivalent
- Decisions are based on statistical triggers
  - ✓Based on pre-defined analysis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

STEP enduring platform- Therapy domains can be perpetually added



STEP employs response adaptive randomization (RAR)



STEP Statistical Model

- **Single inferential model:** model the primary outcome as a function of each randomized treatment from each domain

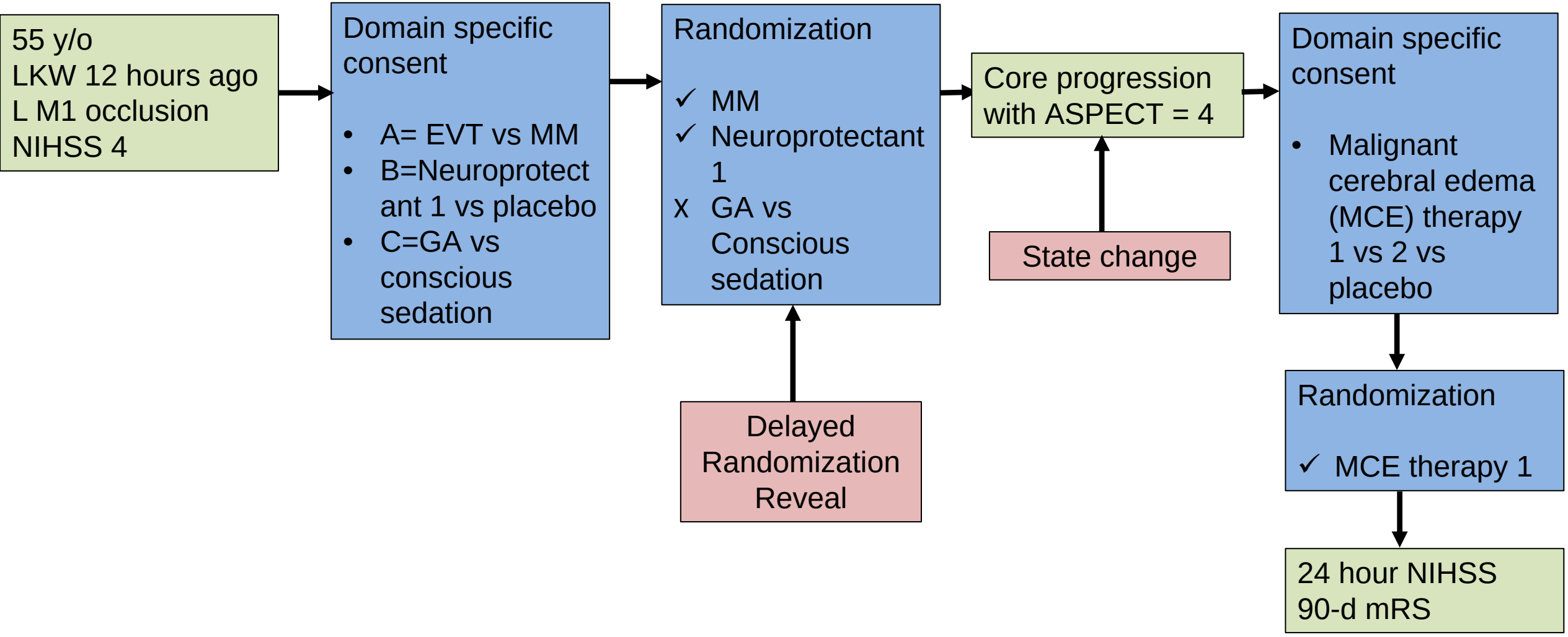
$$Y = [\text{covariates}] + [\text{intervention effects}] + [\text{intervention} \times \text{stratum}] + [\text{intervention} \times \text{intervention}] + [\text{error}]$$

- Can address across domain interactions

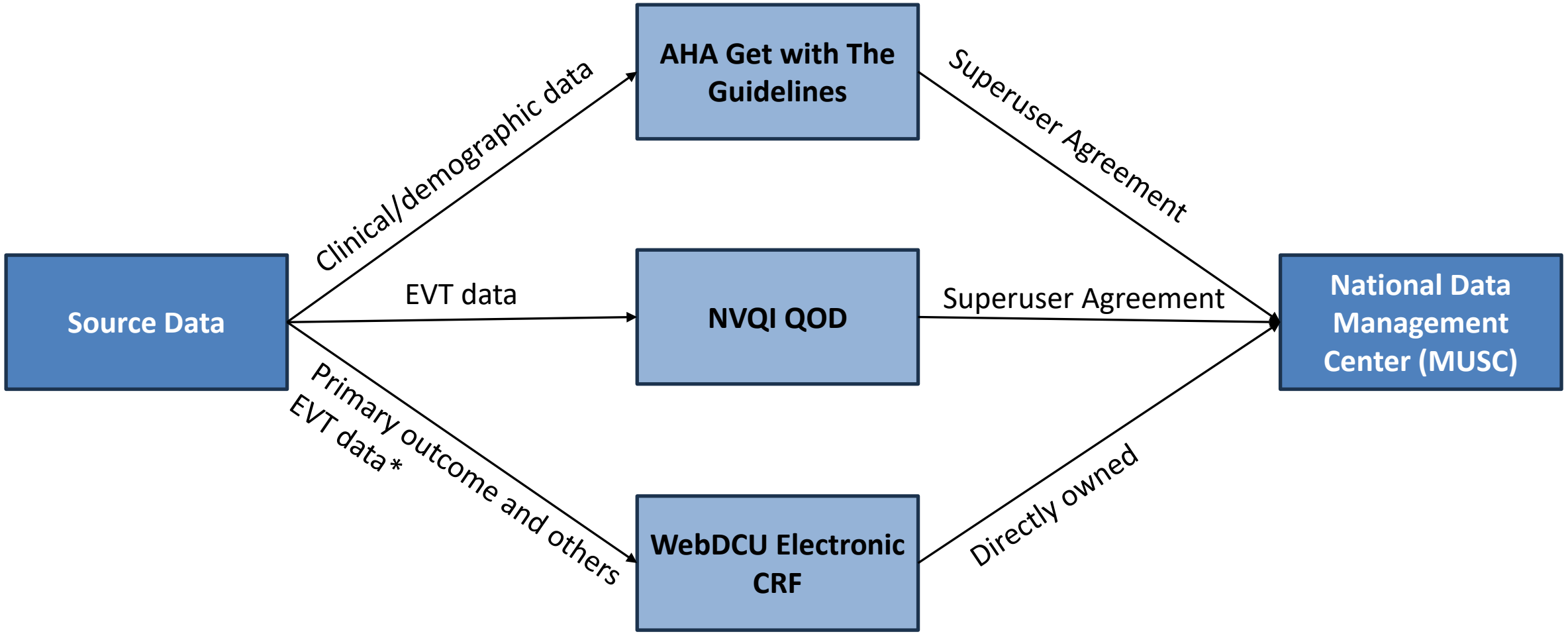
STEP- Consent Procedures

- Domain specific consent forms:
  - Electronic consent is required (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
    - Two- page sheet explaining the concept of platform in lay language
    - Does not need to be signed

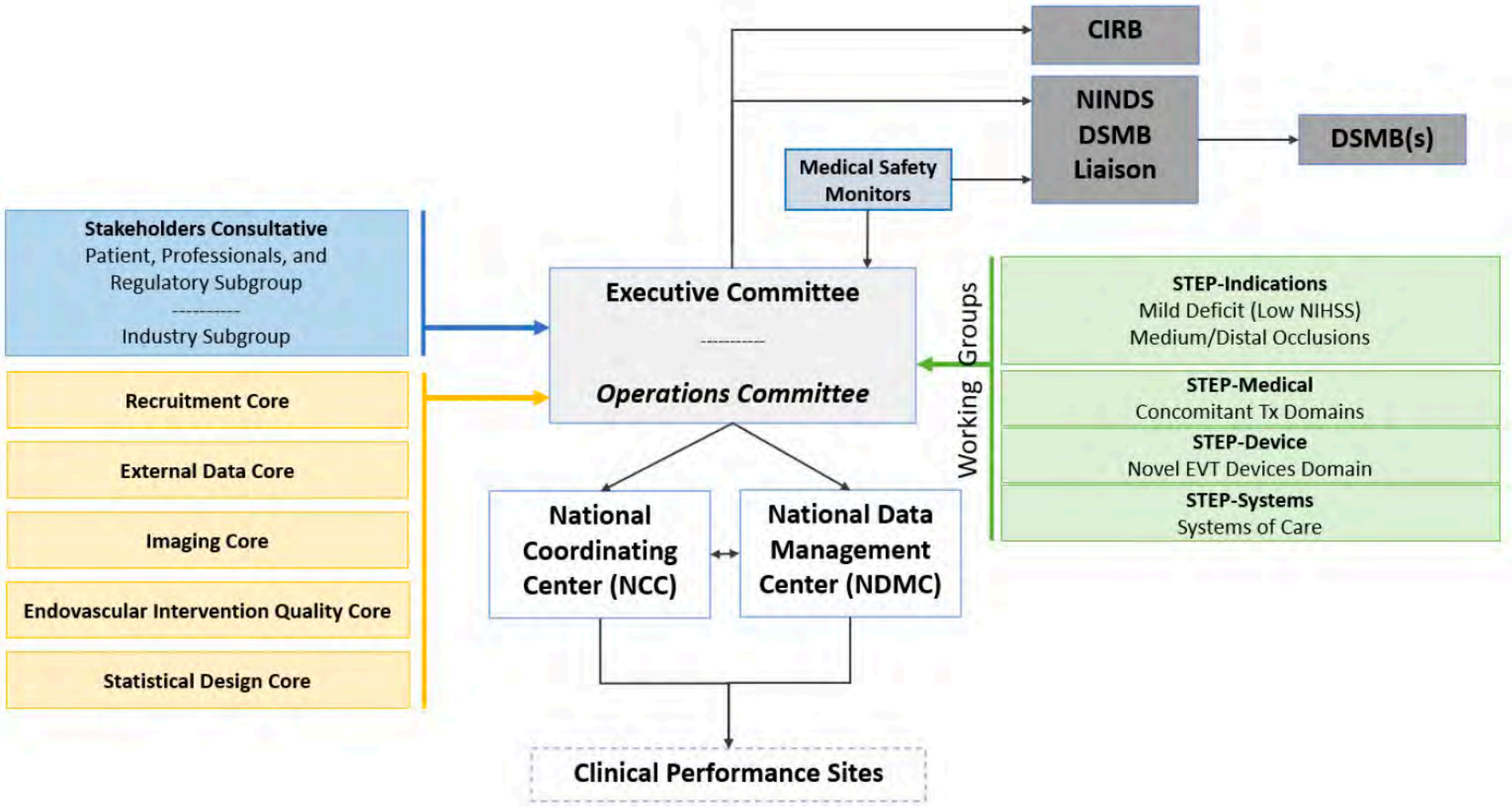
Enrollment Example-1



STEP Data Transfer Procedures



STEP Community - Organization



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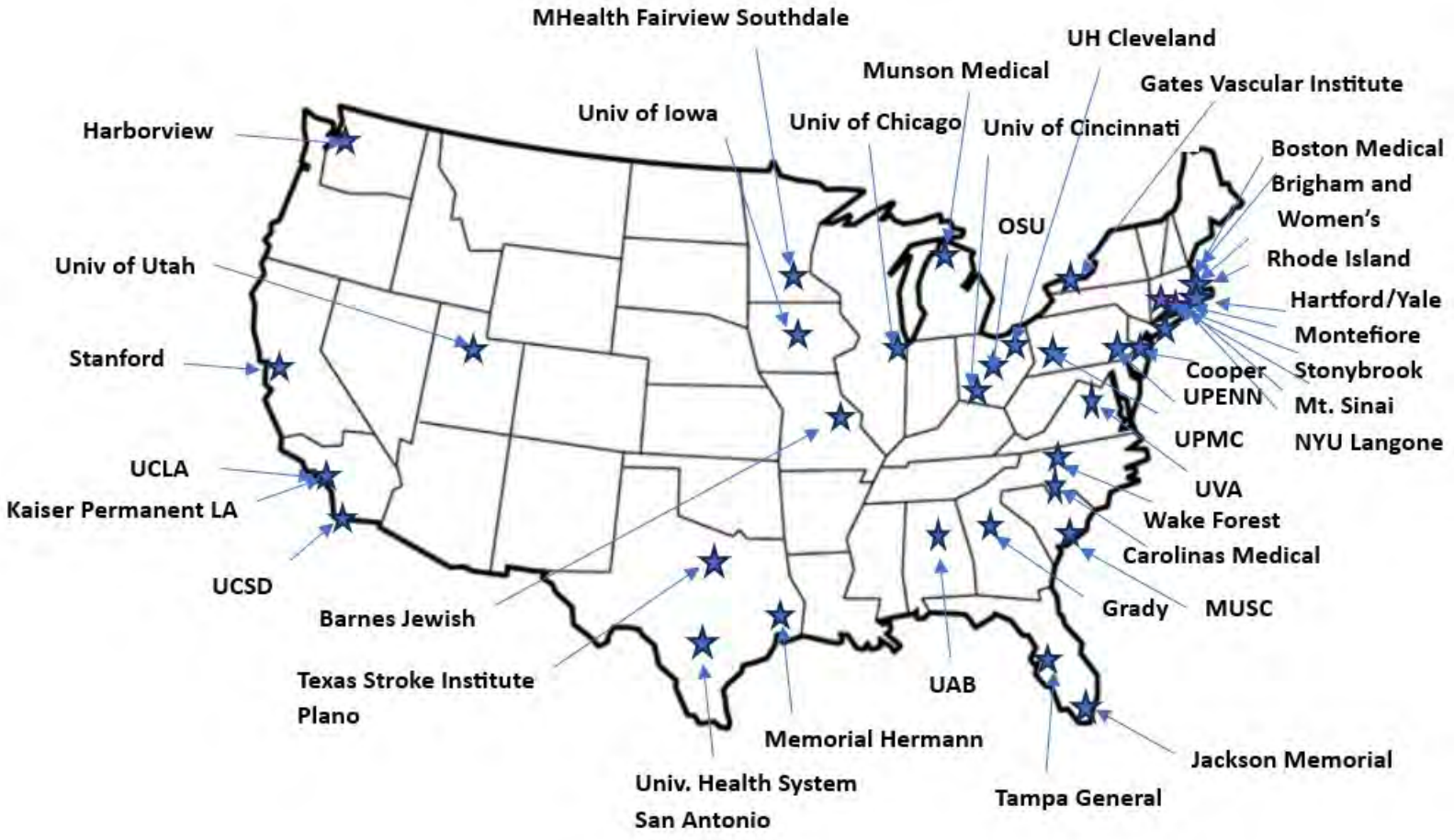
STEP Community- Participating Sites

STEP Platform



Thank you!

Eva A. Mistry, MBBS, MSCI, FAHA
Associate Professor
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University of Cincinnati

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STEP: Updates and Timelines of Rollout

Jordan Elm, PhD

On behalf of the STEP Executive Committee

Professor of Biostatistics
Medical University of South Carolina
Department of Public Health Sciences

Financial Disclosures

- Grants NIH/NINDS
- CSL Behring Advisory board

Start-Up Phase: 9/2022-12/2023

STEP Executive Committee

MILESTONE 1: Platform Design and Master Protocol

- Weekly Design meetings (Berry)
- Weekly Protocol Writing meetings
- Adaptive Design Report and SAP
- Final Master Protocol and Domain A Approved by FDA (Aug 2023)

Start-Up Phase: 9/2022-12/2023

STEP Executive Committee

MILESTONE 2: Establish Registry Data Transfer Processes

- To establish procedures for data sharing from GWTG and NVQI-QOD
- Data Transfer Specifications Document
- Mapping registry CRFs to STEP CRFs

Start-Up Phase 2023 Wrapped

- Submitted application for STEP funding (June 2023)
- ***Specific Aim 1: Implement STEP platform trial***
  - ***Infrastructure-- STEP Consortium rostered with national leader of multi-disciplinary expertise related to EVT, design, ….***
- ***Specific Aim 2: Domain A (STEP-Indications Expansion)***

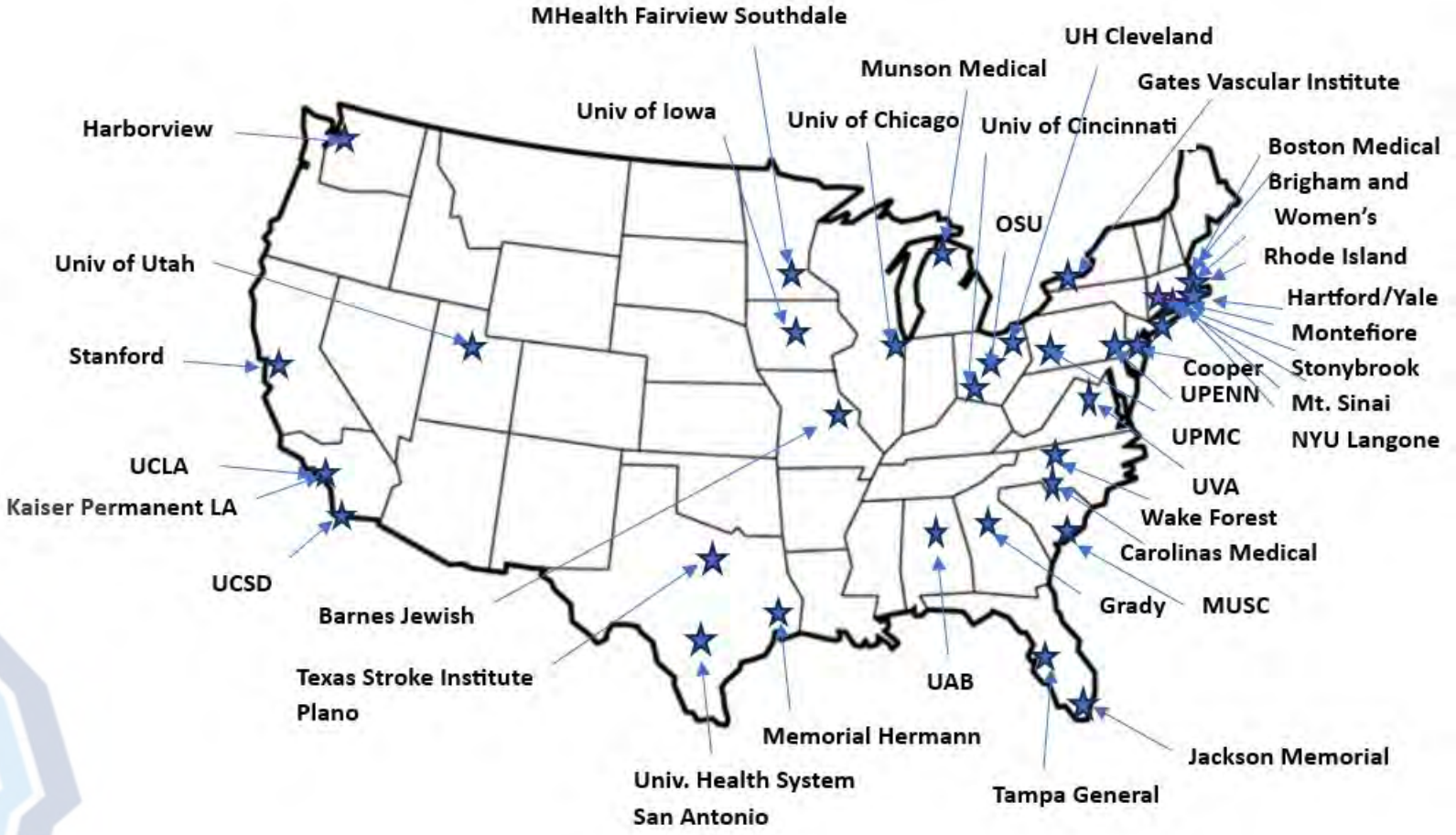
- Responded to Scientific Reviewers (Fall 2023)
- Negotiated Budget & Milestones with OT officer (December 2023)
- Funding Jan 1, 2024

Stakeholder input Informed Consent (Sept 2023)

- Sought input from StrokeNET patient partners
- Revision of process
  - Master→Domain
  - Domain-specific consents
- eConsent (REDCAP)

STEP Enrolling Centers:

network of 38 Comprehensive Stroke Center sites



STEP Start-Up Timeline

Jan 2024	Sites selected
Feb 2024	NCC to issue clinical trial agreement (CTA) to sites
Feb 2024	NCC to issue central IRB (Advarra IRB) packet to sites
Spring 2024	Sites to complete CTA and CIRB packets within 4-6 weeks of receipt
Late Spring 2024	Virtual Investigator meeting
Early Summer	Site Readiness Calls
Summer 2024	First participant enrolled

Timeline for Launch

STEP Data Core (Feb 2024)

- Develop CRFs/ Study Database
- Integrating with GWTG and NVQI-QOD registries to populated CRF data for enrolled subjects (Timelines for data transfer)

STEP Imaging Core & Biomarker Core

- Develop CRFs to align with related external trials and for unification across domains

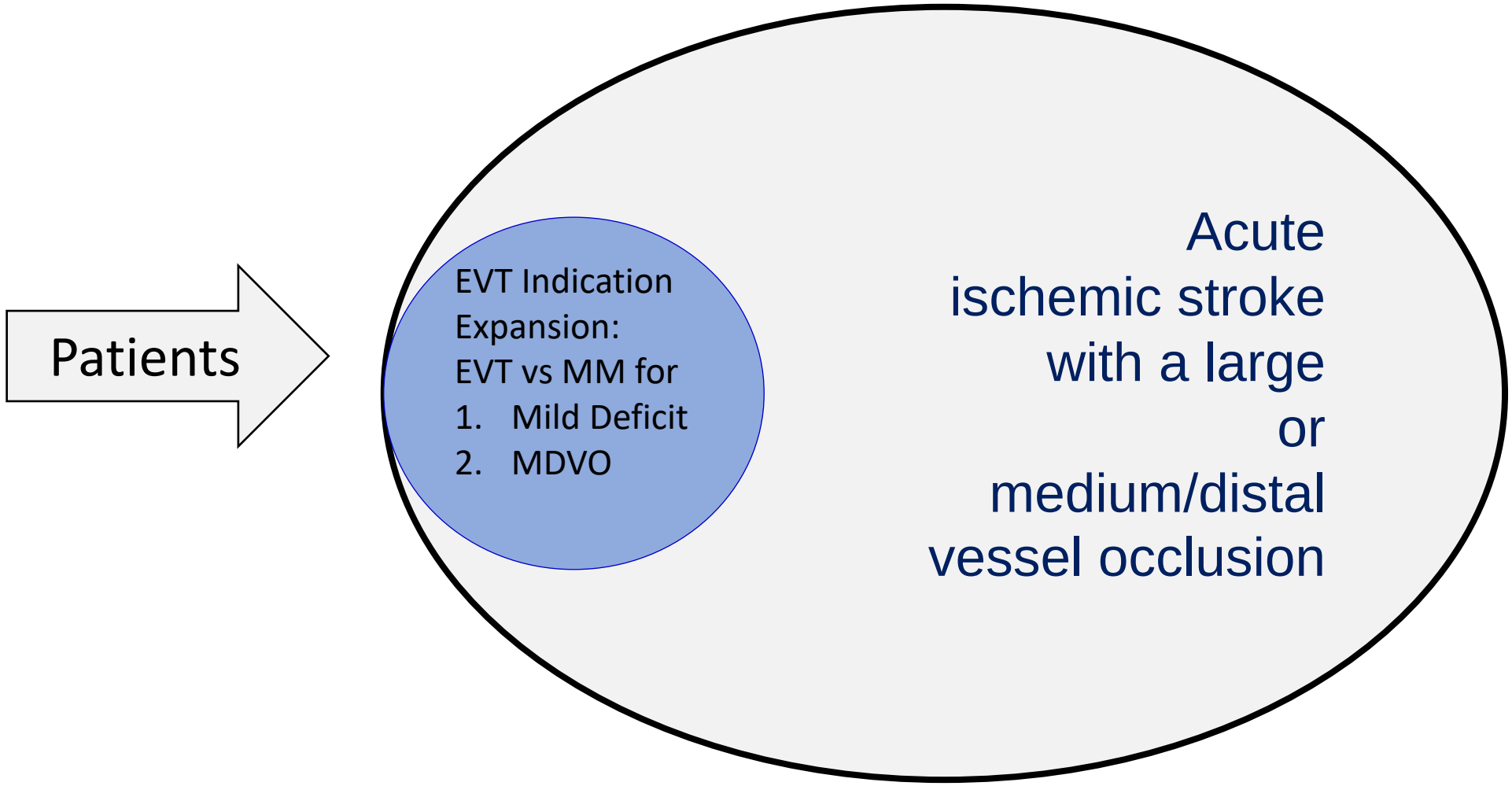
IRB/FDA/DSMB

- Spring 2024

STEP Recruitment Core

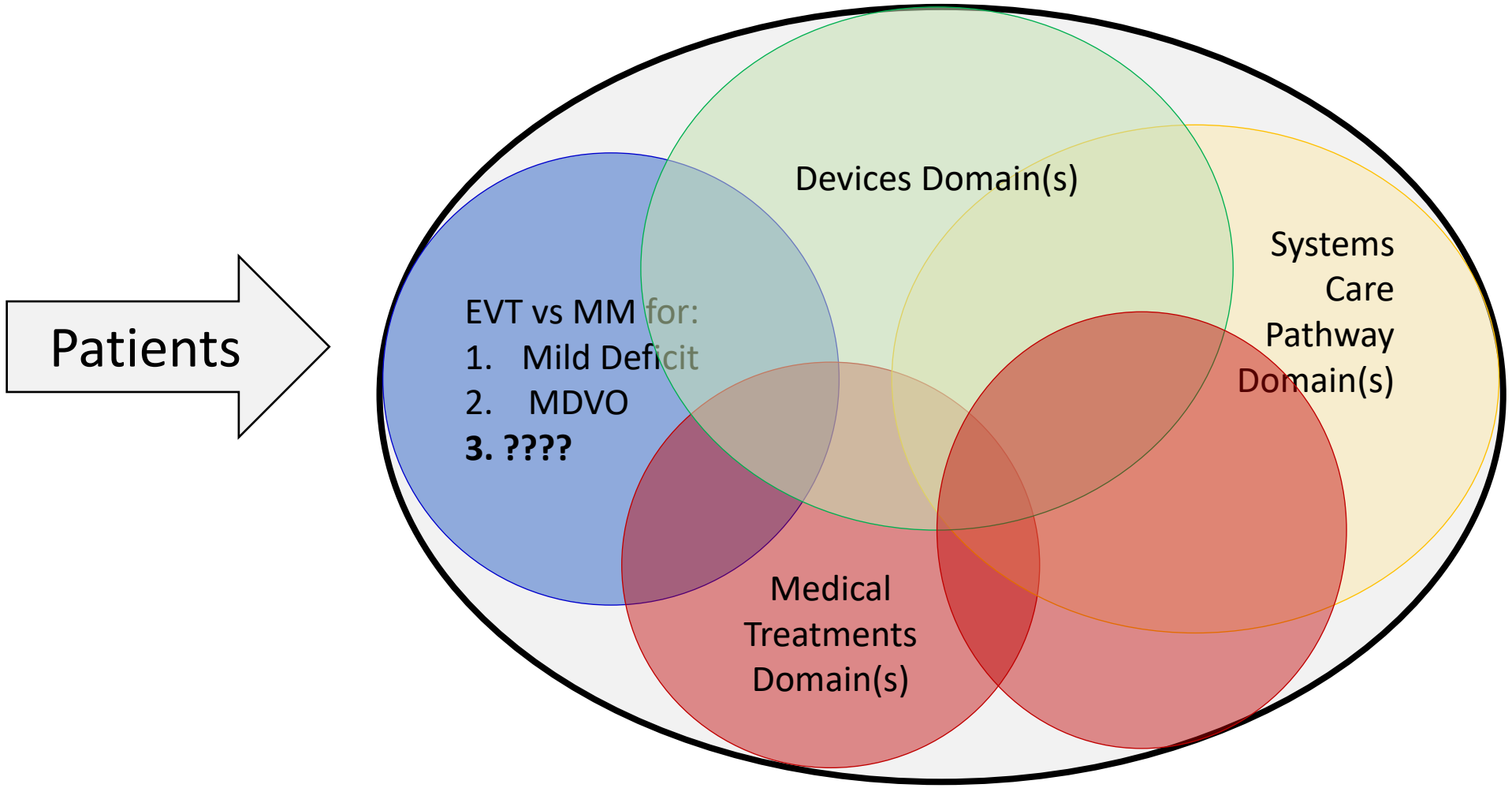
- Summer 2024

Domains “Research Questions”

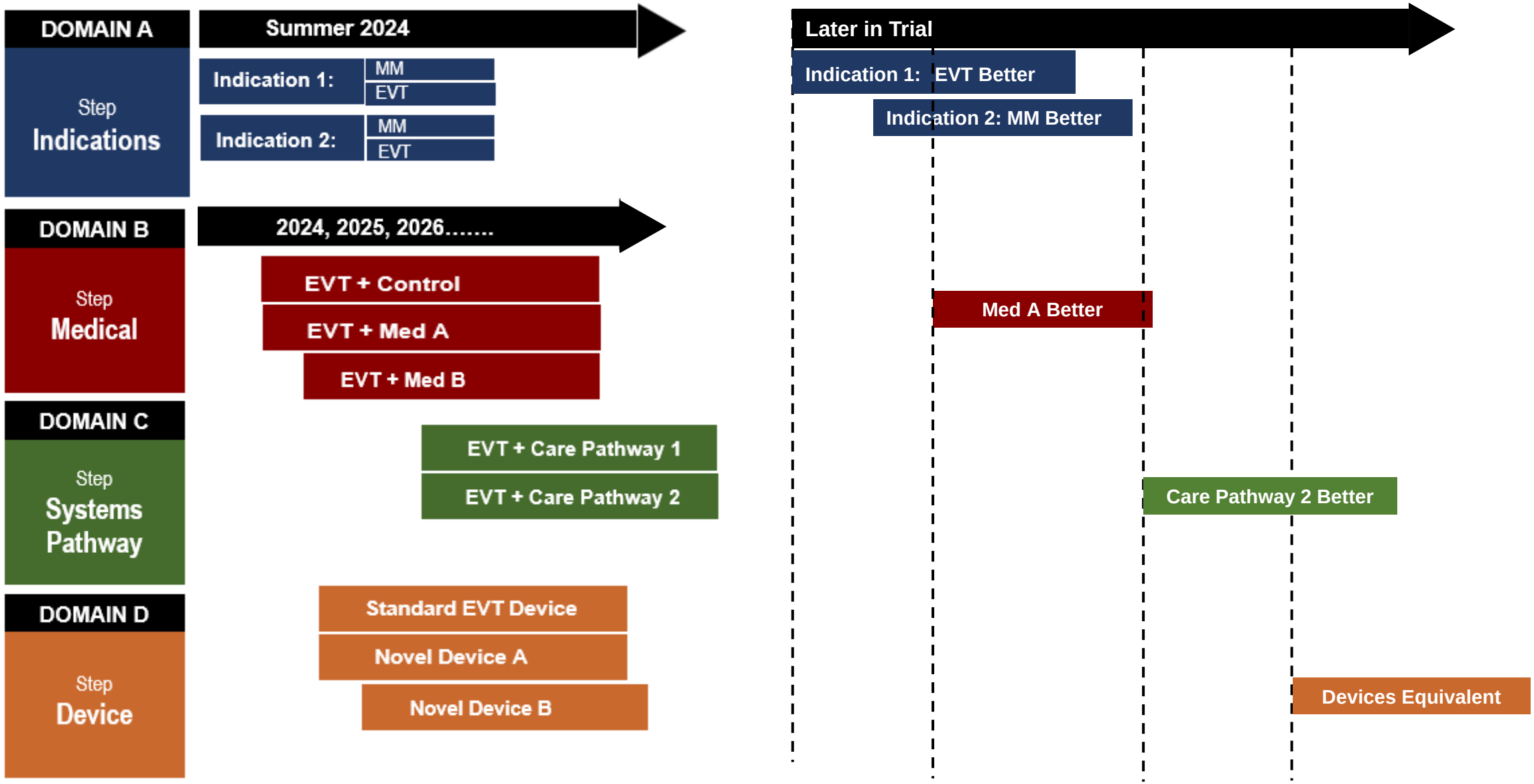


Master Protocol

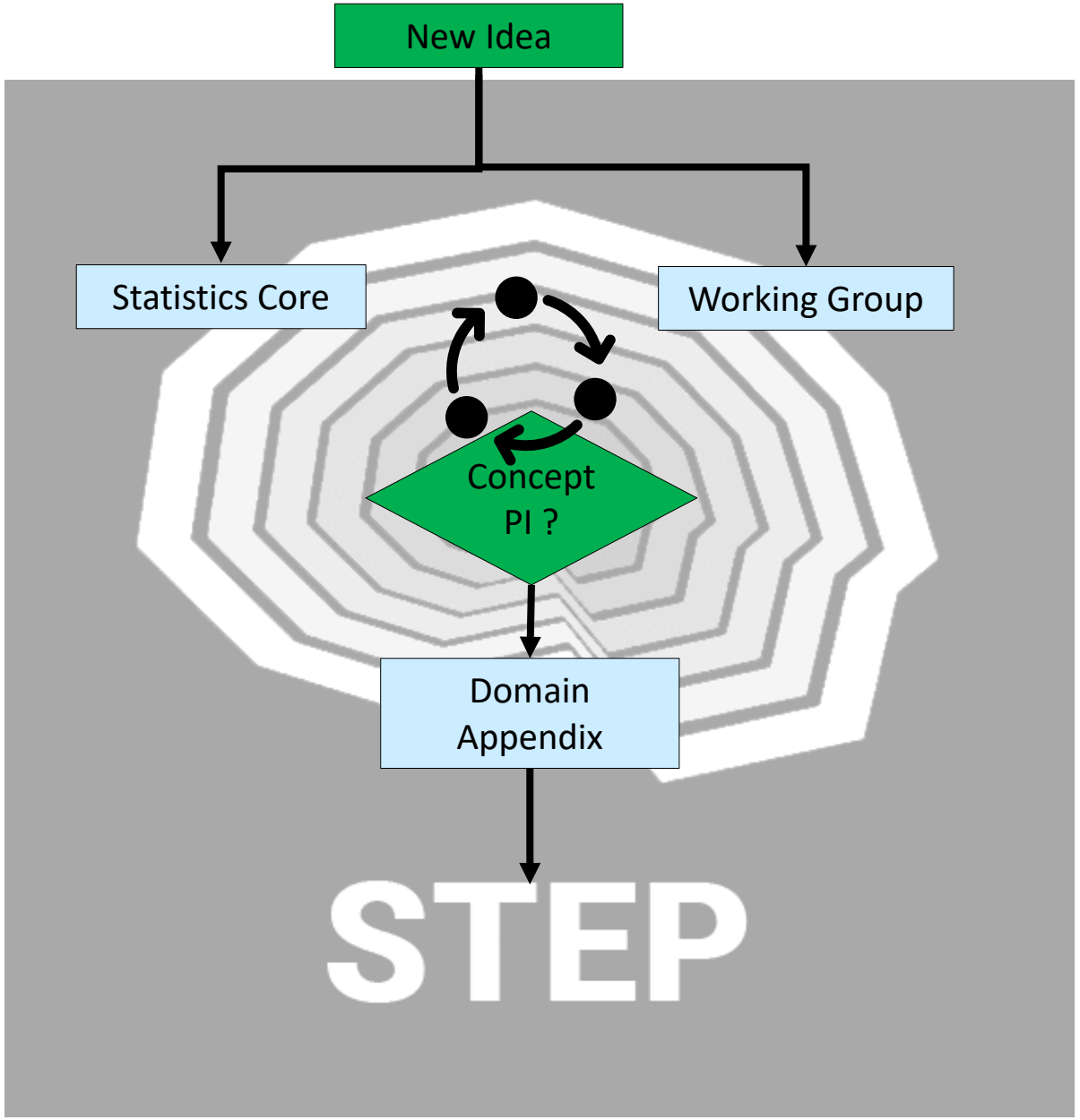
Domains “Research Questions”



Schema of Study Design



STEP New Concept Development Process Work Flow: Rolling Basis



Collaborations with External Trials

ACT GLOBAL

shared protocol, same design team

ENDOLOW

merged with Mild Deficit Strata

Large Core EVT Story ISC 2023

–> STEP design changed (drop strata)

Full Body of data will advance the treatment of ischemic stroke patients

Thank you!

StrokeNet Thrombectomy Endovascular Platform (STEP)

Regulatory Aspects

Colin Derdeyn, MD

Disclosures:

NIH/NINDS

DSMB/CEC: Penumbra (THUNDER, MIND trials); Silk Road (NITE trial); NoNO (ESCAPE NEXT, FRONTIER trials)

Polling Question

Are you familiar with the IDE process?

Yes, No or Not Sure

Investigational Device Exemption (IDE)

- Charge of the FDA
  - Safety and efficacy
  - Approval of the label – the indications for use - that a company can use to market the device
- IDE required for studies that involve new devices or off-label uses of an approved devices
  - Off-label use of devices will occur in STEP – M2s for example
- IDE process
  - Pre-IDE meetings – Qsub – request for feedback -critical step for STEP
  - Investigator-Initiated IDE - common for off-label use of devices when the intent of the study is not to change the label
  - Application submitted to FDA for approval – includes protocol, data analysis plan, preclinical testing (for new devices), consent forms

STEP IDE Status

- FDA IDE application approved for the Master Protocol
  - Population being studied
  - Data collection
  - Statistical plan
- Indication Expansion domain (Low NIHSS, Distal Vessel Occlusion) has been approved as a supplement under the existing IDE
- Future domains will be submitted as additional supplements as well
  - May cover investigational drugs or new devices
- Other studies maybe outside of the IDE (genetics)

Current Device Indications/IFUs

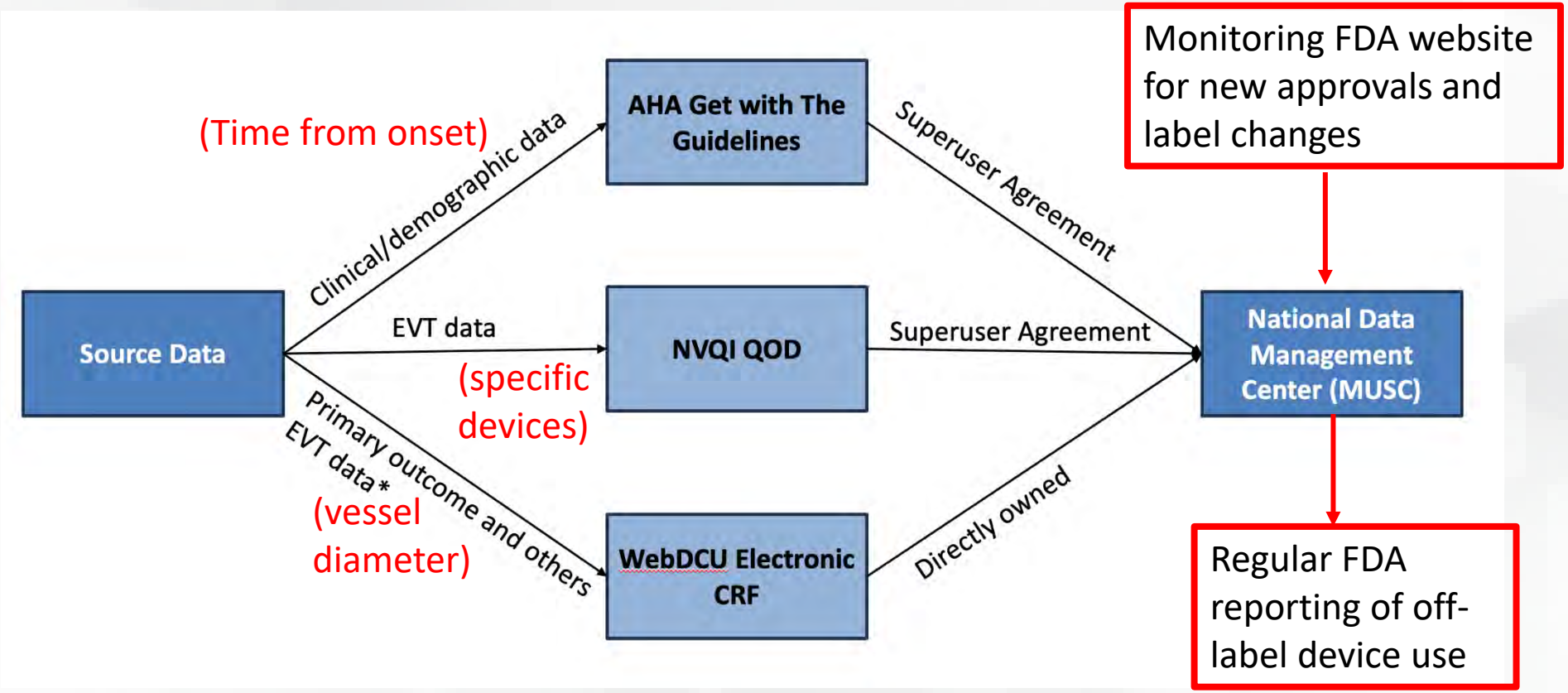
Device	Purpose	Time	tPA	Vessel Diameter	Location
Aspiration catheters	Restore blood flow	< 8 hours	Ineligible or failure	Smaller than target vessel	ICA/M1/M2
Stentreiver	Restore blood flow	<8 hours	Ineligible or failure	1.5 or 2~4mm	proximal anterior circulation
	and reduce disability	<6 hours	Ineligible or failure		proximal anterior circulation
	and reduce disability	6-24 hours, DAWN criteria			ICA/M1
Large Bore catheters	introduce interventional devices into the peripheral or neuro vasculature				
Large Bore catheters	general intravascular use, noncoronary				

Red Box indicates areas where off-label use is expected

STEP FDA Reporting

- Off label device use will be reported to FDA on a regular basis
- Developing an automated reporting process
  - Relevant fields will be identified in GWTG and NVQI-QOD registries and created for WEB-DCU CRFs to identify the device used and determine if the use was on or off label
  - FDA website will be monitored monthly for new devices or changes to approvals and the reporting algorithm changed accordingly

STEP FDA Reporting



(Red text are examples of variables to determine on label use)

February 8, 2024

Process of Proposing, Developing, and Activating a Scientific Question Within STEP

Scott Janis, Ph.D., M.A.
Program Director, StrokeNet
Division of Clinical Research,
NINDS

NIH National Institute of Neurological Disorders and Stroke

STEP Platform

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Financial Disclosures

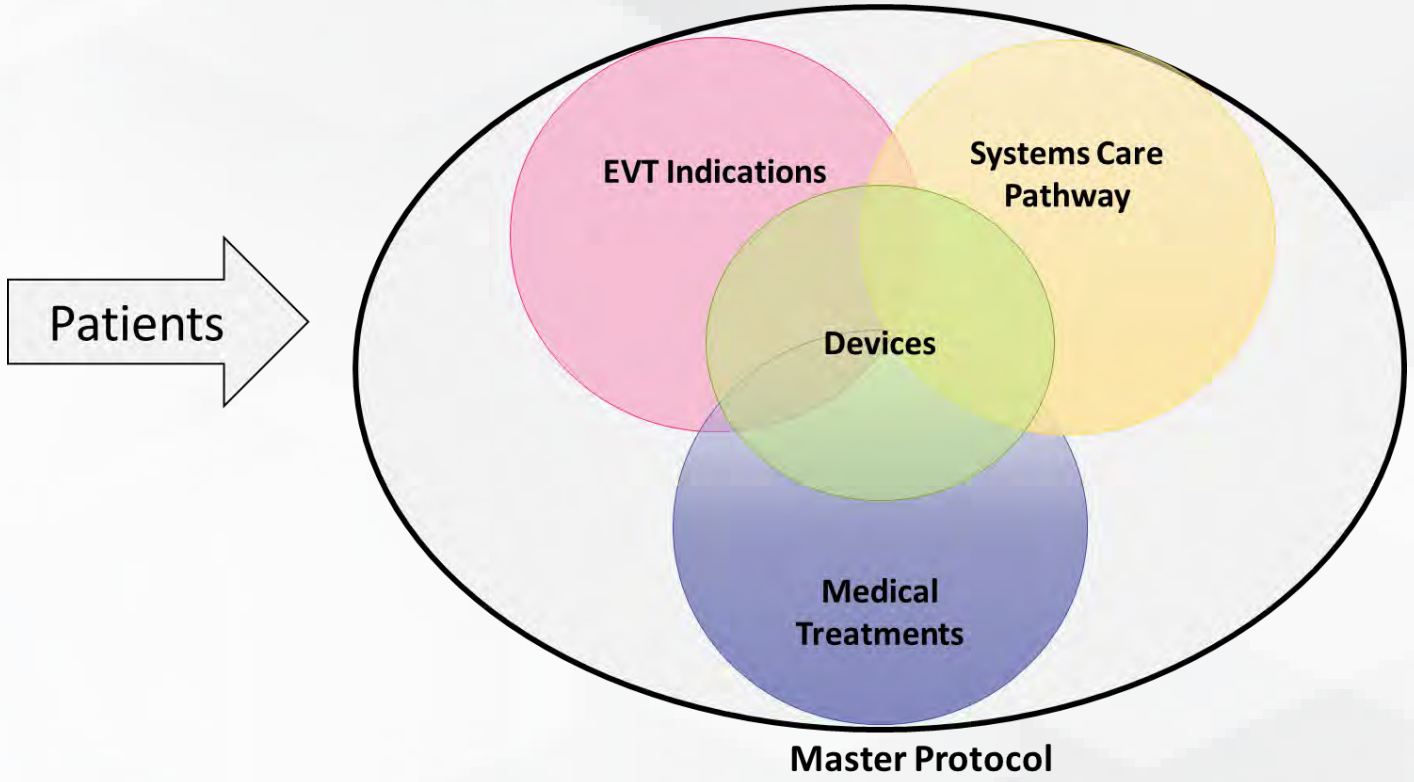
None

StrokeNet Thrombectomy Platform (STEP)

Objective: To determine the optimal strategy for treatment of patients with Arterial Ischemic Stroke (AIS) due to Large Vessel Occlusions (LVOs) or Medium Vessel Occlusions (MVOs)

Population: Patients with AIS due to proximal large or distal medium vessel occlusion who are potentially amenable to endovascular therapy

What types of projects for STEP



Clinical trials that will address:

- Indication expansion of current endovascular therapy (EVT) criteria
  - *e.g., EVT for low NIHSS, children, etc.*
- Concomitant medical therapies added to EVT
  - *e.g., BP control, avoiding tPA, general anesthesia or sedation, novel neuroprotective agents, etc.*
- Systems of care for EVT
  - *e.g., prehospital identification for EVT routing, etc.*
- Novel EVT devices

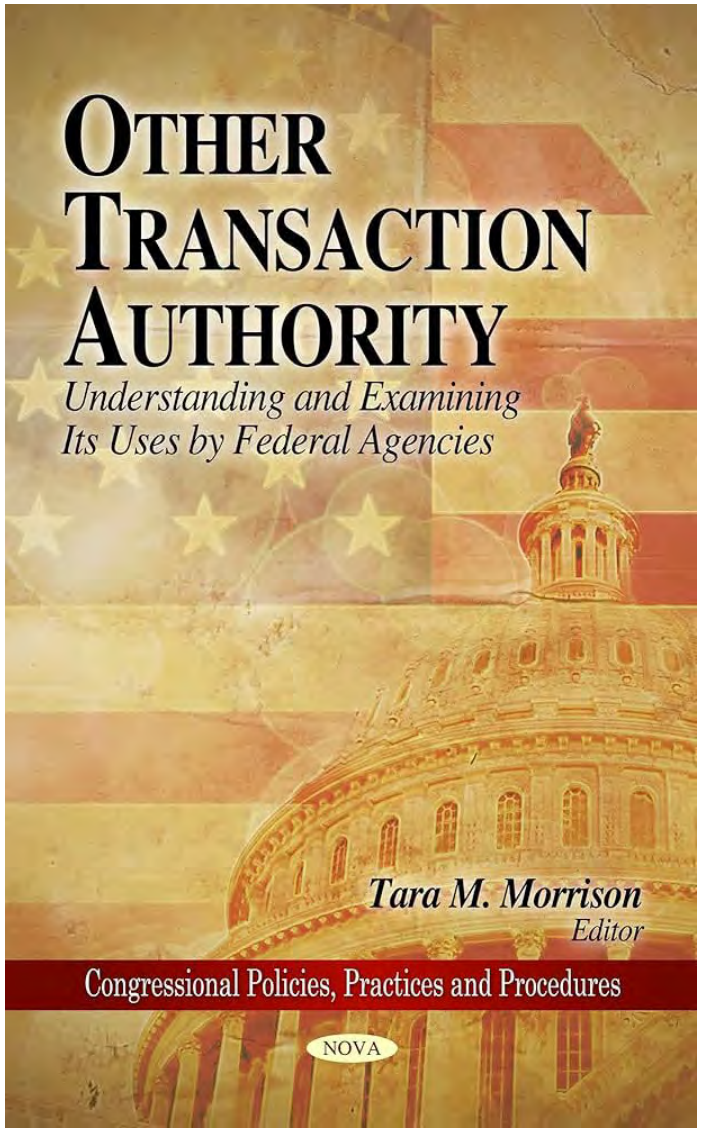
How STEP is funded

- NINDS is using a different mechanism to fund the platform called Other Transactional Authority (OTA).
- Unique type of legal funding instrument **other than** a contract, grant, or cooperative agreement.
- A single OT agreement has been created with the NDMC in the NIH StrokeNet that will be used to provide money for all future STEP clinical trial projects.

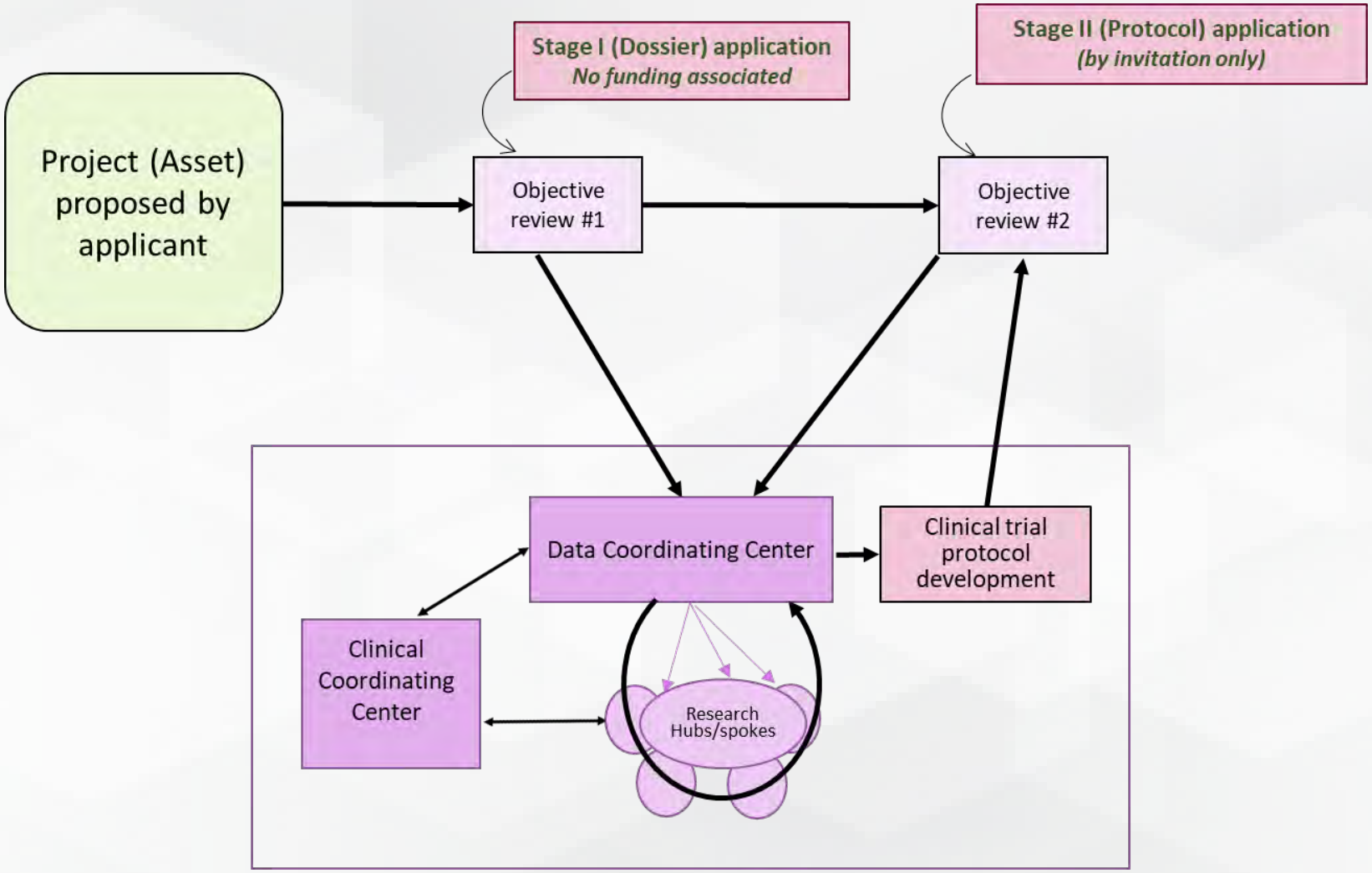
- Project questions to be included in STEP will be solicited through an ROA (Research Opportunity Announcement).
- The solicitation, review and award of platform trials will follow a similar process as currently used to award an NIH grant.

How the OTA works

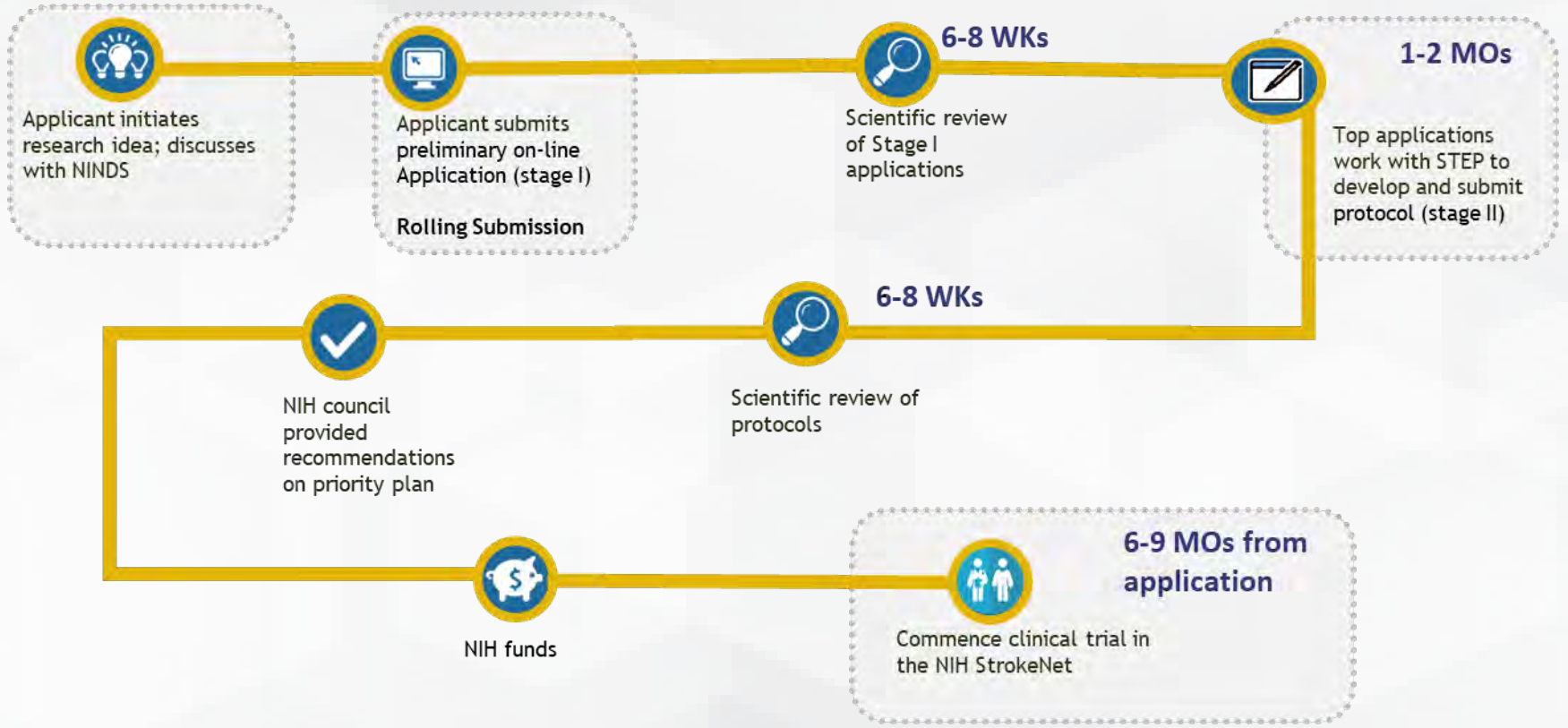
- Proposed STEP projects (asset) may be submitted by both academic and company partners.
- Each asset added to STEP will be led by the PI(s) proposing the question.
- This asset PI(s) will work with STEP to develop the protocol. The STEP contact PI will then submit the protocol for funding.
- Funding will be provided though the OTA to the NDMC and subcontracts established to support the Asset PI(s) effort.
- The asset PI(s) role in the project will be listed in the NIH Reporter and they will be responsible for leading the project.



Application Process for Proposed STEP Studies



How the Application & Review Process will work



How to Apply – Research Opportunity Announcement

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	National Institute of Neurological Disorders and Stroke (NINDS)
Research Opportunity Title	**StrokeNet Thrombectomy Platform (STEP) – Domain Clinical trials to be conducted in STEP: Stage 1 Preliminary Application (OT2)**
Activity Code	OT2: Application for an Other Transaction Agreement
Research Opportunity Number	OTA-24-009
Related Notices	
Key Dates:	Posted Date: February 8, 2024
	Open Date (Earliest Submission Date): March 1, 2024
	Application Due Date(s): Rolling Submission

https://www.ninds.nih.gov/funding/find-funding-opportunities/research-opportunity-announcements

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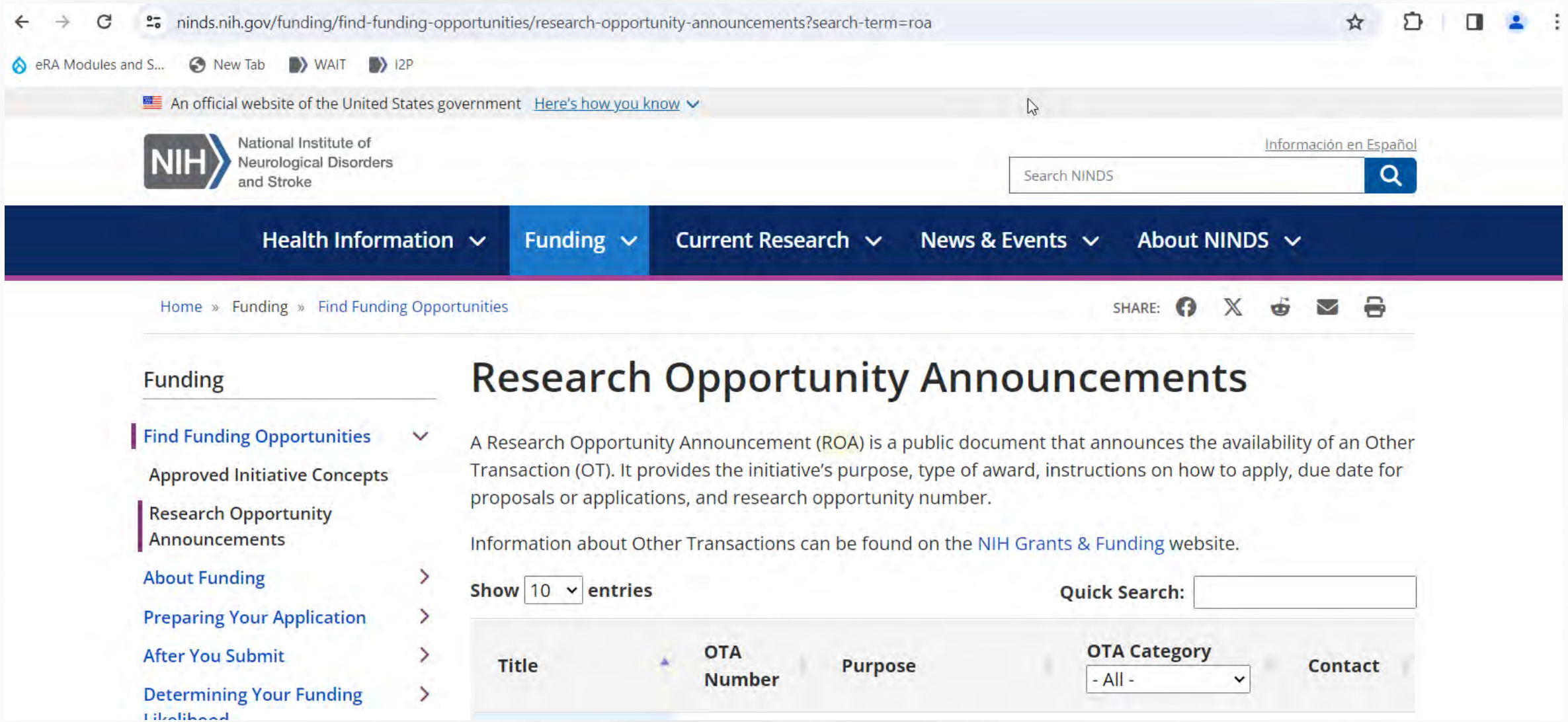
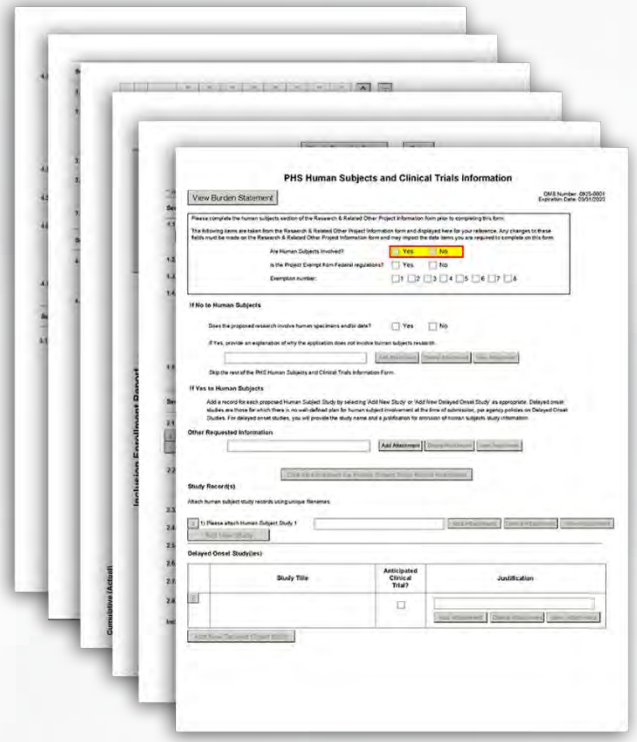


Stage 1 Submission Information

- PIs from academic or industry institutions are invited to submit a preliminary application
- Applications will be submitted via NIH eRA ASSIST using ROA number OTA-24-009 in NIH eRA Commons
- Full application will be submitted as a single text-recognizable PDF
- **NO** budget is submitted with the Stage-1 application

Stage 1 Applications will include:

- Scientific Rational/Background for the proposed EVT intervention
- Preliminary data supporting the proposed EVT intervention
- Relevant clinical trial plan (Brief description – No protocol)



Stage 1 will be evaluated on:

- The Significance/Innovation of the proposed EVT intervention rationale and population
  - how the therapeutic asset will address an unmet clinical need
- Justification and readiness for the proposed intervention
  - including the proposed target, mechanism of action, drug pharmacokinetic and pharmacodynamic profile, dose, toxicology and/or device specifications
- Relevant pre-clinical data on mechanism of action, target engagement, safety, and efficacy
  - including a relevant description of the preclinical ***findings that include*** randomization, masking of treatment assignment, sample sizing and power analyses, inclusion/exclusion criteria, replication in multiple laboratories, inclusion of sex and age as biological variables, and use of other relevant co-morbidities that may impact the treatment outcome, such as diabetes, hypertension, etc.
- Relevant clinical data
  - Including data from any existing IND, IDE or Investigator Brochure, etc.

Stage 1 evaluation Criteria (cont.):

- Description of the proposed study plan to test the proposed EVT intervention
  - CT phase, objectives, additional outcome measures, inclusion/exclusion criteria, therapeutic procedures, projected samples size, etc.

- Applications deemed of high priority to NINDS based on the independent objective review, will be invited to submit a Stage-2 application.

Invited Stage 2 Applications

- Asset PI invited to work with the STEP protocol PI and the STEP contact PI at the NIH StrokeNet NDMC to develop a full clinical protocol, statistical analysis plan, timeline/milestones, and budget
- The NDMC STEP contact PI will submit the protocol and SAP for Objective review by the NINDS
- Protocols deemed ready through peer review and approved by NINDS will be awarded through the existing STEP OTA to the NIH StrokeNet NDMC

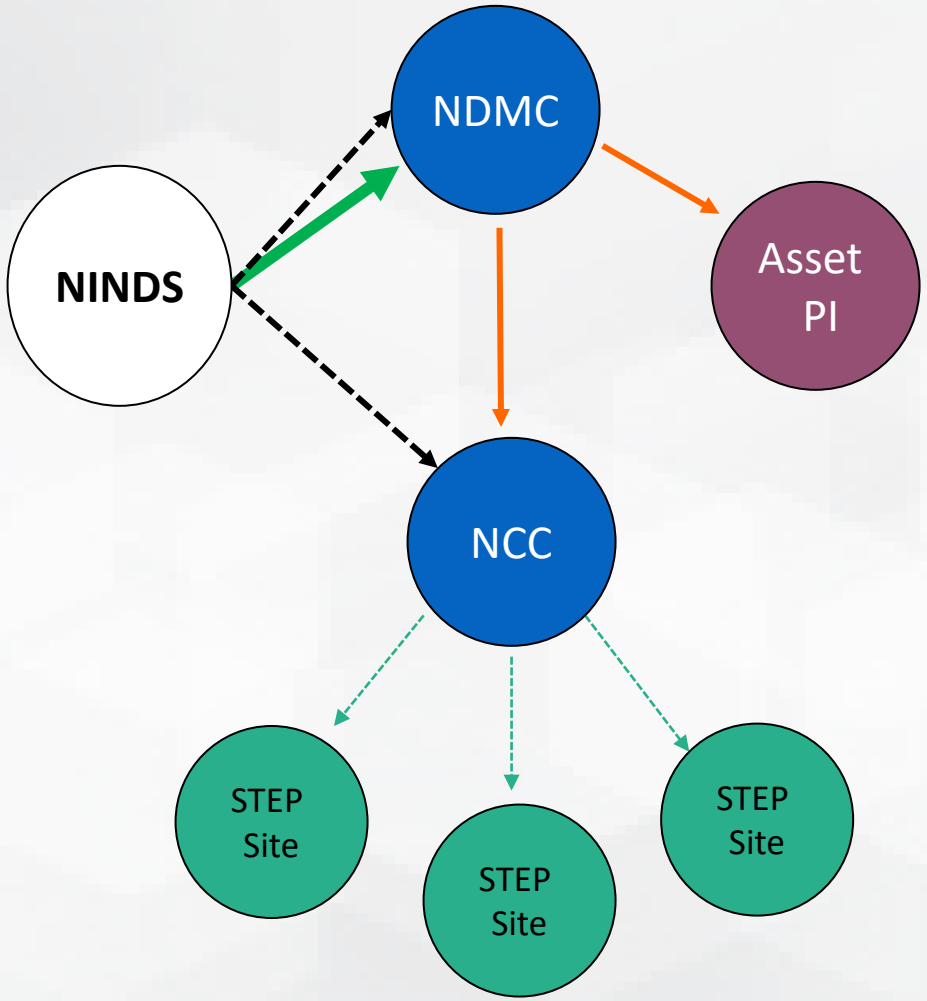
Stage 2 will be evaluated on:

- The Significance/Innovation of the Protocol
  - How will successful completion of this clinical trial change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field? E.g., consistent with the approved concept in Stage 1
  - Does the protocol mitigate weaknesses/critical barriers or fill gaps in prior research?
  - If the aims of the protocol are achieved, how will scientific knowledge or treatment development for the condition under study be advanced?

- Approach/study design of the Protocol
  - Is the overall approach well-reasoned, feasible, and appropriate to accomplish the study specific aims?
  - Will the approach generate balanced, unbiased data?

- Expertise and Resources
  - Will the study benefit from being conducted within the STEP network environment?
  - Are the institutional support, equipment and other physical resources available adequate for the project proposed?
  - Does the application adequately address the capability and ability to conduct the trial?

STEP Program



Flow Of Funds

Infrastructure award directly from NINDS

OTA Award for project

Subcontract

CT agreement with NCC

- Funds provided to STEP program through the existing OTA with the NDMC
- The asset is added to the master protocol with management through the NIH StrokeNet
- The new project led by the Asset PI working directly with the STEP program team

Opportunities to collaborate with STEP

NINDS is open to consider research projects that fall outside of the scope of STEP but are designed to leverage and collaborate with the STEP infrastructure. These projects would be submitted as regular research grants.

- e.g., genetic projects, etc.

Questions about STEP

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Thank You