NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NIH StrokeNet and the Future of Stroke Research

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

NIH
Funded by a grant from the National Institutes of Health

UNIVERSITY OF Cincinnati

Vision of NIH StrokeNet

- To be the leading platform for stroke trials in the U.S. and globally

NIH StrokeNet Infrastructure

Coordinating Center

Renewal RCC

New RCC

Legacy RCC

Overview

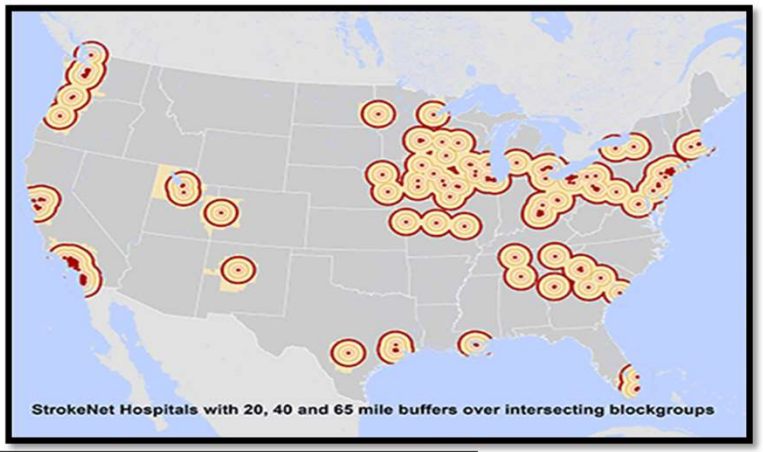
- 2013 - present
- 27 regional centers with nearly 500 satellite stroke hospitals, a coordinating center, and a data management center
- Phase 2 and phase 3 clinical trials (ancillary studies) and biomarker studies to advance acute stroke **treatment**, **prevention**, and **recovery**

http://nihstrokenet.org/

Additional infrastructure

- The NIH StrokeNet infrastructure includes:
  - Central Institutional Review Board (CIRB) at the University of Cincinnati, and CIRB with Advarra
  - StrokeNet central pharmacy at UC Health Research Pharmacy
  - Imaging Core at the University of Cincinnati (Dr. Vagal)
  - Training and Education Core

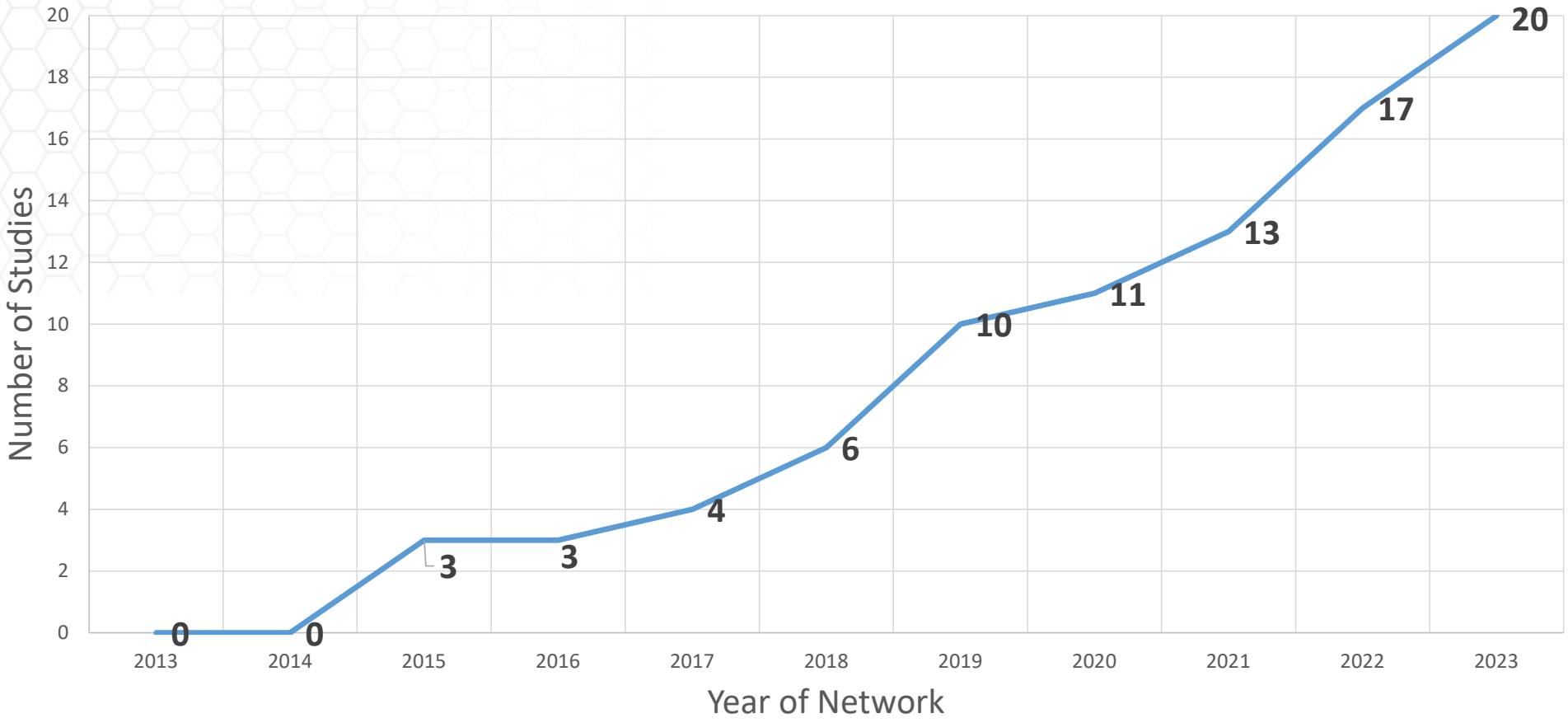
Population covered by network



Characteristic	Distance from StrokeNet Center						Total (50 States)	% of Total
	20 Mile Radius	% of Total	40 Mile Radius	% of Total	65 Mile Radius	% of Total		
Total Population	120,758,537	38.3%	157,727,442	50.0%	189,572,54	60.1%	315,219,560	100.0%
Male (adult)	44,518,863	38.1%	58,121,547	49.8%	70,121,776	60.1%	116,781,403	100.0%
RACE								
White	80,374,323	34.5%	109,783,22	47.1%	136,388,020	58.5%	233,168,413	100.0%
Hispanic/Latino	24,695,940	44.6%	29,719,245	53.6%	33,189,395	59.9%	55,429,828	100.0%
Black	18,115,454	45.9%	21,868,666	55.4%	24,323,226	61.7%	39,451,870	100.0%
Asian	9,952,233	65.3%	11,108,254	72.9%	11,888,761	78.0%	15,244,082	100.0%
Other	8,048,767	53.3%	9,567,560	63.3%	10,560,177	69.9%	15,111,418	100.0%
American Indian	509,505	20.0%	675,804	26.5%	866,548	34.0%	2,550,780	100.0%
Pacific Islander	197,664	37.6%	235,546	44.8%	267,158	50.8%	526,408	100.0%

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Zero to 20 Ongoing Studies in 10 Years



4 Completed Trials

- **MISTIE-3** Minimally Invasive Surgery for ICH evacuation (N=500)
- **i-DEF** Deferoxamine mesylate treatment for ICH (N=293)
- **DEFUSE-3** Delayed endovascular therapy for select patients (N=182)
- **TeleRehab** Home-based telerehabilitation stroke recovery (N=124)

MISTIE III

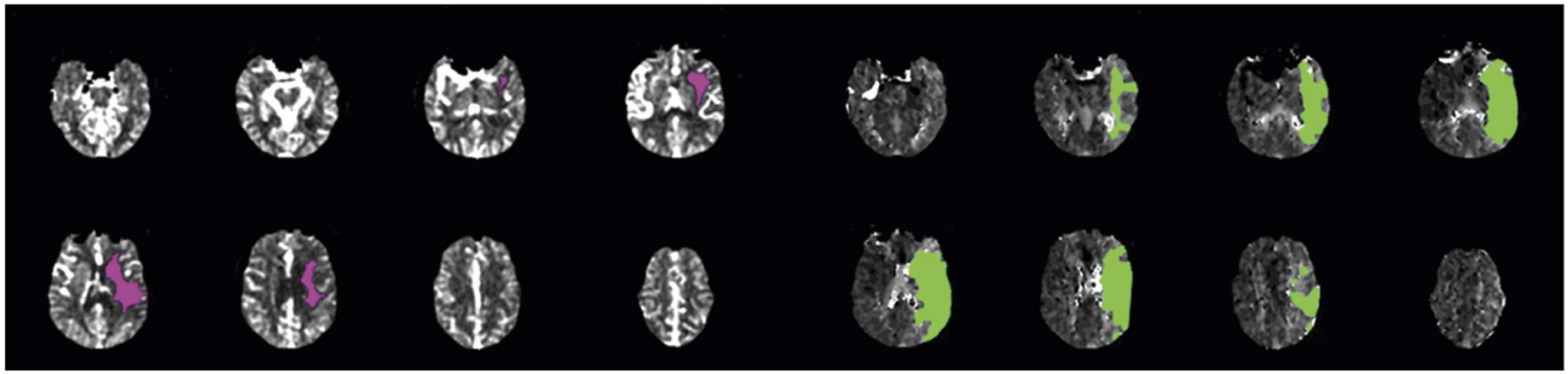
defuse·3

iDEF
Intracerebral Hemorrhage Deferoxamine Trial

Telerehab Trial

Outcomes and impact of StrokeNet trials

- DEFUSE 3, stopped early, highly positive trial Albers GW et al. N Engl J Med 2018;378:708-718.
  - Immediate change in clinical practice and Stroke Guidelines with lives changed throughout the world. Distinguished Clinical Research Achievement Award – Top 3 of all clinical trials in US for 2018.



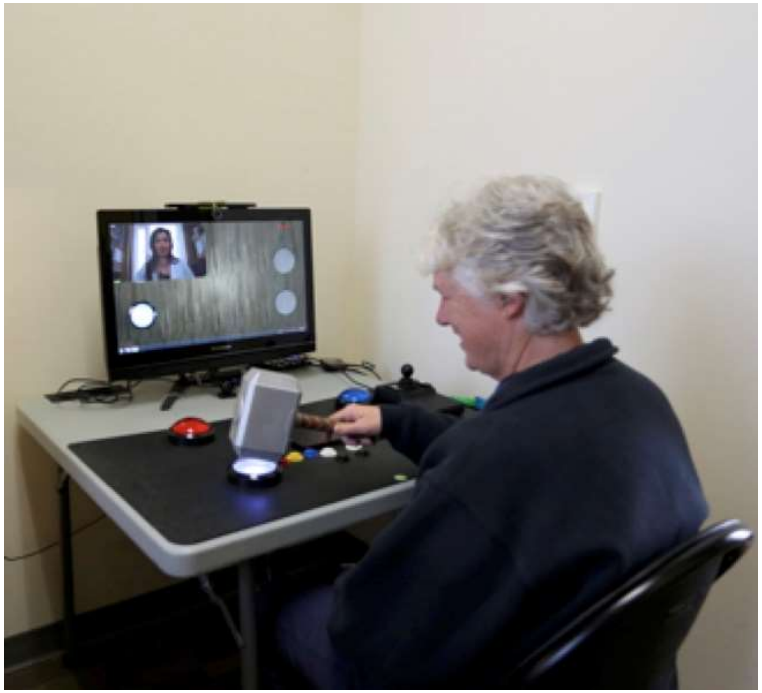
Volume of Ischemic Core, 23 ml

Volume of Perfusion Lesion, 128 ml

Mismatch volume, 105 ml
Mismatch ratio, 5.6

Outcomes and impact of StrokeNet trials

- Telerehab Trial – first randomized trial of rehabilitation for stroke patients published in JAMA Neurology. Trial demonstrated that Telerehab is not inferior to in-clinic therapy for improving arm motor status in patients with recent stroke.
  - COVID experience demonstrated the future importance of this technique and how those with limited ability to travel can have impactful rehab therapy.
  - "With widespread adoption of telerehabilitation catalyzed by the COVID-19 pandemic, there is great potential for improved care equity by addressing geographic, demographic, and socioeconomic barriers." Duncan and Bernhardt, Stroke: 2021.



Cramer et al. JAMA Neurology: 2019 Sep 1;76(9):1079-1087

Telerehab Trial

20 Ongoing Trials

PREVENTION OF STROKE (11)

CREST-2 Treatment of asymptomatic carotid stenosis (N=2480)

CREST-H Hemodynamic impairment ancillary study in CREST-2 (N=500)

ARCADIA Apixaban vs. aspirin for cryptogenic stroke (N=1100)

ARCADIA-CSI Apixaban for cognition and silent infarcts (N=500)

SATURN Statin use in ICH survivors (N=1456)

SATURN-MRI Statins for silent stroke (N=912)

ASPIRE Anticoagulation of atrial fibrillation in ICH survivors (N=700)

CAPTIVA Anticoagulation vs antiplatelets for intracranial stenosis (N=1683)

CAPTIVA MRI MRI biomarkers of recurrent stroke in intracranial atherosclerotic stenosis (n=300)

Sleep-SMART Treatment of obstructive sleep apnea (N=3062)

FOCUS Corticosteroids for pediatric stroke due to focal cerebral arteriopathy (n= 80)

ACUTE STROKE TREATMENT (5)

MOST Adjunctive antithrombotics (epfibatide, argatroban) to thrombolysis (N=1200)

FASTEST FVIIa for acute hemorrhagic stroke (N=860)

RHAPSODY-2 3K3A-APC with thrombectomy and thrombolysis (N=1400)

SISTER Dose-finding novel clot-dissolving Ab, TS23, in extended time window ischemic stroke patients (n=300)

STEP Platform Adaptive, registry-supported trial platform to optimize outcomes after LVO

STROKE RECOVERY & REHABILITATION (3)

TRANSPORT-2 Transcranial direct stimulation to aid recovery (N=129)

I-ACQUIRE Intensive infant rehabilitation for pediatric stroke (N=240)

VERIFY Acute prediction of motor recovery (N=657)

PRIMARY STROKE PREVENTION IN COVID (2)

ACTIV 4A Antithrombotic approach for inpatient COVID-19 patients

ACTIV 4C Antithrombotic approach for post-discharge COVID-19 patients - Completed

20 Ongoing Trials

PREVENTION OF STROKE (9)

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Five Upcoming Trials

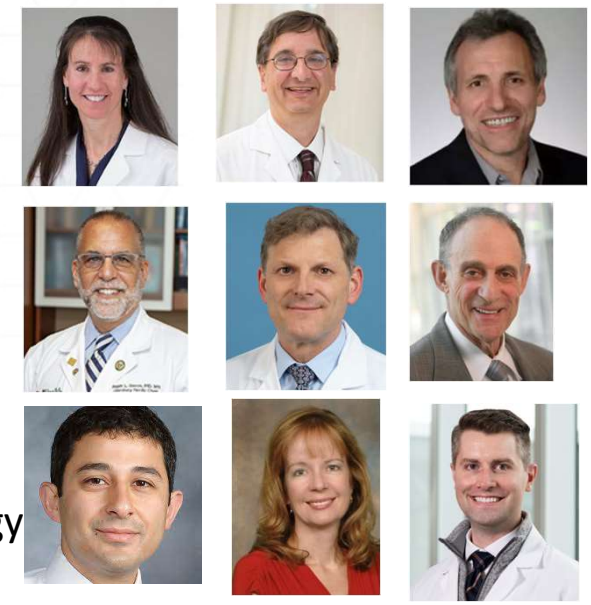
- **FOCAS** Corticosteroids for pediatric stroke due to focal cerebral arteriopathy (n= 80)
- **CAPTIVA-MRI** MRI biomarkers of recurrent stroke in intracranial atherosclerotic stenosis (n=300)
- **SISTER** Dose-finding novel clot-dissolving Ab, TS23, in extended time window ischemic stroke patients (n=300)
- **STEP Platform** Adaptive, registry-supported trial platform to optimize outcomes after LVO - 2023
- **CLARITY** – large secondary prevention study of cilastazol likely to be funded in 2024.

Trial Development Process

1. Working groups
   - Acute
   - Prevention
   - Recovery/rehab

2. Feasibility assessments
   - Trial-specific and annual surveys
   - Population-level epidemiology assessment
     - DEFUSE-3 example

3. StrokeNet leadership grant review prior to submission



Success Rate:

Aug/2018 to now:

- *16 StrokeNET trial concepts were submitted to NIH*
- *7 (44%) of these grants approved funded*

Future Directions:

- *GWTG data*
- *More utilization of advisory groups*
  - *DEI core*

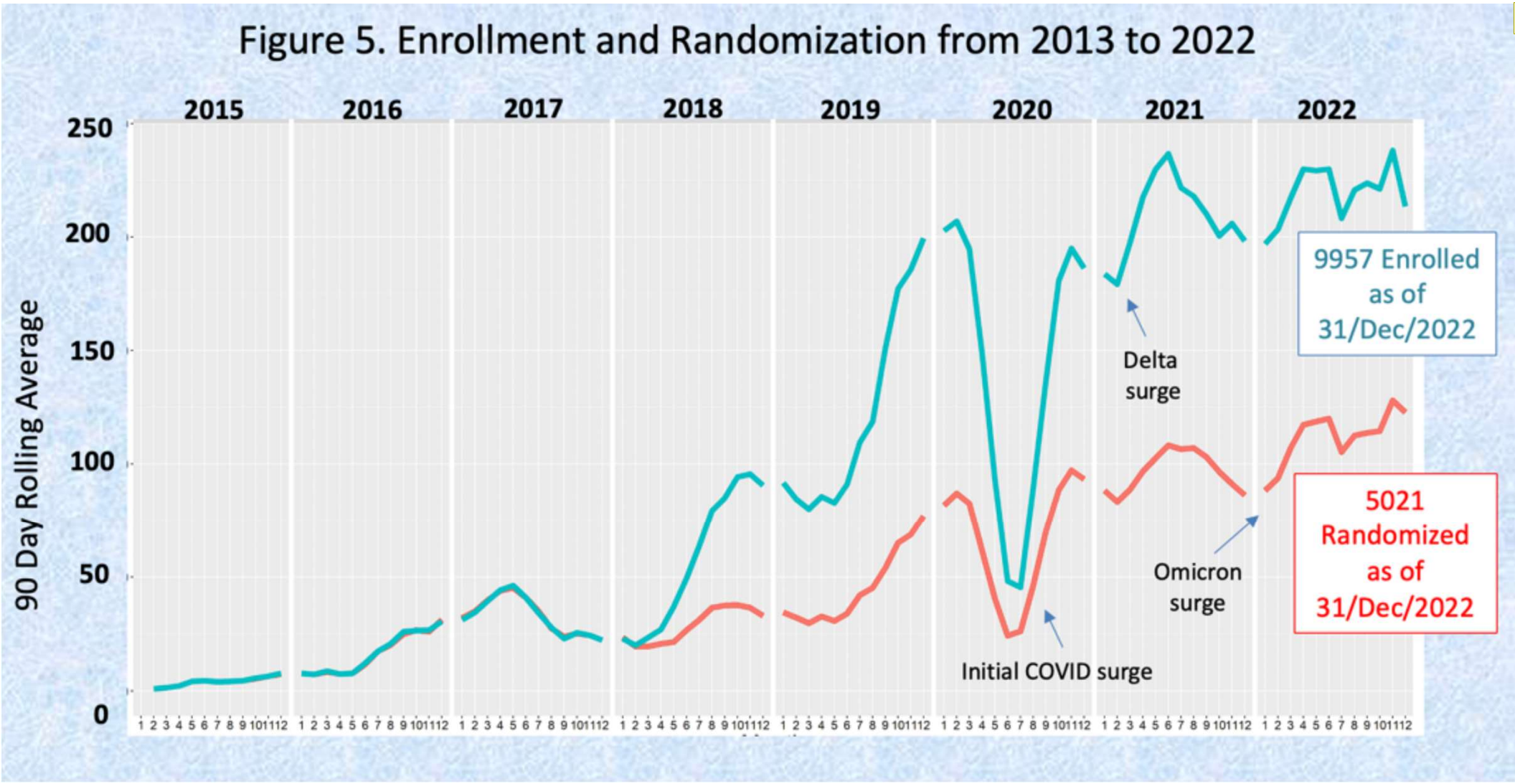
Working Groups

Acute Stroke	Primary and Secondary Prevention	Rec
• Chair: Karen Johnston, University of Virginia • Co-chair: Jeff Saver, UCLA • Renee' Martin, NDMC • Greg Albers, Stanford Imaging Core • David Liebeskind, UCLA Imaging Core • Adrianne Haggins, U Michigan, Minority Recruitment and Retention • Kate Amlie-Lefond, U Washington, Pediatric Advisory Committee • Osama Zaidat, Mercy Toledo/CWRU • Aneesh Singhal, Massachusetts General • Robert Dempsey, U Wisconsin • Enrique Leira, U Iowa • Toby Gropen, UAB • Raul Nogueira, UPMC • Maarten Lansberg, Stanford University • Thomas Hemmen, UCSD • Stacie Demel, U Cincinnati • Alejandro Rabinstein, Minnesota • Pete Panagos, Washington University • Cemal Sozener, U Michigan • Coordinator: Kinga Aitken, U Utah	• Chair: Marc Chimowitz, Medical University of South Carolina • Co-chair: Ralph Sacco, University of Miami School of Medicine • Christy Cassarly ,NDMC • Colin Derdeyn, U Iowa Imaging Core • Steve Warach, UT Austin Imaging Core • Bernadette Boden-Albala, UCLA/UCI Minority Recruitment and Retention • Heather Fullerton, UCSF, Pediatric Advisory Committee • Dawn Meyer, UCSD • Tanya Turan, MUSC • Jose Romano, U Miami • Walter Kernan, Yale University • Brad Worrall, UVA/Medstar • Sepideh Amin-Hanjani, U Chicago • Latisha Sharma, UCLA • Brett Cucchiara, U Penn • Rizwan Kalani, U of Washington • Tracy Madsen, Brown Rhode island Hospital/Yale • Anthony Kim, UCSF • Chris Streib, Minnesota, Telemedicine Advisory Committee • Coordinator: Sara Jasek, Yale	• Chair: Steve • Co-chair: Ste • NINDS repre • Caitlyn Mein • Max Winter • Dorothy Edw Recruitment • Warren Lo, U Cincinnati/OSU, Pediatric Advisory Committee • Oluwole Awosika, U Cincinnati • Wayne Feng, Duke/Wake Forest • Carolee Winstein, USC/UCLA • Randy Marshall, Columbia University • Sean Savitz, UT Houston • Jin Moo Lee, Washington University • Cheryl Bushnell, Wake Forest University • Jayme Knutson, MetroHealth/VA/CWRU • Tomoko Kitago, Burke Neurological /Columbia • Cassandra List, Brooks Rehab/U Miami • George Wittenberg, UPMC • Jennifer Majersik, U Utah • Coordinator: Aimee Reiss, Emory University

9/14/2022

Recent Developments

- *Added research coordinators*
- *Added patient representatives*
- *Improved diversity*

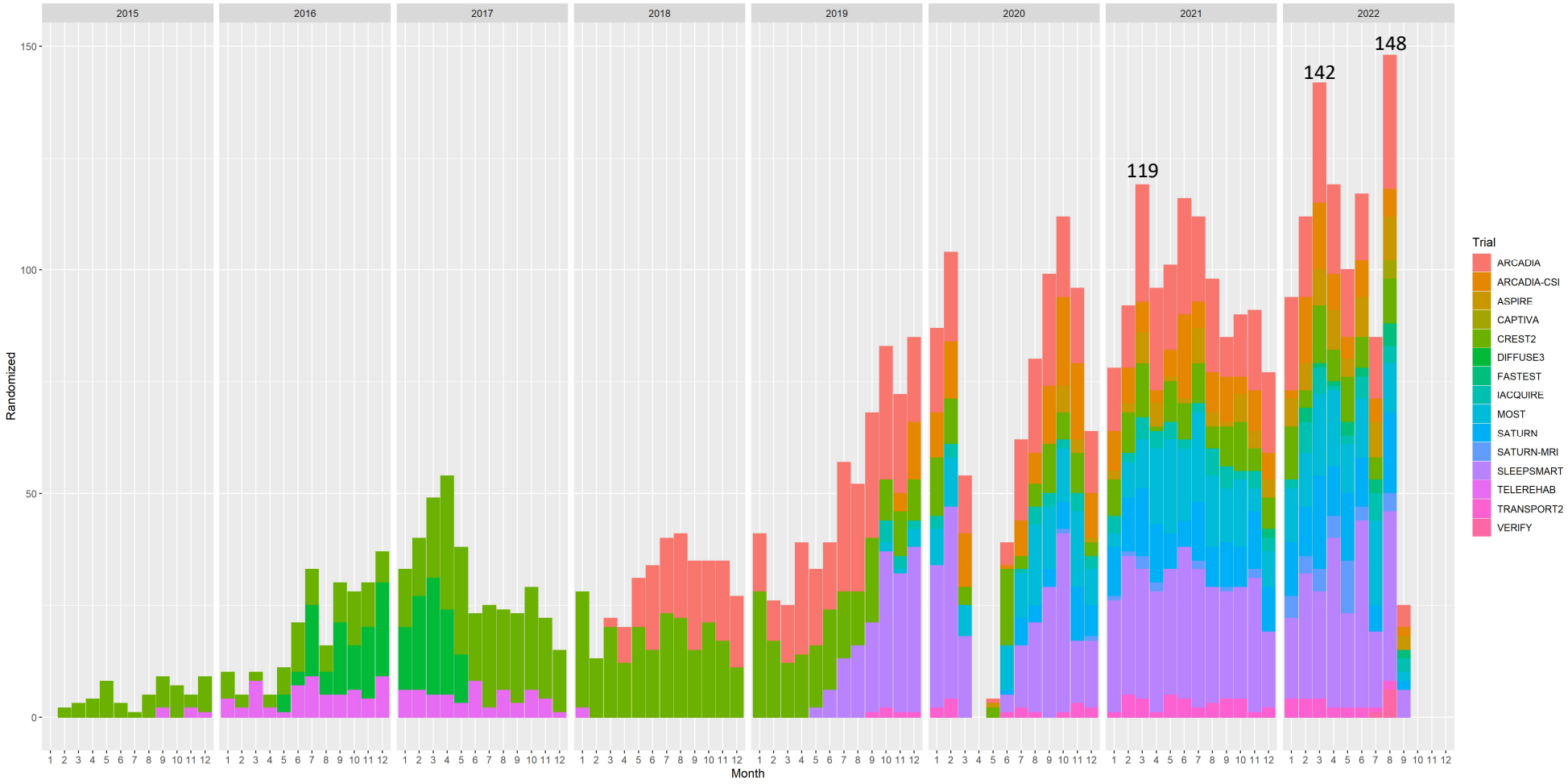


5-10-2023 update: Enrolling sites: 276. Randomized 5872

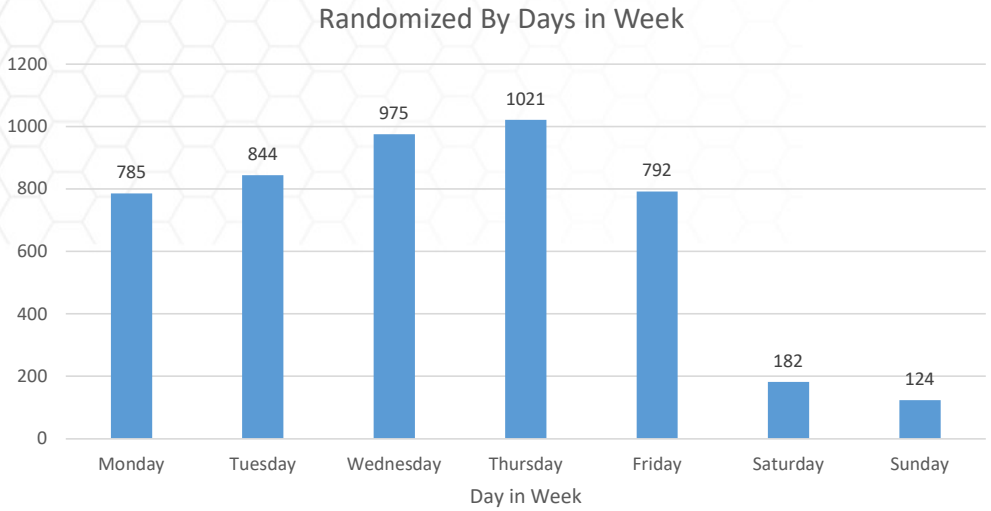
Slide 15

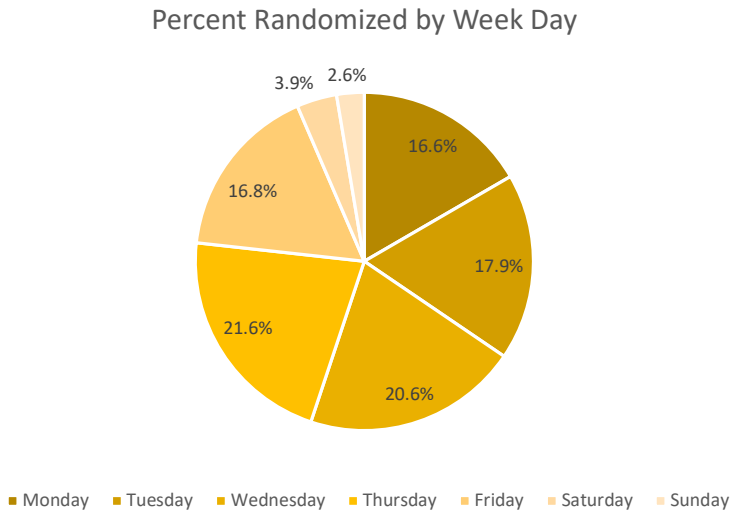
BJ(1 Broderick, Joseph (broderjp), 3/6/2023

Total Randomizations by Month

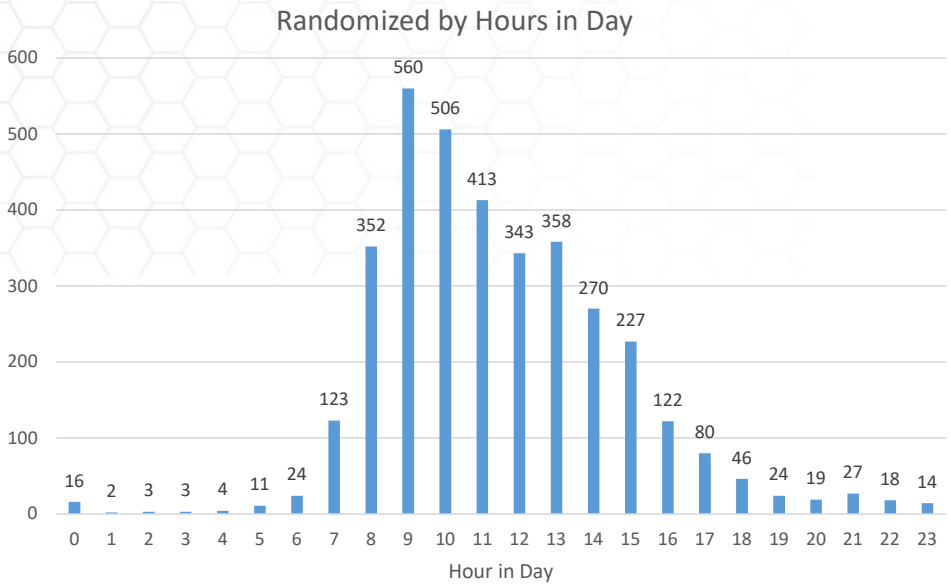


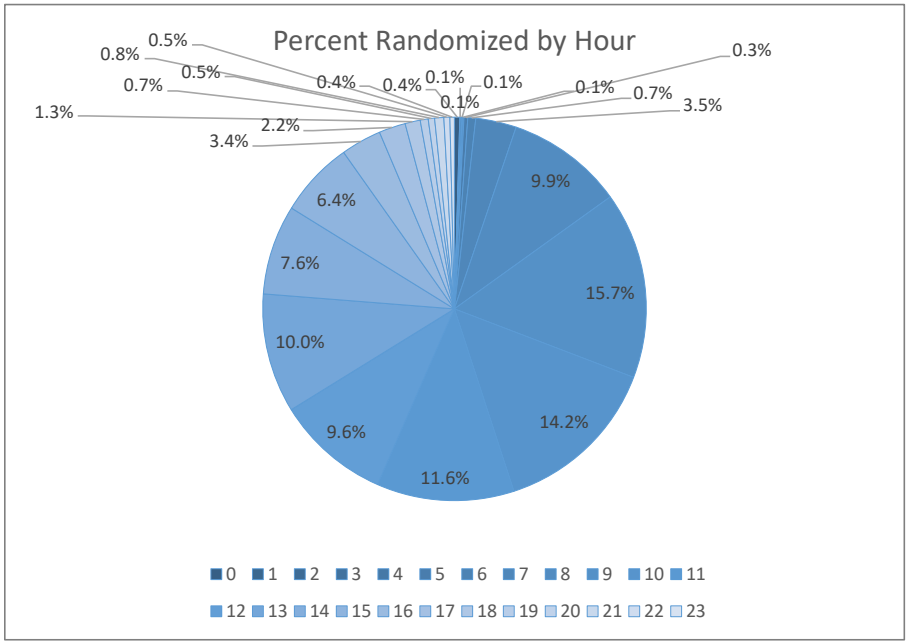
Days of the Week



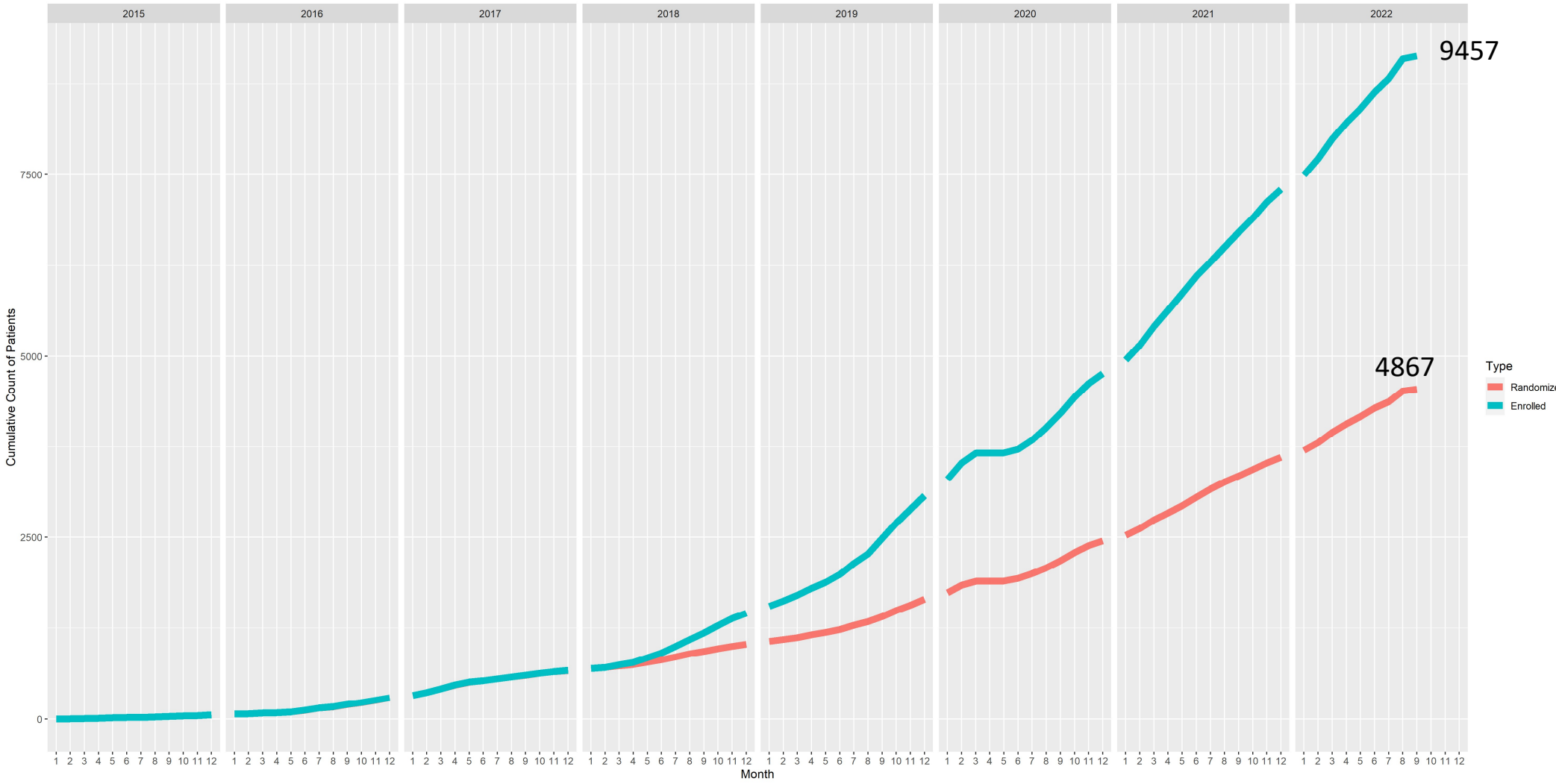


Hour of the Day





Cumulative Enrollments/Randomizations by Year



Innovations

- **A highly effective new treatment**, proving the benefit of thrombectomy for imaging-selected patients within 4.5-24h from ischemic stroke onset with a number-needed-to-treat of 3-4 to one functionally dependent patient. (US congressional award was provided to the DEFUSE 3 PI, Greg Albers, MD).
- **First multi-center randomized trial of telerehab.**
- **Innovative trial design features**
  - Multi-arm, multistage adaptive trial (MOST)
  - Emergency consent global trial for ICH (FASTEST)
  - Randomized, embedded, multi-factorial, adaptive platform trial (STEP)
  - Utility score-based dose-finding trial (SISTER).
- **A novel randomized trial population**: recovery after stroke in infants (I-ACQUIRE)

Innovations

- **Strong multidisciplinary efforts**
  - Neurology (including neurocritical care), emergency medicine, cardiology, sleep, pediatrics, rehabilitation, neurosurgery, neuroradiology, neuroscience, and statistics have emerged to design and implement these trials,
  - Contact PIs from emergency medicine (MOST), neurosurgery (CAPTIVA), developmental psychology (I-ACQUIRE), and statistics (STEP).

- **Crossing between traditional stroke domains**, such as an acute-recovery (VERIFY), prevention-recovery (SLEEP Smart, SATURN), prevention after ICH (SATURN & ASPIRE – overlap of neurology and cardiology).

- **Trial Expansion beyond US sites:**
  - Arcadia, SATURN, FASTEST, RHAPSODY 2, MOST, FOCUS, and CAPTIVA

Platform trials for endovascular patients

Deluge of EVT Proposals to NINDS/StrokeNet

Trial Name	PIs	Stage in StrokeNet*	Topic
ENDOLOW	Demchuk et al	Interest in submitting Q2 RAH2018	EVT for low NIHSS
MATRICS	Lansberg, Albers, Yoo, Zaidat, Nogueira et al.	Held pre-Concept synopsis Q4 2018	EVT for large core
(DEFUSE M)	Lansberg, Albers, et al	ESC review 2018	EVT for large core
(MIRACLE)	Nogueira et al	ESC review 2018	EVT for large core
(TESLA)	Yoo, Zaidat, et al	Concept synopsis 2018	EVT for large core
PETITE	Lee, Albers	Submitted NIH review Q4 2019	EVT for children
AITES	Qureshi	Interest in submitting Q4 2019	Avoid tPA prior to EVT
DEFUSE TNK	Lansberg, Albers, Campbell, Parsons	Concept synopsis Q3 2018	TNK prior to 4.5-16h EVT
ETHER	Mayer	Feasibility survey Q3 2017	BP control after EVT
HEMERA	Linfante, Nogeuira	Held pre-Concept synopsis Q4 2018	Sanguinate peri-EVT
RHAPSODY2	Lyden	Submitted NIH review Q4 2019	3K3A ACP in AIS including prior to EVT
SERENE	Raychev, Kallmes	ESC review Q1 2018	General anesth vs proc sedation during EVT
(ASSIST)	Kallmes et al	Concept synopsis Q2 2017	General anesth vs proc sedation during EVT
(SEACOAST)	Raychev et al	Concept synopsis Q2 2017	General anesth vs proc sedation during EVT
PAST TIME	McMullan, Adeoye	Submitted NIH review Q2 2018	Prehospital LVO scales for EVT routing

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ENDOLOW	Demchuk et al	Interest in submitting Q2 RAH2018	EVT for low NIHSS	EVT Indication Expansion
MATRICS	Lansberg, Albers, Yoo, Zaidat, Nogueira et al.	Held pre-Concept synopsis Q4 2018	EVT for large core	
(DEFUSE M)	Lansberg, Albers, et al	ESC review 2018	EVT for large core	
(MIRACLE)	Nogueira et al	ESC review 2018	EVT for large core	
(TESLA)	Yoo, Zaidat, et al	Concept synopsis 2018	EVT for large core	
PETITE	Lee, Albers	Submitted NIH review Q4 2019	EVT for children	
AITES	Qureshi	Interest in submitting Q4 2019	Avoid tPA prior to EVT	Novel / Improved Concomitant Therapy to EVT
DEFUSE TNK	Lansberg, Albers, Campbell, Parsons	Concept synopsis Q3 2018	TNK prior to 4.5-16h EVT	
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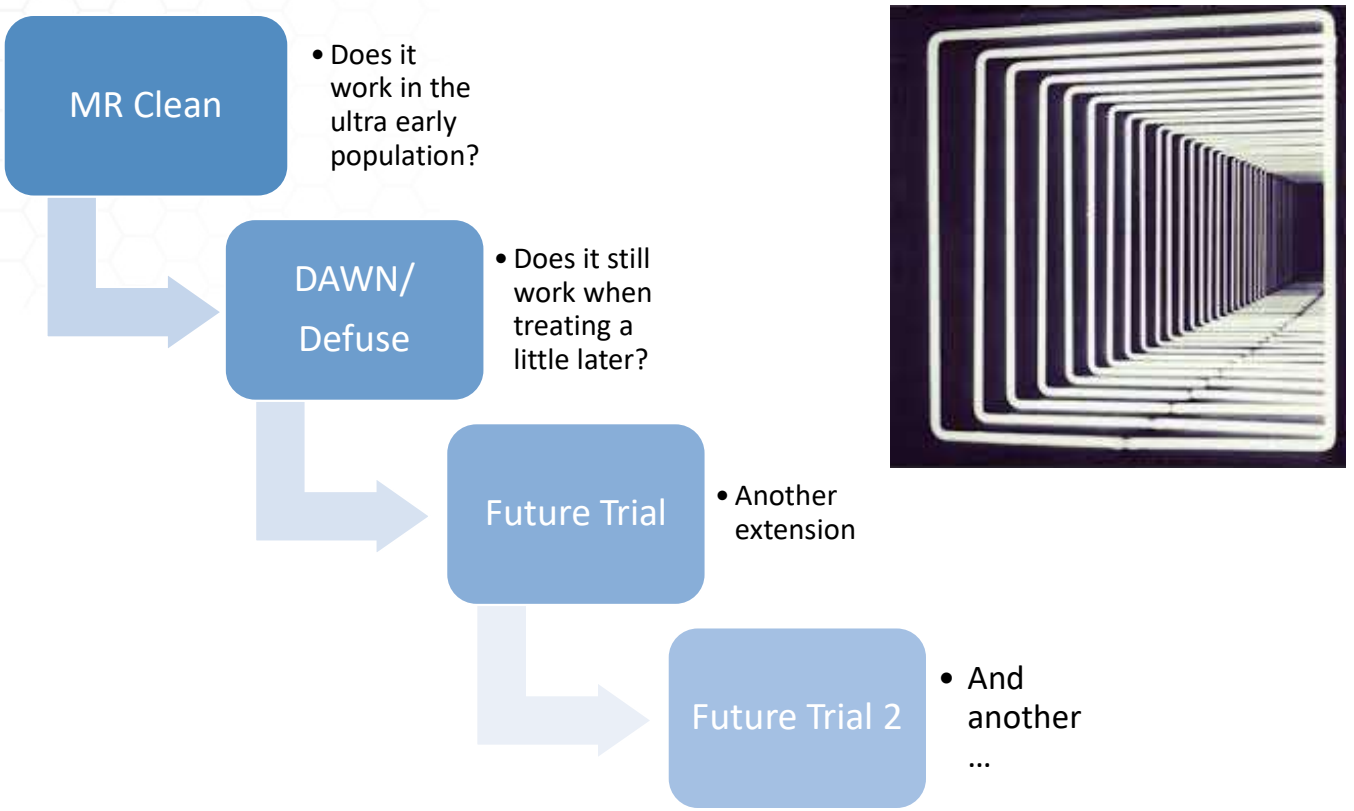
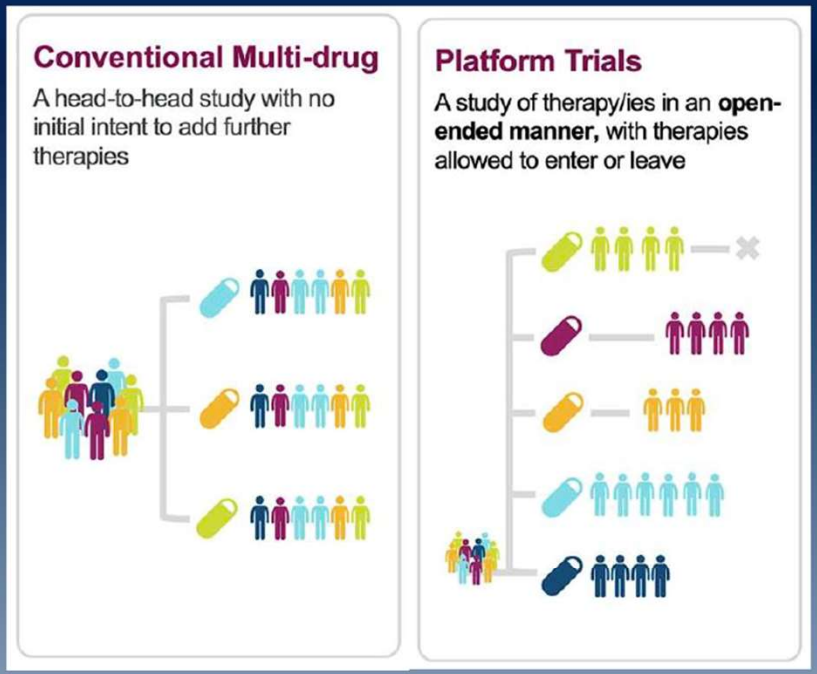
Current Approach to Clinical Trials



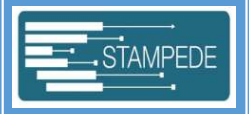
Multi-Arm Multi-Stage (MAMS) Trial Platforms Subtypes

- Umbrella
  - Multiple treatments, one disease
- Basket
  - Multiple diseases, one treatment
- Minesweeper*
  - One treatment, one disease, multiple subgroups



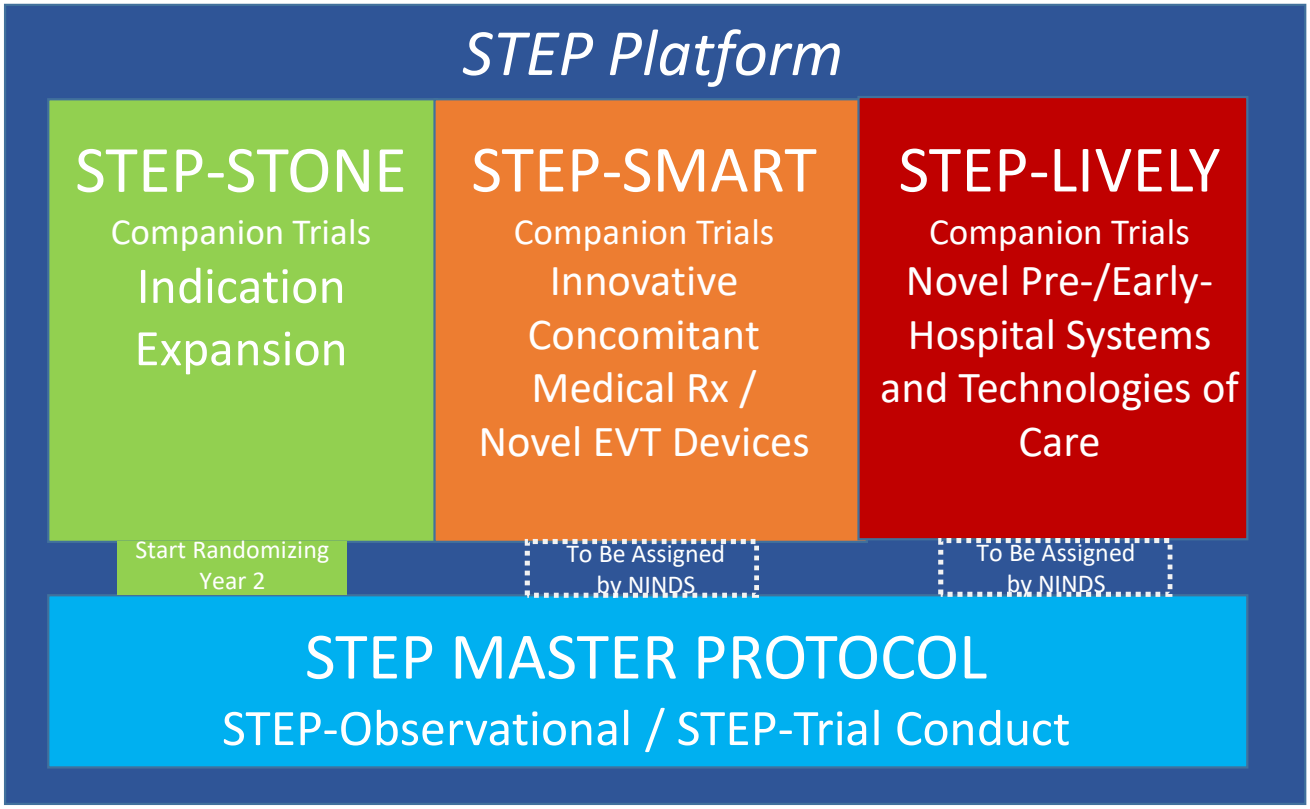
*--Berry et al, JAMA 2015; -*Meinzer, Saver, et al, in preparation*

Platform Trials – Expanding Adoption

						
Platform	STAMPEDE	I-SPY2	GBM AGILE	Healey ALS	EPPIC NET (HEAL)	STEP
Condition	Prostate CA	Breast CA	Glioblastoma	ALS	Pain	Stroke
Year started	2005	2010	2019	2020	2020	2023
Agents/pops tested	10	16	4	5	>4	>4
Centers	>120	>20	>23	>54	>24	38
Patients	>10,000	>1400	>550	>1000	>1000	>3000

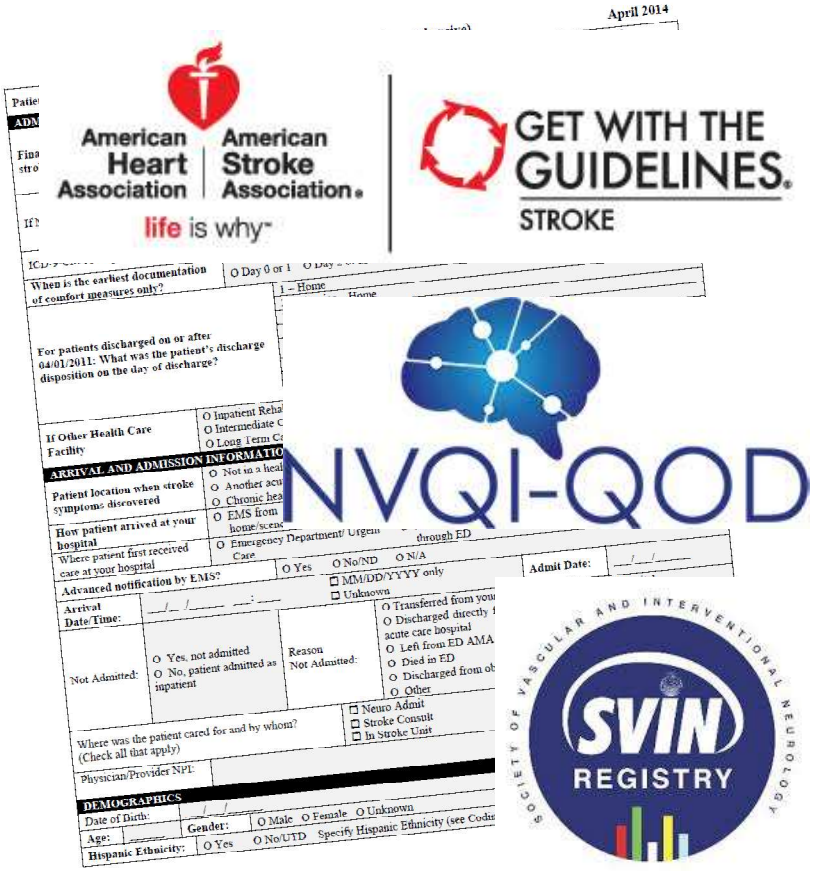
Master Trial Protocols (Platforms)

- Eliminate cost and duplication of resources with traditional, free-standing, parallel-group RCTs
- Able to compare multiple interventions (arms)
- Examine effects across subgroups of patients with distinct but related clinical features
- Minimize downtime between trials
- Share control groups
- Drop arms early when treatments fail
- Combine promising treatment arms

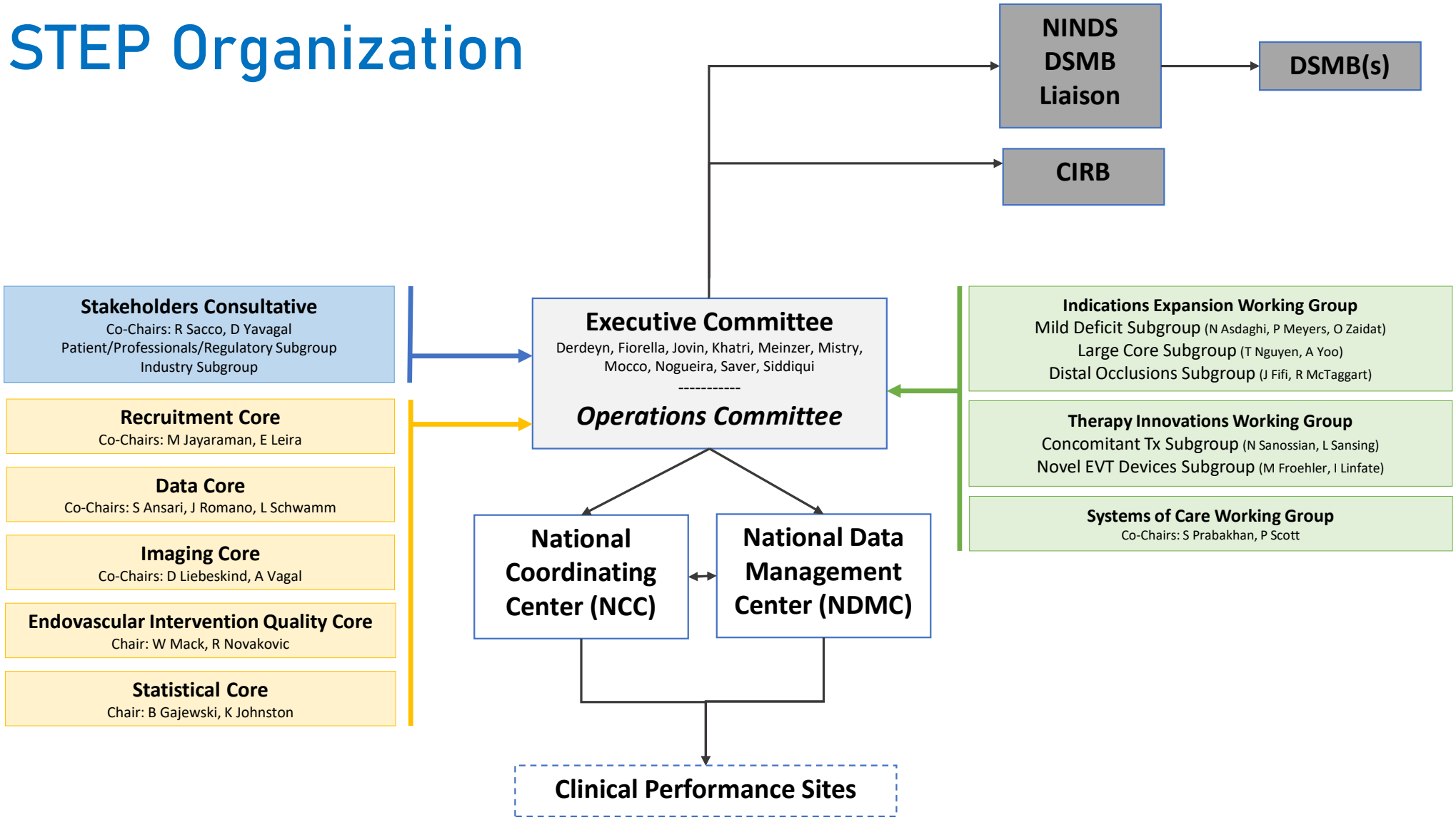

STEP Platform
STEP-STONE
Companion Trials
Indication Expansion
STEP-SMART
Companion Trials
Innovative Concomitant Medical Rx / Novel EVT Devices
STEP-LIVELY
Companion Trials
Novel Pre-/Early-Hospital Systems and Technologies of Care
Start Randomizing Year 2
To Be Assigned by NINDS
To Be Assigned by NINDS
STEP MASTER PROTOCOL
STEP-Observational / STEP-Trial Conduct

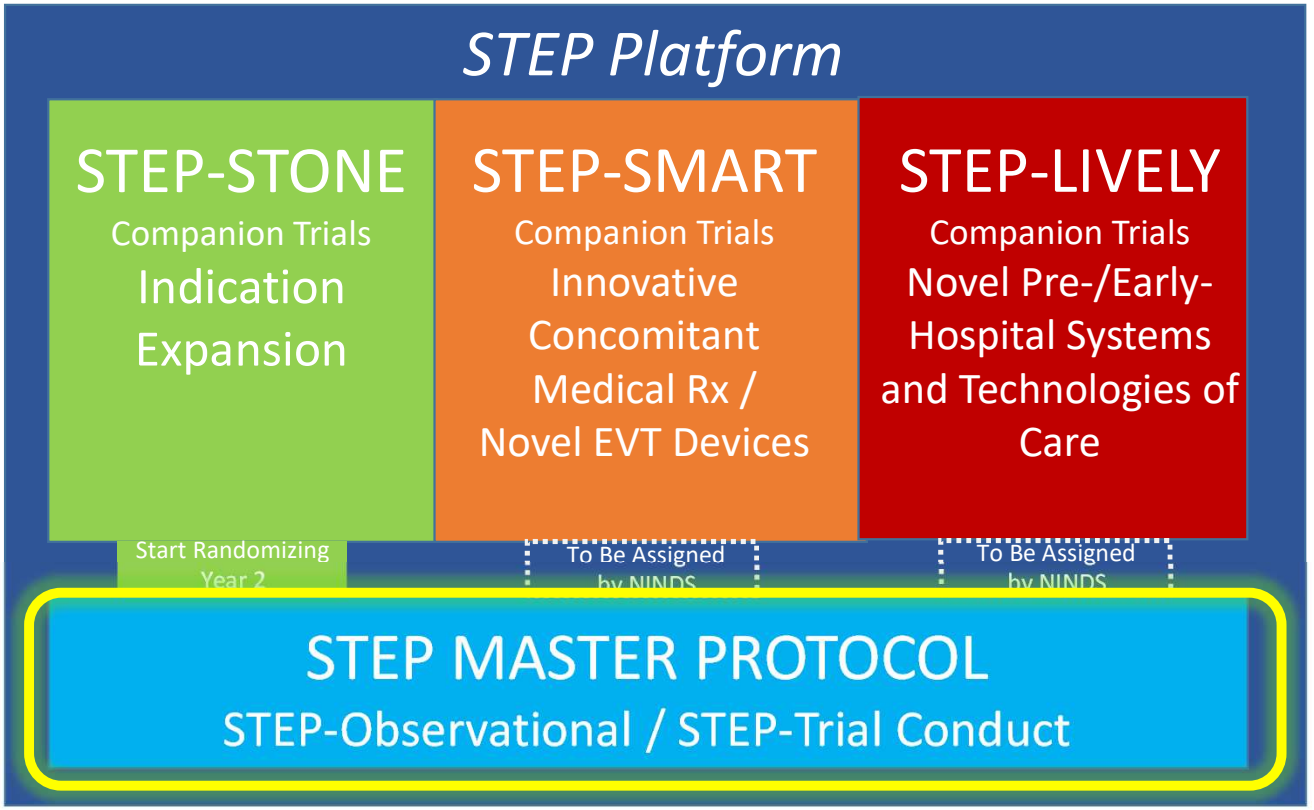
Registry Based Platform

- Both MM + EVT Patients
  - **Get with the Guidelines – Stroke (GWTG-Stroke)**
    - AHA/ASA
- EVT Patients
  - **Neurovascular Quality Initiative-Quality Outcomes Database (NVQI-QOD)**
    - SNIS, AANS/CNS CV Joint Section
  - **SVIN Neuroendovascular Registry (SVIN-R)**
    - SVIN



STEP Organization





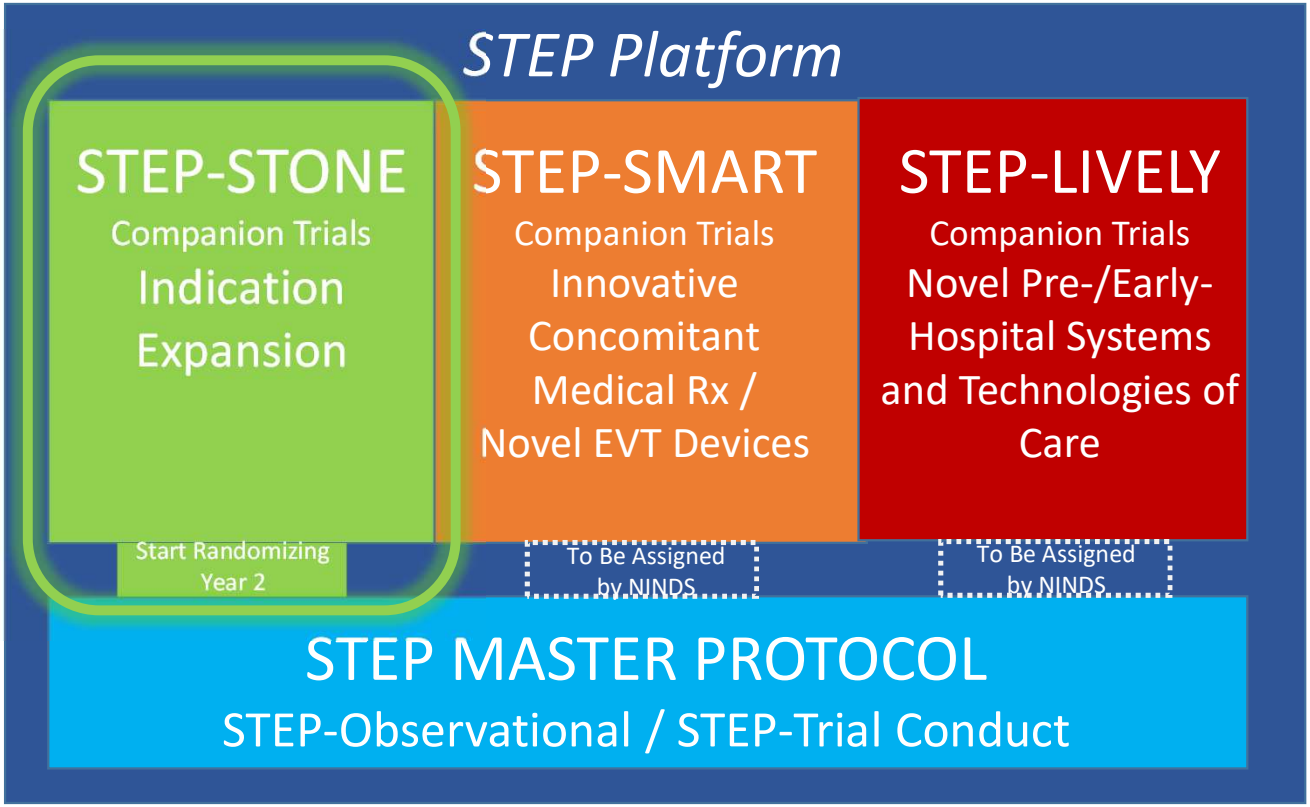
- 18+ years
- Up to 48h
- Any visualized occlusion

- 18+ years
- Pre-stroke mRS 0-2

Large Core
- ASPECTS 0-5
- LVO
- Up to 6 hours

Low NIHSS
- NIHSS 0-5
- LVO
- Up to 24h

Nondominant/ Co-dominant M2s
- LVO
- Up to 24h
- Salvageable brain



Research Opportunity Announcements

A Research Opportunity Announcement (ROA) is a public document that announces the availability of an Other Transaction (OT). It provides the initiative's purpose, type of award, instructions on how to apply, due date for proposals or applications, and research opportunity number.

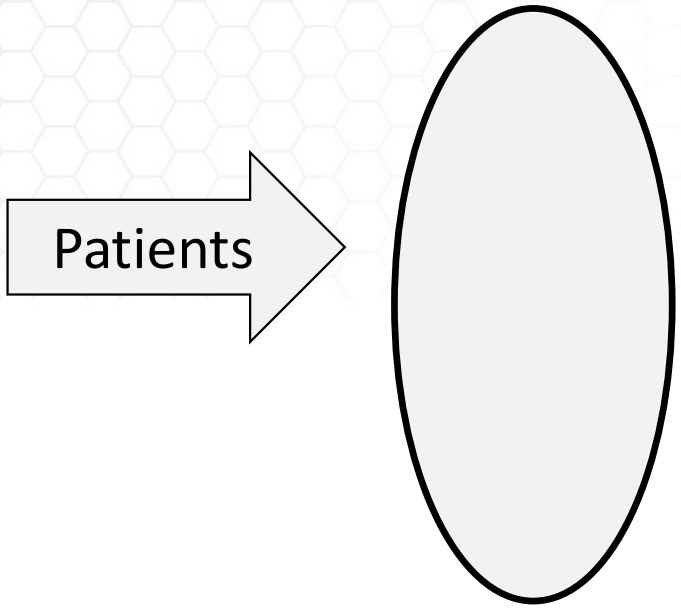
Platform Trials of Thrombectomy in Acute Stroke (OT2)	OTA-22-001	NINDS is interested in establishing master protocols to enable platform trials in thrombectomy in acute stroke using a seamless rolling approach to be conducted within the existing NIH StrokeNet infrastructure. Trials that further refine patient groups that do or do not benefit from mechanical thrombectomy, and using which management approaches, will also open the door to testing neuroprotectant strategies in an efficient, timely, and cost-effective manner. This ROA will establish the groundwork to include the master protocol for platform trials with the NIH StrokeNet.	StrokeNET	Scott Janis, PhD

OTA initiated with StrokeNet on Sept 1, 2022

StrokeNet Thrombectomy Platform (STEP)

- Randomized Multifactorial Adaptive Platform (REMAP design)
- 38 NIH StrokeNet sites across the US
- Leverages existing registries for data collection
  - **Get with the Guidelines Stroke Registry** (ASA/AHA)
  - **Neurovascular Quality Initiative-Quality Outcomes Da**tabase (NVQI-QOD)NI AANS/CNS CV Joint Section
  - **SVIN Neuroendovascular Registry** (SVIN-R)

STEP- Master Protocol



Master Protocol

- Defines the largest set of Inclusion/Exclusion Criteria to be studied
  - ✓All acute ischemic stroke patients with a large or medium/distal vessel occlusion who present within 24 hrs of LKW
- Broadly defines overall study terminology and research procedures
- Specifies a single underlying statistical model

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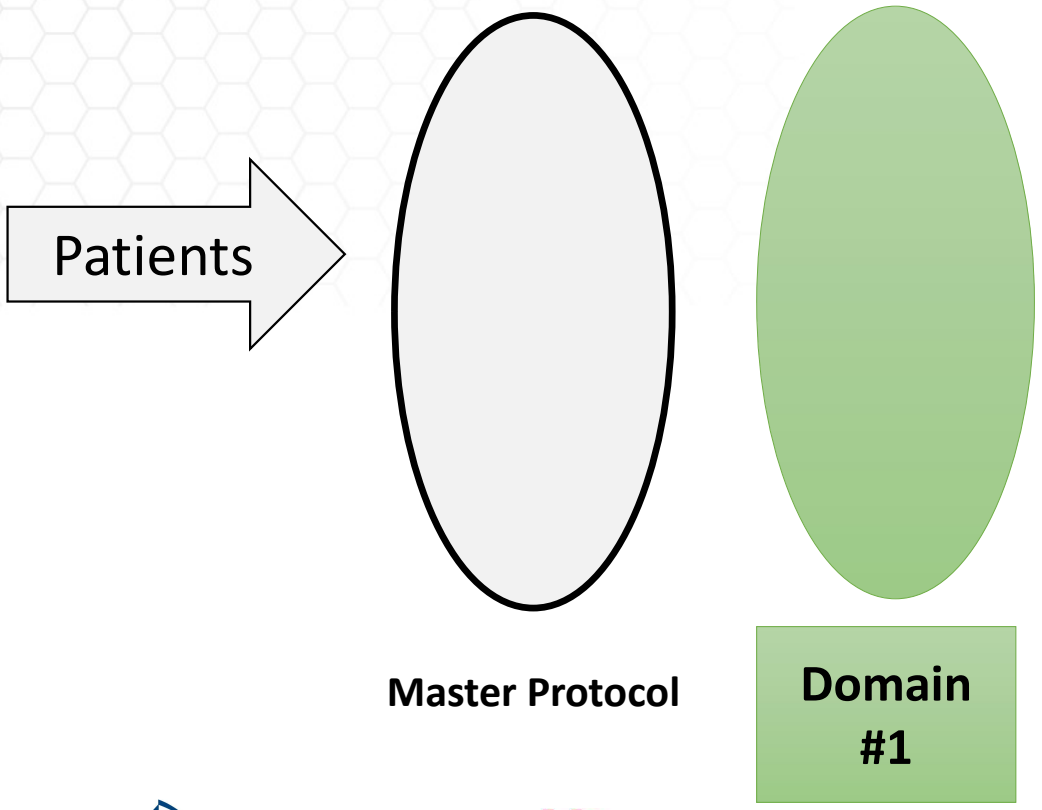
STEP- Domains



- Studies of **mutually exclusive** interventions
  - ✓EVT vs MM
  - ✓Neuroprotectant 1 vs Neuroprotectant 2 vs control
- Patients can be randomized within multiple domains (**multifactorial**)

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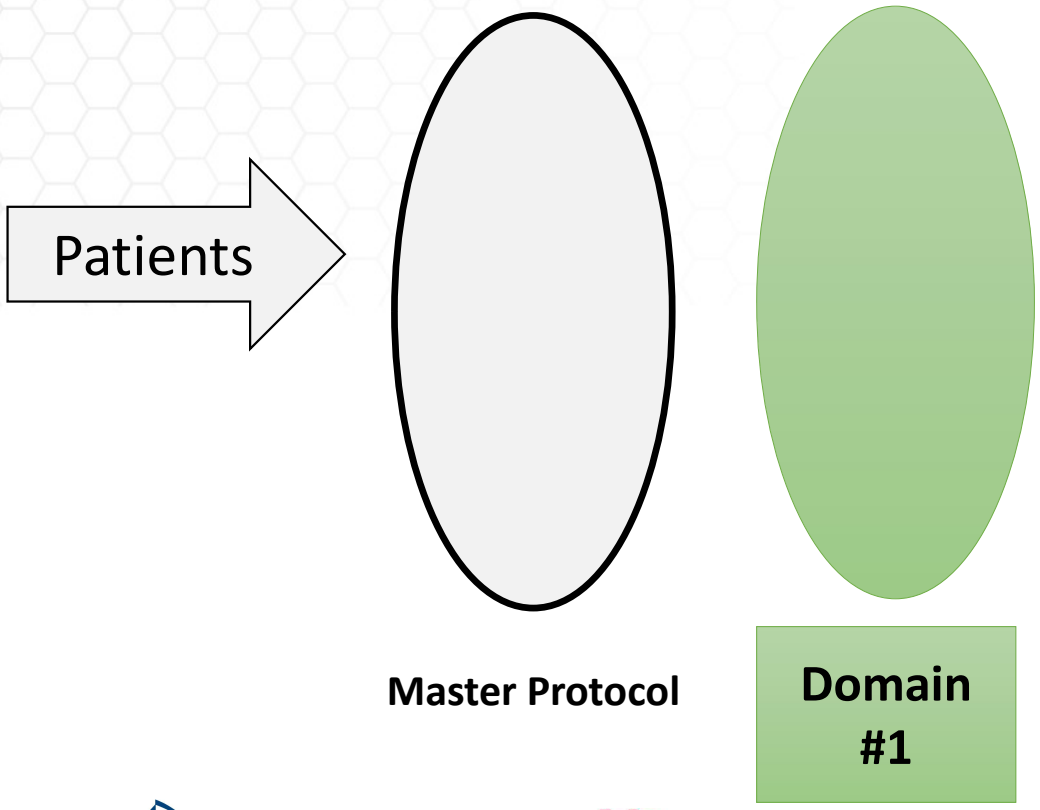
STEP- Domain Specific Appendices



- 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

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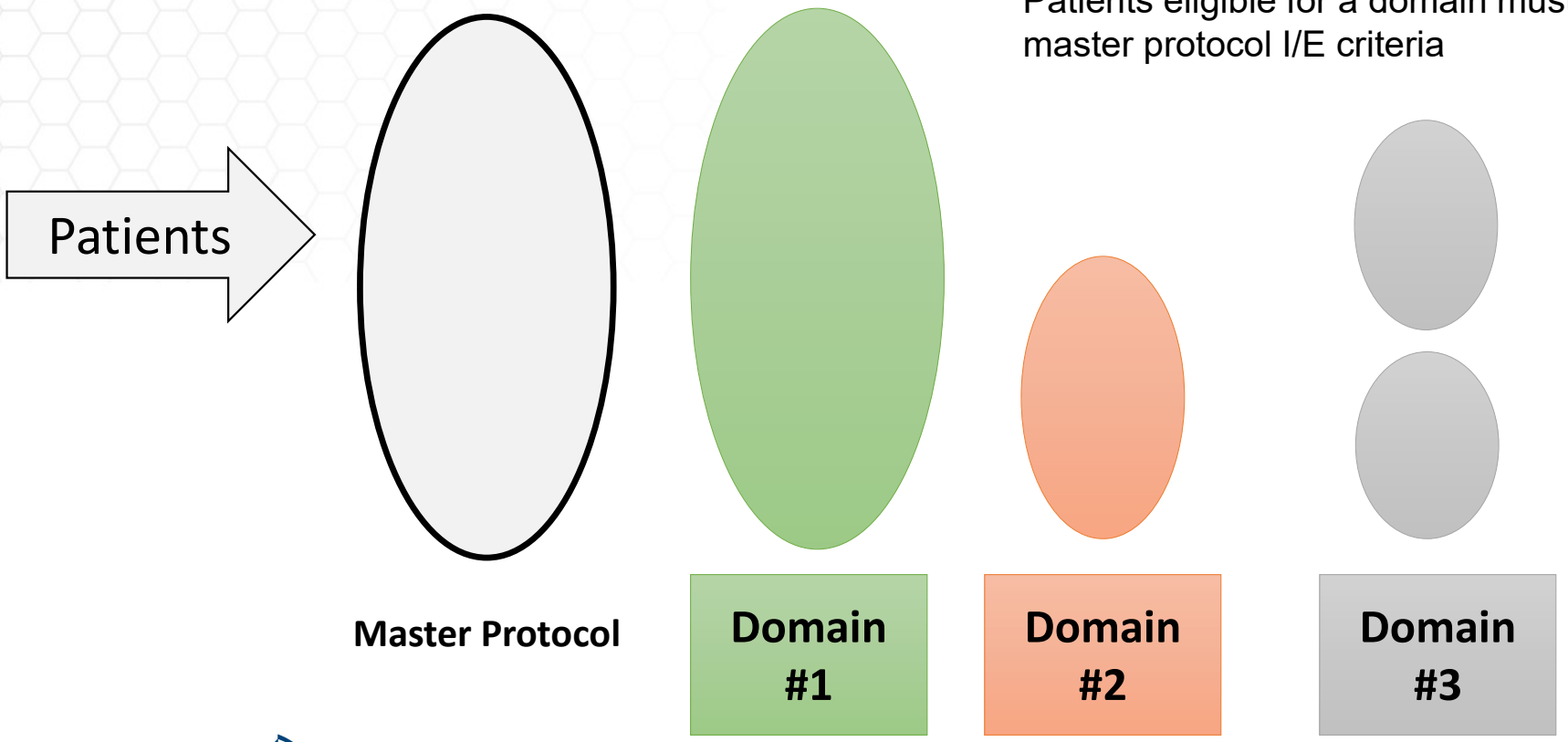
STEP-Domains

Patients eligible for a domain must be subset of master protocol I/E criteria



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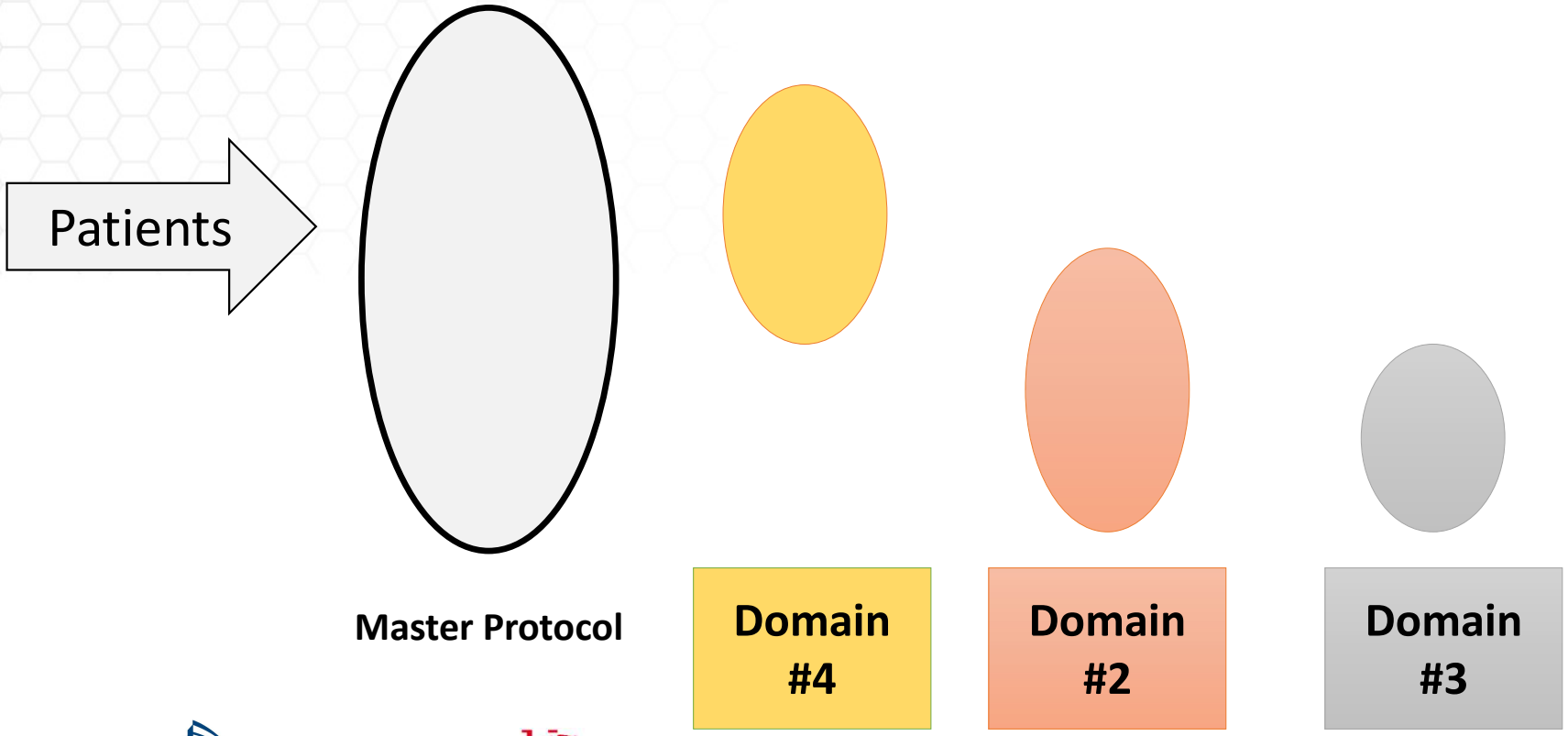
STEP-Domains



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STEP- Consent Procedures

Master short consent form:

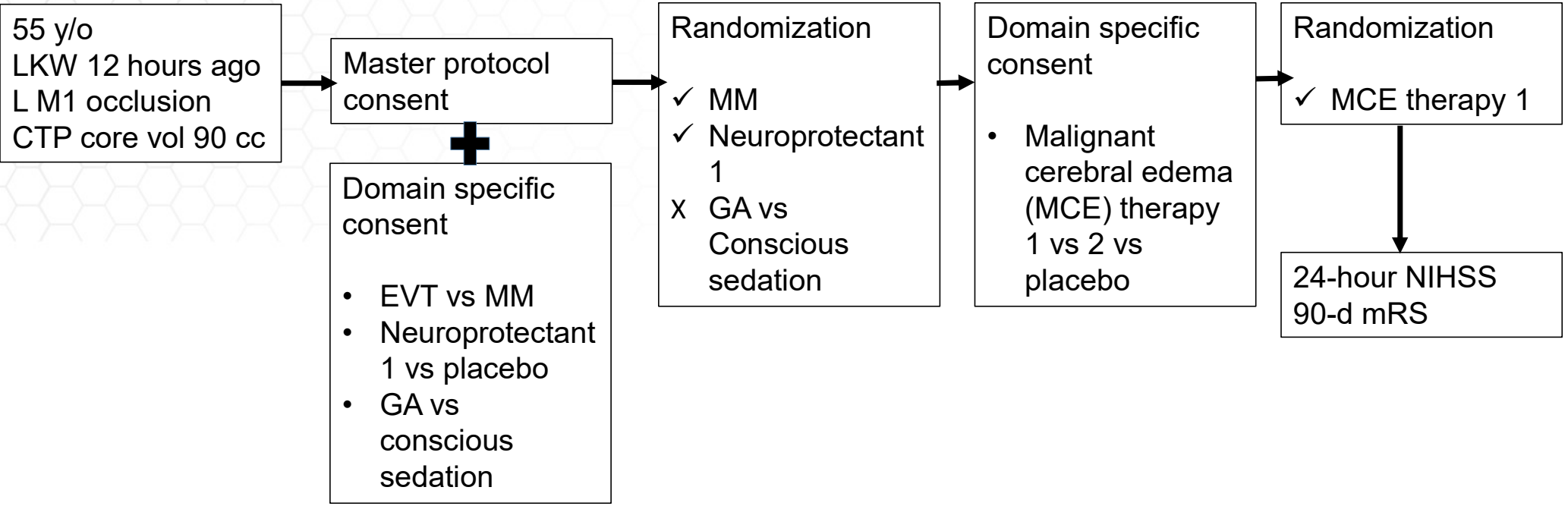
- Administered to consecutive patients meeting the master protocol inclusion/exclusion criteria
  - ✓ All AIS patients within 24 hours of LKW with a visible intracranial vessel occlusion
- Signed by patient or LAR
- Consenting process will follow NIH StrokeNet policies

STEP- Consent Procedures

Domain specific consent appendices:

- Interactive form
- Domain specific consent appendices are generated according to specific inclusion/exclusion criteria for given domains
- Interactive form can be filled out at specific time points to generate DSA consent forms for all possible domains that a patient may be eligible for at a given time point.

Enrollment Example-1



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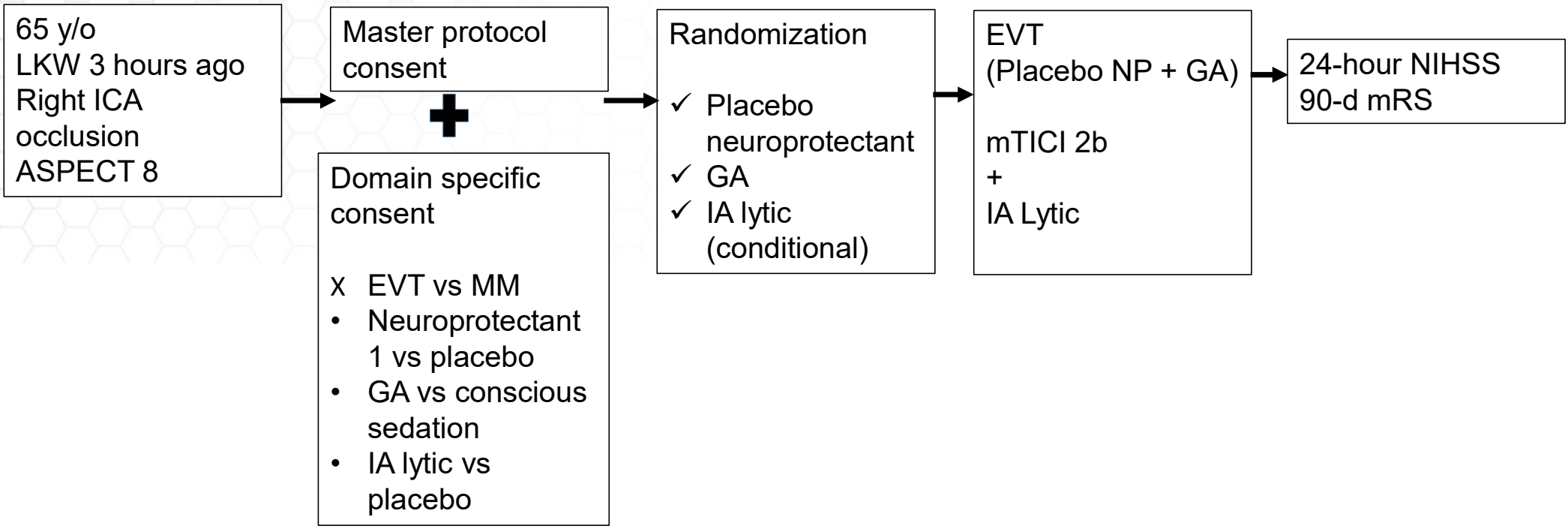
Enrollment Example-2



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STEP Data Transfer Procedures

- STEP leverages two major acute stroke/endovascular registries to minimize the burden of data collection through superuser agreements
  - AHA GWTG
  - NVQI-QOD (SNIS, SVIN, AANS/CNS)
- Direct data entry is required for critical data elements for randomized patients

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Primary Specific Objective – FASTEST Trial

- The *objective* of the rFVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time (FASTEST) Trial is to establish the first treatment for acute ICH within a time window and subgroup of patients that is most likely to benefit.

NIH Funded: 1U01NS110772-01

Design

- Randomized, double-blind controlled efficacy trial of rFVIIa plus best standard therapy vs. placebo plus best standard therapy (including INTERACT 2 goal of target systolic BP of 140 mm Hg).
- Includes subjects:
  - Age 18-80, inclusive
  - Baseline volume of spontaneous ICH ≥ 2 cc and < 60 cc (measured by ABC/2 or by an FDA-cleared automated ICH volume imaging software (e.g., VIZ.ai, RAPID).
  - No or smaller volume of IVH (IVH score ≤ 7)
  - **Treated within 120 minutes of stroke onset/last known well** (goal: ½ treated within 90 minutes).

How to Minimize Time to Treatment

- Mobile stroke care units
- Exception from informed consent*/emergency research consent procedures
- Improved acute stroke treatment processes as for ischemic stroke, including automatic calculation of ICH volume, door to needle, etc.

* You can enroll participants acutely if consent cannot be obtained (following proper guidelines) but then you must get consent later from the participant or LAR

Inclusion Criteria

- Age
- Spontaneous ICH
- Able to treat with rFVIIa **within 120 minutes of stroke onset or last known well**
- Efforts to obtain informed consent per EFIC guidelines (U.S.) or adherence to country-specific emergency research informed consent regulations (Canada, Germany, Spain, U.K., Japan)

Major exclusion criteria

- Score of 3 to 7 on the Glasgow Coma Scale
- **Secondary ICH related to known causes (e.g., trauma, aneurysm, arteriovenous malformation (AVM), oral anticoagulant use (warfarin or novel oral anticoagulants) within the past 7 days, coagulopathy, etc.)**
- **ICH volume < 2 cc or ≥ 60 cc**
- **IVH score > 7**
- Pre-existing disability (mRS > 2)
- Symptomatic thrombotic or vaso-occlusive disease in past 90 days (e.g., cerebral infarction, myocardial infarction, pulmonary embolus, deep vein thrombosis, or unstable angina)
- Clinical or EKG evidence of ST elevation consistent with acute myocardial ischemia
- Brainstem location of hemorrhage (patients with cerebellar hemorrhage may be enrolled)
- Refusal to participate in study by patient, legal representative, or family member
- Known or suspected thrombocytopenia (unless current platelet count documented above 50,000/µL)
- Unfractionated heparin use with abnormal PTT

Intervention

- Randomize participants in a 1:1 ratio to intravenous rFVIIa or placebo at a dose of **80 µg/kg (maximum 10,000 µg or 10 mg**) and administered intravenously over 2 minutes – all investigators and participants will be blinded throughout the course of the trial
  - **Enrollment and randomization in the trial will occur upon injection of the study medication**
- Only a baseline non-contrast CT is required
- CT angiogram will be collected, if done, but is not required

Blood Pressure Control

- Background:
  - Reduction of SBP <= 140 mm Hg is predictive with improved outcomes (INTERACT2)
  - Further reductions are harmful (ATACH-2)
  - FASTEST will **target** SBP <= 140 mm Hg
- To achieve SBP reduction, calcium channel blockers (e.g., nicardipine) and peripheral alpha blockers (e.g., urapidil) are most common

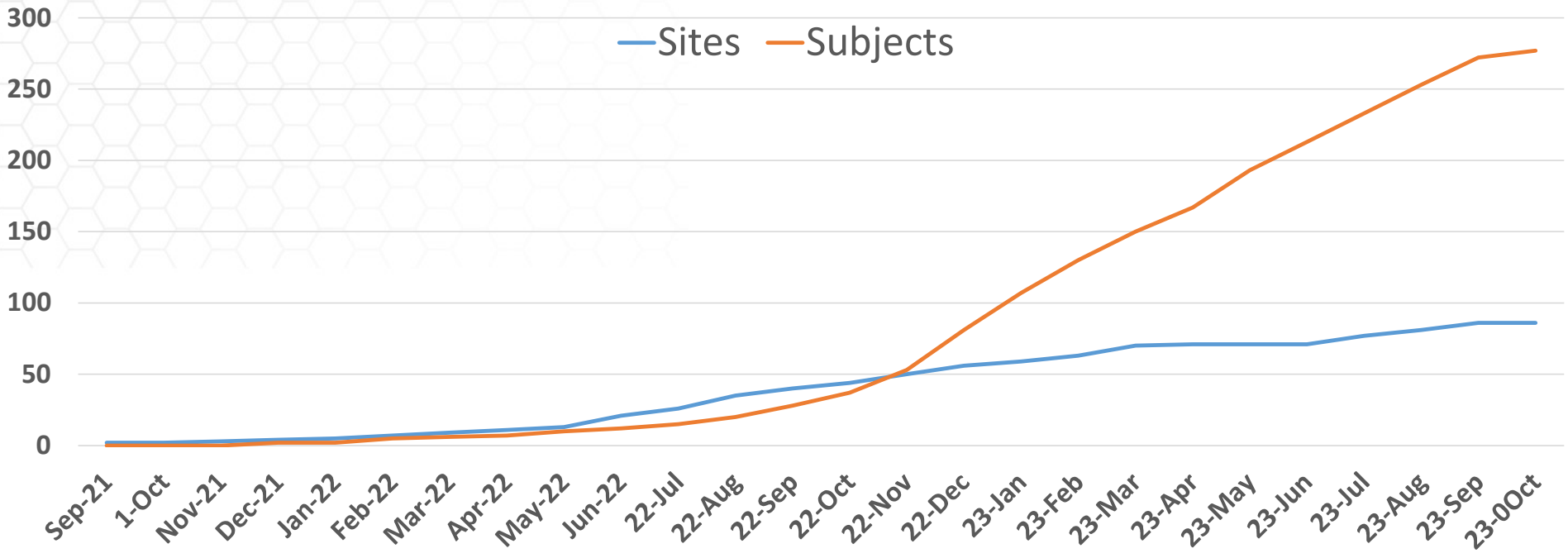
Primary Safety Measure

- Life- threatening thromboembolic complications during the first four days after completion of study drug and mortality.
- A significant life-threatening complication will be defined as development of:
- acute myocardial infarction,
- acute cerebral infarction,
- acute pulmonary embolism.

Enrollment of Study Population

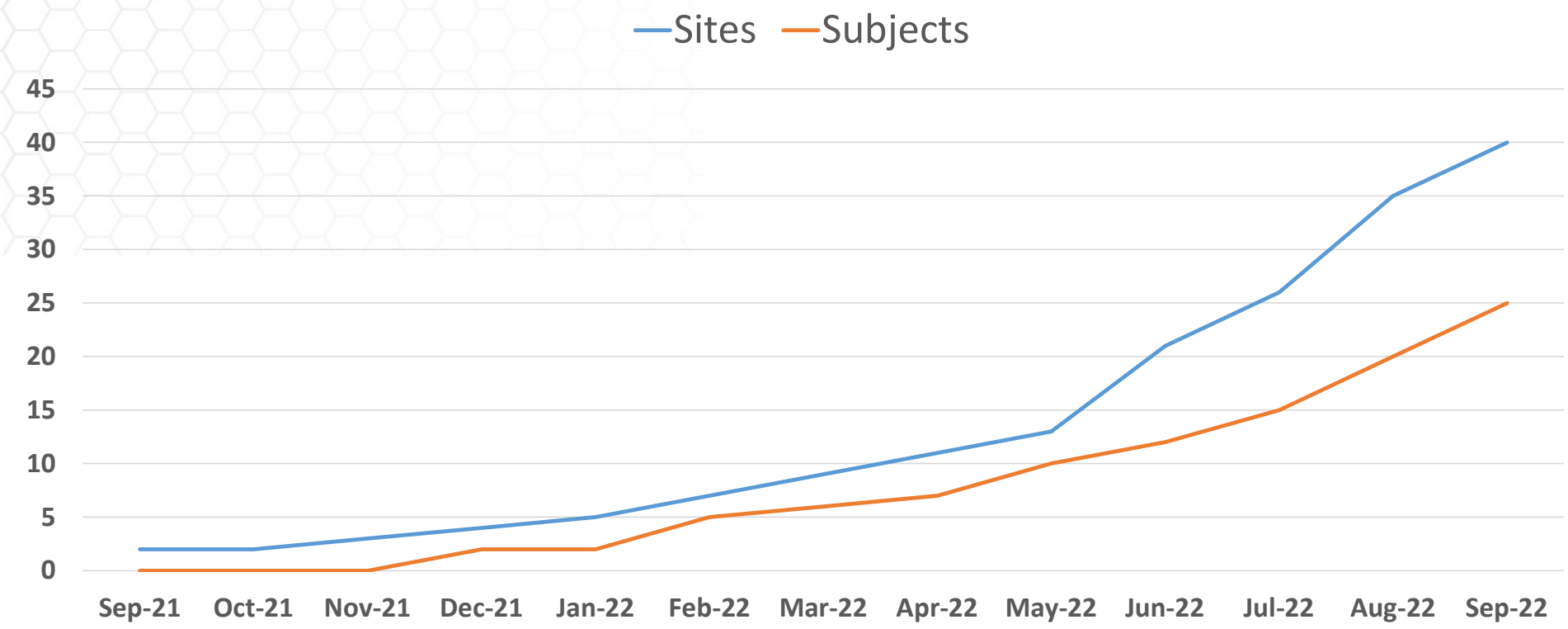
- Subjects to be enrolled – maximum 860.
- Anticipated number of trial sites – 100 including 15 mobile stroke units.
- Countries participating – U.S., Canada, Germany, Spain, U.K., and Japan.
- The primary outcome measure is the distribution of the ordinal mRS at 180 days (specifically: 0-2, 3, and 4-6, per FDA).
- Other secondary outcomes including growth of ICH at 24 hours.

Site start-up and subject enrollment



As of 10-5-2023, 277 enrolled – 32% of planned maximum. 86 sites

Site start-up and subject enrollment



CAPTIVA

Comparison of Anti-coagulation and anti-Platelet Therapies for Intracranial Vascular Atherostenosis

Brian Hoh, MD, MBA
Marc Chimowitz, MBChB
Sharon Yeatts, PhD
Renee Martin, PhD
Tanya Turan, MD, MSCR
Larisa Cavallari, PharmD

UF | UNIVERSITY of FLORIDA

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Funding sources

- NINDS
- Janssen providing rivaroxaban and funding for placebo
- AstraZeneca providing ticagrelor

CAPTIVA Trial – Three arm trial

- 1683 subjects with symptomatic infarct due to 70-99% sICAS
- Participants: non-disabling symptomatic infarct <30 days with 70-99 stenosis of ICA, MCA, basilar, or intracranial VA by DSA, CTA, or MRA
- Randomize 1:1:1, double-blinded
- Ticagrelor (180mg load, then 90mg BID) + Aspirin (81mg QD)
- Rivaroxaban (2.5mg BID) + Aspirin (81mg QD)
- Clopidogrel (600mg load, then 75mg QD) + Aspirin (81mg QD)
- Sample for CYP2C19 genotype test, blinded
- Intensive Risk Factor Management (same as SAMMPRIS and CREST-2)
- Follow-up visits 1 month, 4 months, 8 months, 12 months

Rationale for a 3-Arm Study

- Timely
- Compelling data for clopidogrel + aspirin (POINT[1] and CHANCE[2]) ticagrelor + aspirin (THALES[3] and PRINCE[4]) and low dose rivaroxaban + aspirin (COMPASS[5] and COMMANDER HF[6])
- Efficient: one control arm
- Comparison is to clopidogrel arm not against each other

1. Johnston et al, NEJM 2018
2. Wang et al, NEJM 2013
3. Johnston et al, BMJ 2019
4. Wang et al, BMJ 2019
5. Eikelboom et al, NEJM 2017
6. Zannad et al, NEJM 2018

Ticagrelor

- Direct P2Y12 receptor antagonist
- Maximal platelet reactivity inhibition 1 hour vs clopidogrel 6-12 hours[1]
- Does not require CYP2C19 activation
- However, ticagrelor more effective than clopidogrel irrespective of CYP2C19 LOF carrier status (PLATO[2], ONSET/OFFSET,[3] RESPOND[3])

1. Gurbel et al, Circulation 2009
2. Wallentin et al, Lancet 2010
3. Tantry et al, Circ Cardiovasc Gen 2010

Ticagrelor + aspirin in large artery atherosclerosis

	Ticagrelor 90 mg bid (N=5523)			Placebo (N=5493)					
Characteristic	**n**	**Patients with events (%)**	**KM %**	**n**	**Patients with events (%)**	**KM %**	**Hazard ratio**	**95% CI**	**p-value**
Patients with ipsilateral atherosclerotic stenosis ≥30%	1136	92 (8.1)	7.9	1215	132 (10.9)	10.9	0.73	(0.56, 0.96)	0.023
In extracranial artery ≥30%	834	63 (7.6)	7.6	873	78 (8.9)	8.9	0.84	(0.60, 1.17)	0.306
In intracranial artery ≥30%	516	53 (10.3)	9.9	558	85 (15.2)	15.2	0.66	(0.47, 0.93)	0.016

THALES Trial: Amarenco P, et al. Stroke 2020

Low dose rivaroxaban and aspirin

COMPASS Trial	Low dose rivaroxaban + ASA	ASA	P-value
Cardiovascular death, stroke, MI	4.1%	5.4%	<0.001
Stroke (ischemic and hemorrhagic)	0.9%	1.6%	<0.001
Major hemorrhage	3.2%	1.9%	<0.0001
ICH	0.4%	0.3%	0.54
Subjects with previous stroke: ischemic stroke	1.1%	3.4%	0.01

12-month dual antithrombotic Rx: Rationale

- SAMMPRIS: rates of recurrent ischemic stroke in territory of stenotic artery more than doubled from 3 (7.8%) to 12 (19.7%) months[1]
- Half of US stroke neurologists surveyed already use clopidogrel + aspirin for longer than 3 months[2]

1. SAMMPRIS medical arm subjects who qualified by symptomatic infarct (Lynn, personal communication)
2. Turan et al, Cerebrov Dis 2014

12-month dual antithrombotic Rx: Rationale

	No clopidogrel beyond 3 months N=158 medical subjects	Clopidogrel + ASA > 3 months N=50 medical subjects
Primary Endpoint >3 months	10.8%	6.0%
Major Hemorrhage > 3 months	2.5%	4.0%

In SAMMPRIS, 50 medical arm subjects took clopidogrel + ASA longer than 3 months for cardiac reasons

CAPTIVA timeline

- Planned for 5-year trial
- 6 months for start-up, 38 months for enrollment, 12 months to follow the last patient to close-out, and 4 months for data analysis
- Project 4.6 subjects per site per year (based on SAMMPRIS)
- 115 sites needed to recruit 1683
- First enrollments just starting – 10 randomized by September 22.

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RHAPSODY-2

NIH StrokeNet National Meeting

September 16, 2022

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Funded by a grant from the National Institutes of Health

UNIVERSITY OF Cincinnati

Coming to you in 2023-24: Rhapsody 2

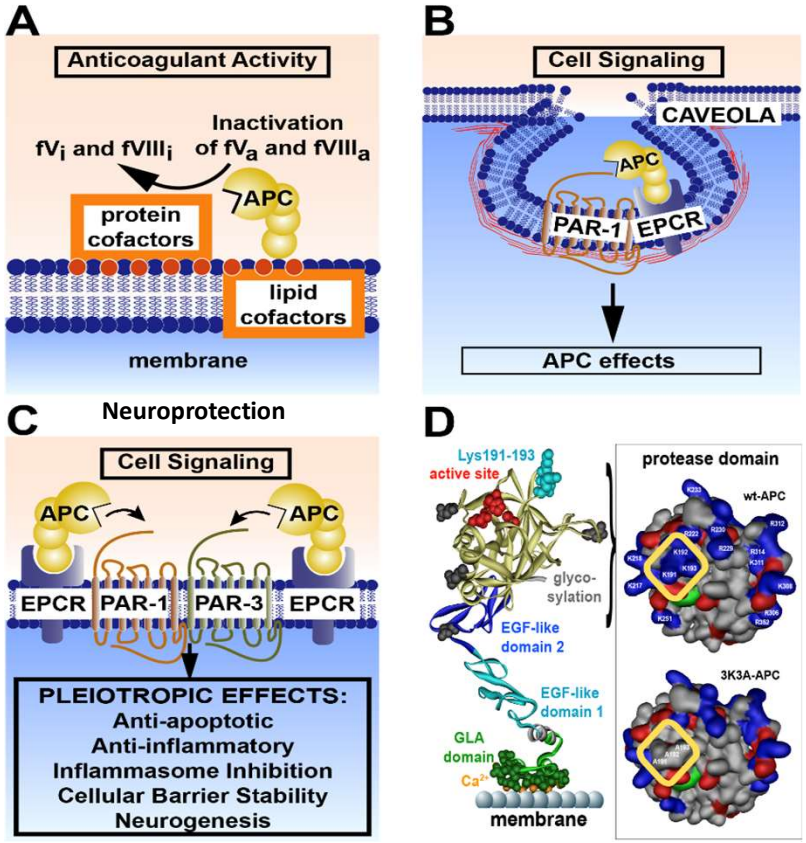
- Neuroprotective global trial in setting of patients undergoing reperfusion within 24 hours of onset.
- Favorable peer review and Council review in 2021
- cIRB approval of ICF on September 29, 2021
- FDA approved protocol pending a few outstanding items:
  - Pediatric study plan
- Company gearing up to manufacture drug and placebo
- OUS sites submitting regulatory documents and grant applications.

ACTIVATED PROTEIN C(APC): Pathways and the Structure of Signaling-Selective 3K3A-APC

APC, a serine protease and active form of **protein C** produced by the liver

- *Anticoagulant activity*
- *Cell signaling activities*

3K3A-APC, a signaling selective *APC mutant* with 3 Lys residues replaced by Ala residues resulting in **<** ***10%*** of the APC anticoagulant activity, and fully preserved cell signaling activities.



Griffin, Mosnier, Zlokovic, Blood 2018

The polypeptide structure
Gla domain
EGF-like domains

Active site:
- Protease domain
- Multiple domain binding exosites:

✓ *loop 37* KKK191-193 for recognition of Va and VIIIa

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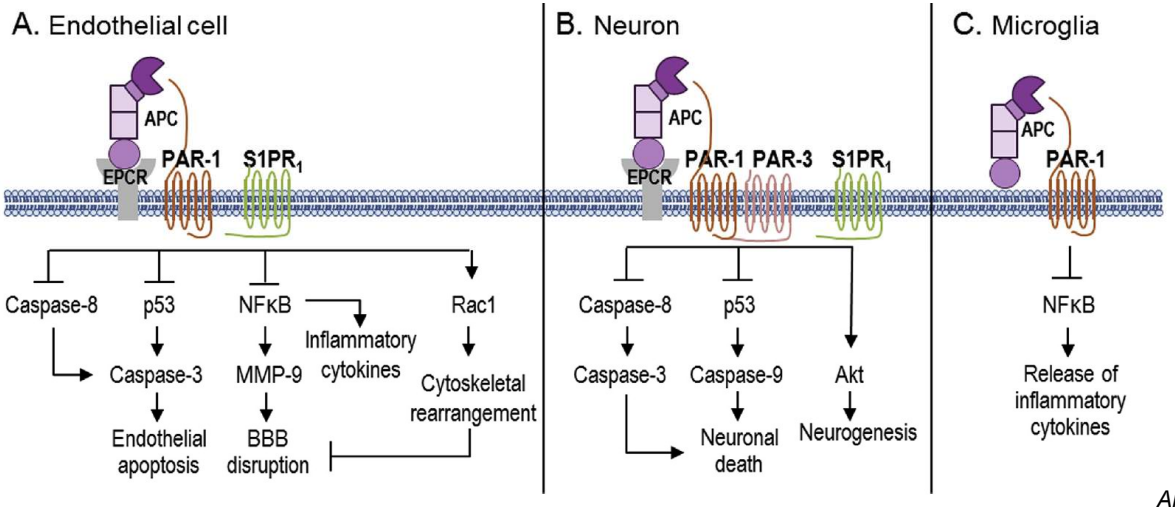
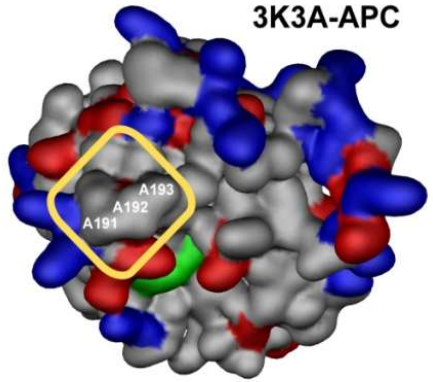
Zilkha Neurogenetic Institute

3K3A-APC: Multiple-action multiple-target approach

- **Endothelium:** Vasculoprotective, Stabilizes BBB integrity
- **Neurons:** Direct Neuronal Protective + promotes neurogenesis
- **Microglia:** Anti-inflammatory
- **Anticoagulant activity:** lowered by >90%





Griffin. Zlokovic, Mosnier, Blood 2018
Amar, …Griffin, Zlokovic, Neuropharmacology, 2018

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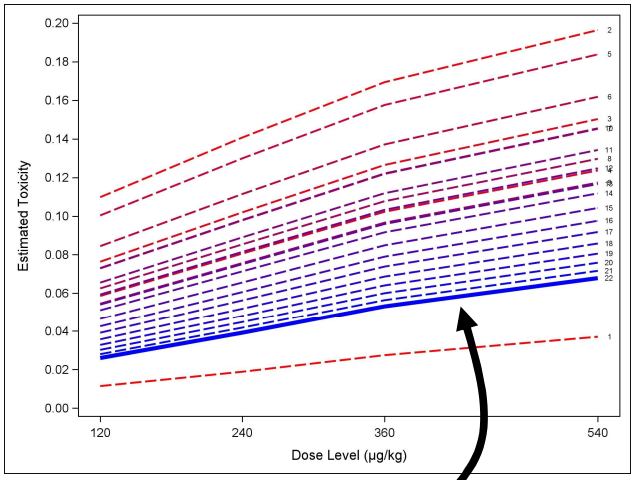
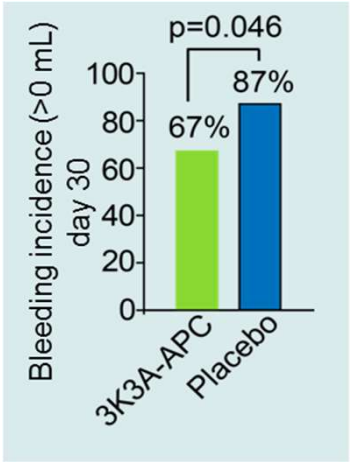
Zilkha Neurogenetic Institute

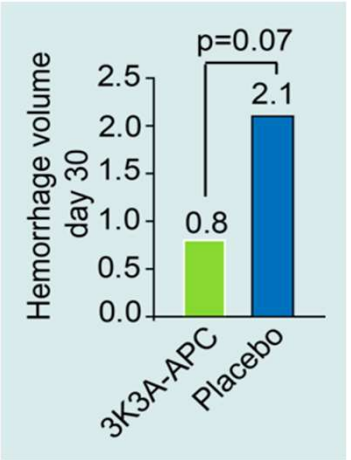
PHASE 2: NN104 (RHAPSODY):

3K3A-APC IS SAFE AND REDUCES HEMORRHAGE (MRI) AFTER TPA/THROMBECTOMY



540 µg/kg** is the maximum tolerated dose, with an estimated DLT rate around **7%





Lyden et al…. Zlokovic, Annals Neurology, 2019

Phase 3 study: RHAPSODY-2 design

Primary Aim

To evaluate the safety and efficacy of 3K3A-APC for acute ischemic stroke in the setting of reperfusion therapy.

Primary Outcome

- Ordinal shift analysis of the 3-month mRS (Rankin)

Key Secondary Outcome

- Proportion of patients alive and without intracerebral hemorrhage at 30 days after ischemic stroke.

Major inclusion criteria

- Age 18 to 90 years, inclusive
- Acute ischemic stroke defined as focal, neurological deficit(s), secondary to a presumed vascular occlusive event
- Eligible to receive standard of care IV thrombolysis within 4.5 hours of last known well time OR standard of care mechanical thrombectomy within 6 hours of last known well time OR standard of care mechanical thrombectomy 6 to 24 hours after last known well time due to favorable salvageable tissue profile on multimodal CT or magnetic resonance imaging (MRI) imaging. Other patients may be considered, subject to the following:
- Patients who awaken with stroke symptoms or have unclear time of onset >4.5 hours from last known well time may be treated if MRI identifies diffusion-positive, FLAIR-negative lesions, and the patient can begin IV thrombolytic administration within 4.5 hours of stroke symptom recognition.
- **Note: Subjects must receive IV thrombolysis OR begin mechanical thrombectomy before they can receive 3K3A-APC.**
- NIHSS score ≥5 at time of randomization

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