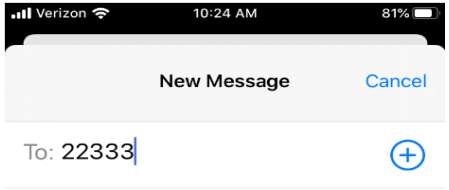
NIH StrokeNet

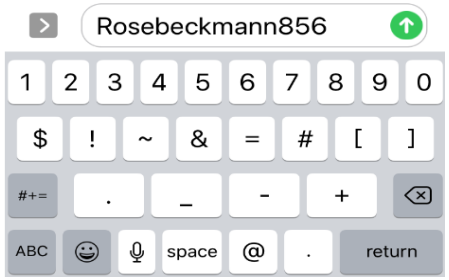
PREVENTION | TREATMENT | RECOVERY

StrokeNet: Update and 5-Year priorities

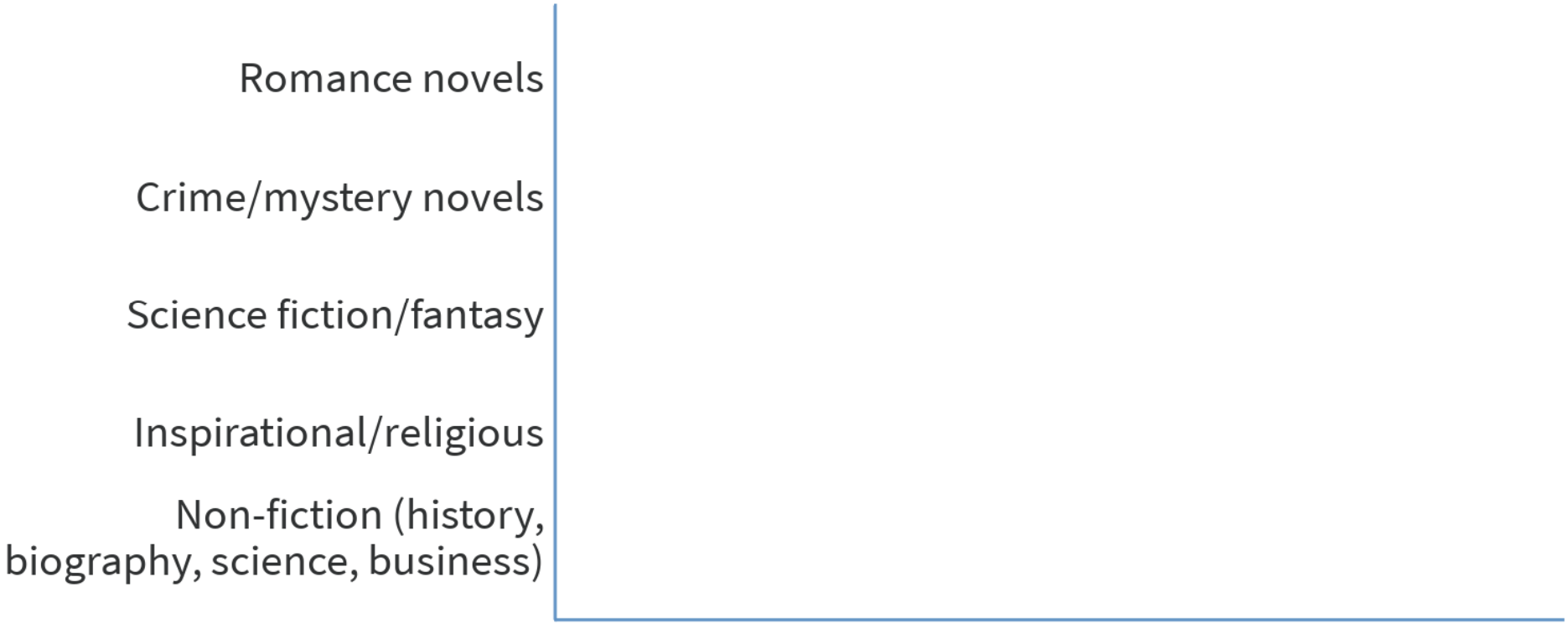
Polling Instructions

- Please silence your phone.
- To join the polling session, text the word “rosebeckmann856” to the number **22333**. You will not have to re-join before each poll. For those who are unable to text to a “short-code”, you can text to (747) 444-3548.





What is your favorite type of book to read for enjoyment?



Vision of NIH StrokeNet

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

EOB-10-2019 Meeting: StrokeNet Challenges Noted in 3-2017

- Network underutilized because not enough funded trials – 2 of 12 reviewed trial applications in fundable range at that point.
- Frustration at clinical sites since not enough currently enrolling in trials
- Issues with review process
    - Reviewers often had limited information given 12 pages of research plan and inability to include other material such as feasibility assessment, statistical protocol.
    - Limited interaction between reviewers and PIs to address questions. Phone call to address reviewers' questions – only twice in 12 trial submissions.
    - Reviewers almost exclusively from other countries – almost everyone in U.S. has related COI in being involved with StrokeNet.

Response to challenges on 3/2017

- StrokeNet leadership worked closely with NINDS to improve review process and interactions
  - **NINDS leadership revised FOA so applications could and must include more components like feasibility assessments, statistical protocol, etc.**
  - **NINDS worked with review group to help frame/bucket overall reviews – red (no go), yellow (good but needs work), green (a few tweaks may be needed but ready to go). More interaction with review group and PIs as needed.**
- StrokeNet leadership continued to expedite high-quality trial proposals – particularly in stroke recovery/rehabilitation.
  - **Increased scientific scrutiny and input by leadership team at NCC and NDMC prior to submission. All key materials had to be sent to NCC and NDMC PIs > 1 month prior to submission date or couldn't be submitted.**
  - **Matched very experienced acute stroke multi-center PIs with stroke recovery PI.**

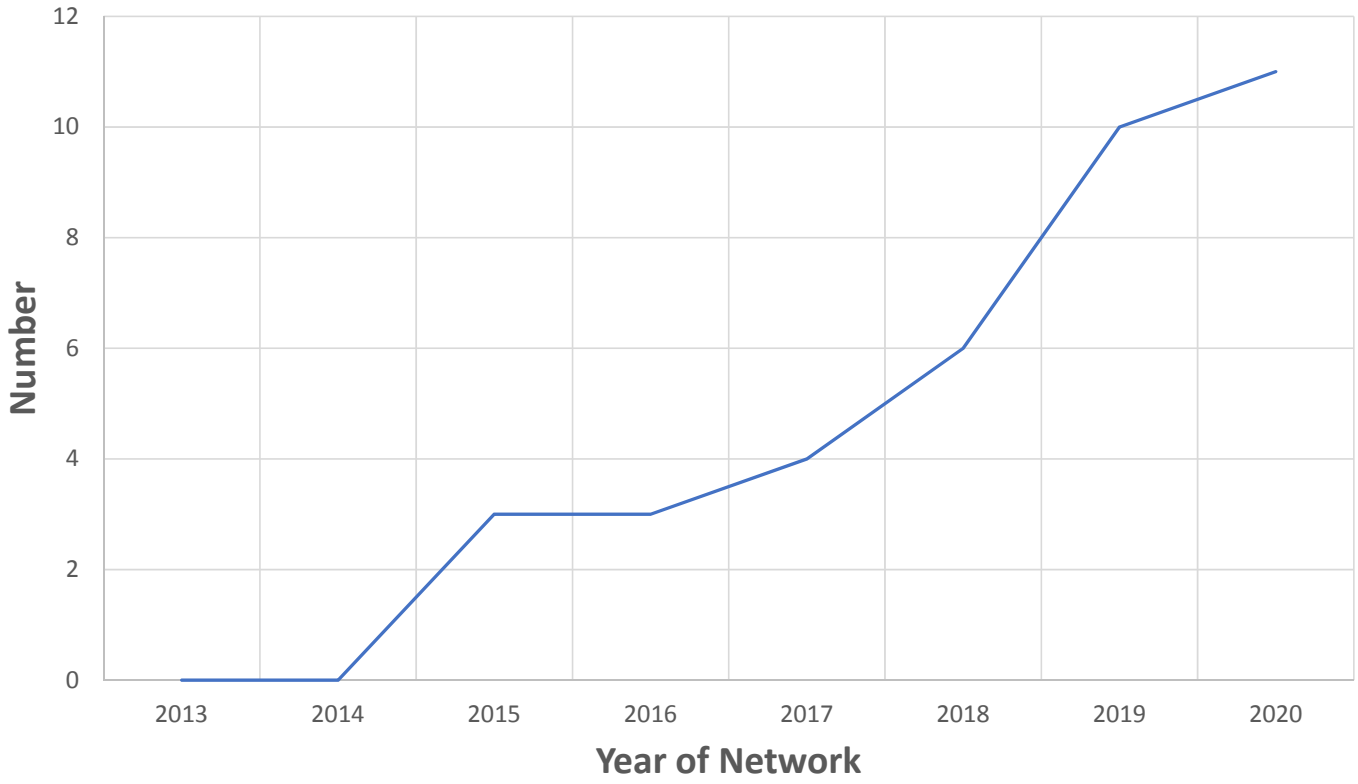
Large Increase in Approved StrokeNet Trials Since 2018

Current Trials	Domain	PIs	Sample Size	No. of sites	Notice of Award	Actively enrolling
ARCADIA	Prevention	**Mitch Elkind**, Hooman Kamel, Dave Tirschwell, Will Longstreth	1100	120	**4/25/2017**	**Yes. N = 341 (3/12/2018)**
SLEEP SMART	Prevention/ Recovery	**Devin Brown,** Ron Chervin	3062	110	**11/14/2018**	**Yes. N = 85 (5/13/2019)**
TRANSPORT2	Recovery	**Wayne Feng,** Gottfried Schlaug	129	12	**8/13/2018**	**Yes. N = 2 (9/9/2019)**
I-ACQUIRE	Recovery	**Sharon Ramey,** Warren Lo	240	12	**2/1/2019**	**Yes. N = 4 (10/9/2019)**
MOST	Acute	**Ope Adeoye,** Andrew Barretto, James Grotta, Joe Broderick	Adaptive design, Max. 1200	110	**5/28/2018**	**Yes. N =1 (10/9/2019)**
ARCADIA-CSI (Ancillary)	Prevention	**Maarten Lansberg**, Ronald Lazar, George Howard, Kevin Sheth, David Tirschwell	700	80	**6/27/2019**	**Yes.**
SATURN	Prevention	**Magdy Selim**	1456	140	**8/28/2019**	Early 2020
ASPIRE	Prevention	**Kevin Sheth,** Hooman Kamel	700	125	**7/1/2019**	Early 2020
FASTEST	Acute	**Joe Broderick**, James Grotta, Andrew Naidech, Jordan Elm	860	100 sites, 15+ MSUs	First quarter of 2020	Mid-late 2020

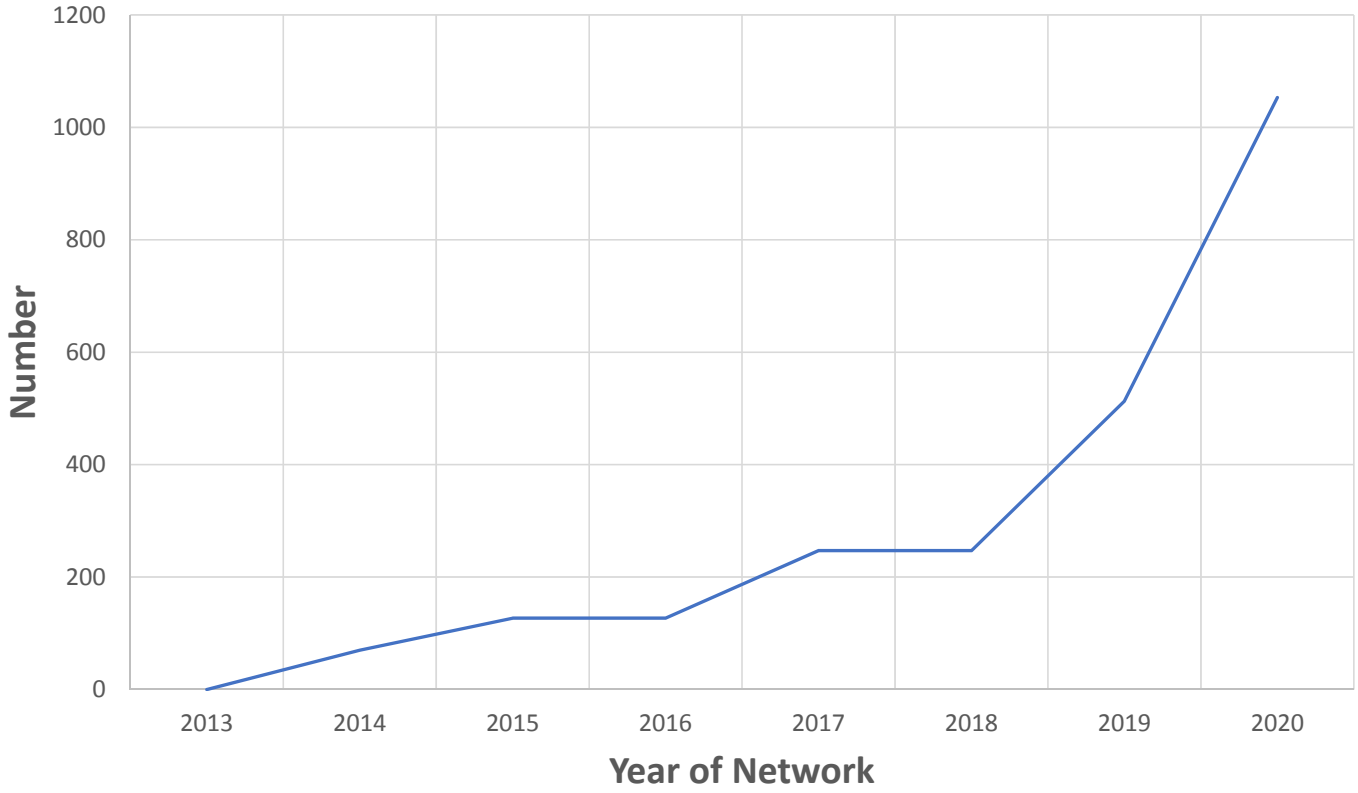
Other StrokeNet CIRB Managed NINDS Studies

Trial	Domain	PI	No. of sites	Active enrolling
CREST-2	Prevention	**T. Brott, MD**	199 (71 CIRB) Global trial	Yes. N = 1544 (Sept 20)
CREST-H	Prevention (Ancillary)	**R. Marshall, MD**	51 (40 CIRB)	Yes. 113 (Sept 20)

Number of StrokeNet Trials



Number of Clinical Trial Protocol Sites



Current Network Size and Distribution of Sites

- 24 funded Regional coordinating Centers and 3 Legacy Centers.
- 486 StrokeNet sites part of RCCs. 10 out of network.
  - 316 with reliance agreements.
  - 249 with a clinical trial agreement for at least one trial (as of 9/18/2019).

Plans for 2nd Five Years of StrokeNet

- **Recruitment** in our funded trials is our highest priority
  - Distribute best practices and innovations to enhance recruitment.
  - Monitor closely the impact of external data/trials on equipoise.
  - Maximize participation in concurrent trials whenever feasible.
  - Aggressively turnover sites with inadequate recruitment rates.
  - When the recruitment rate per site per month lags, need to aggressively add new sites.
  - How to best predict recruitment from feasibility assessments and surveys – what works best.

Plans for 2nd Five Years of StrokeNet

- **Improve efficiency of contracting and start-up**
  - CTAs for entire study duration, eliminated MTA except for RCC.
- **Further optimize cIRB efforts**
  - Utilize industry CIRB best practices to improve efficiency (example only need to submit COI to CIRB for site PI).
  - Hired additional regulatory persons to assist project managers with CIRB submissions.
  - Expand NIH StrokeNet CIRB resources
    - ADVARRA (industry CIRB) will be CIRB for new trials starting with FASTEST.
    - Current UC CIRB is already responsible for 10 large trials.
  - Implement Research Administration Portal (RAP)
    - Will improve efficiency of protocol administration by linking research sites to trial protocol

Plans for 2nd Five Years of StrokeNet

- **Further collaborate with other stroke networks internationally**
  - Continue growth of GAINS alliance to address multinational concerns, including training, and developing/funding new multinational trials
    - Manuscript under review at Lancet about funding challenges/opportunities for global trials
  - NINDS/ICMR and StrokeNet/INSTRuCT meeting in New Delhi (Sept 2019)
    - First trial network in developing country, SN Advisory Committee, sharing best practices
- **New faces**: Jordan Elm replacing Yuko Palesch as PI of NDMC. Karen Johnston assuming Chair of Acute Stroke Working Group.

Questions and Discussion

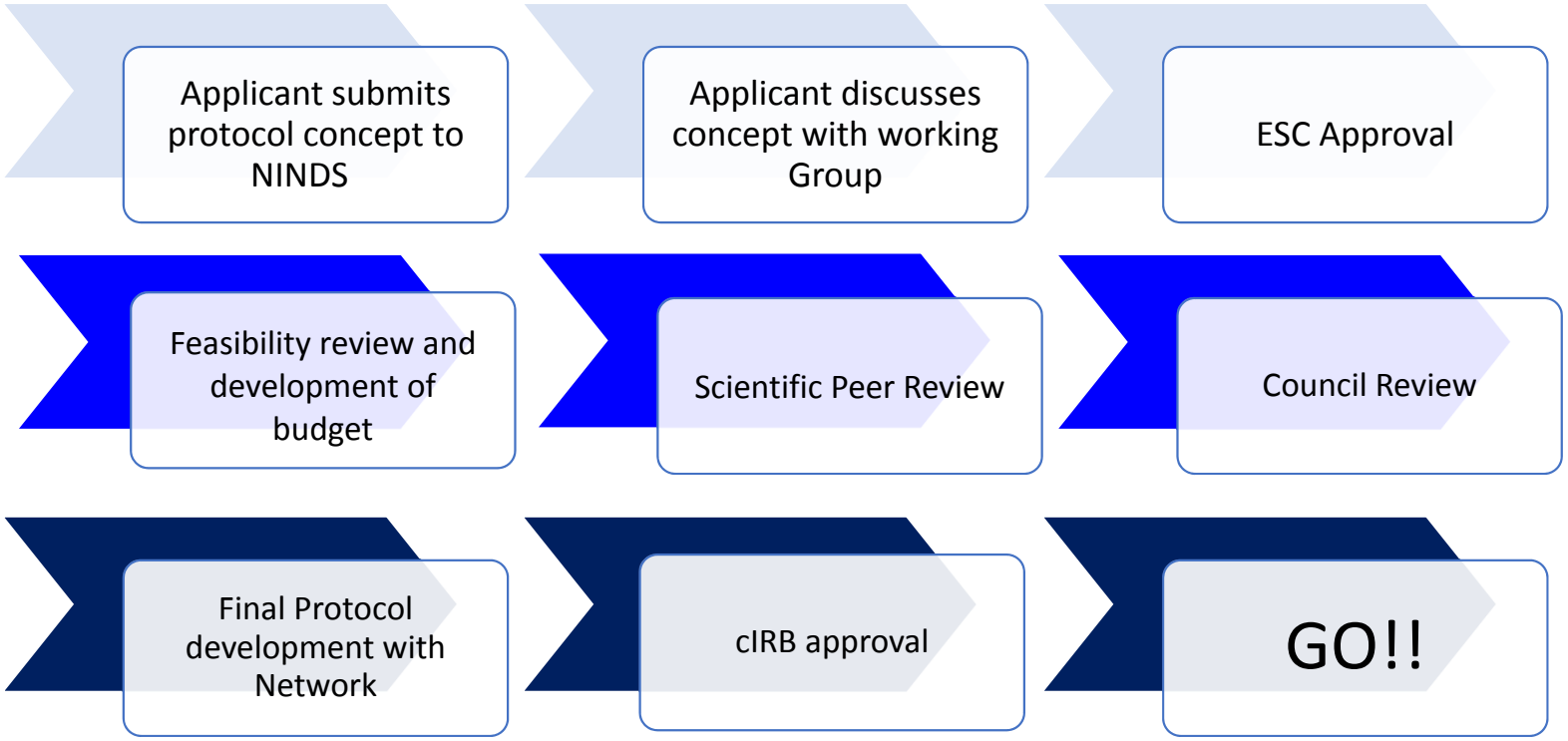
Our Current Feasibility Approach

What Do We Do Right Now and How Should We Proceed?

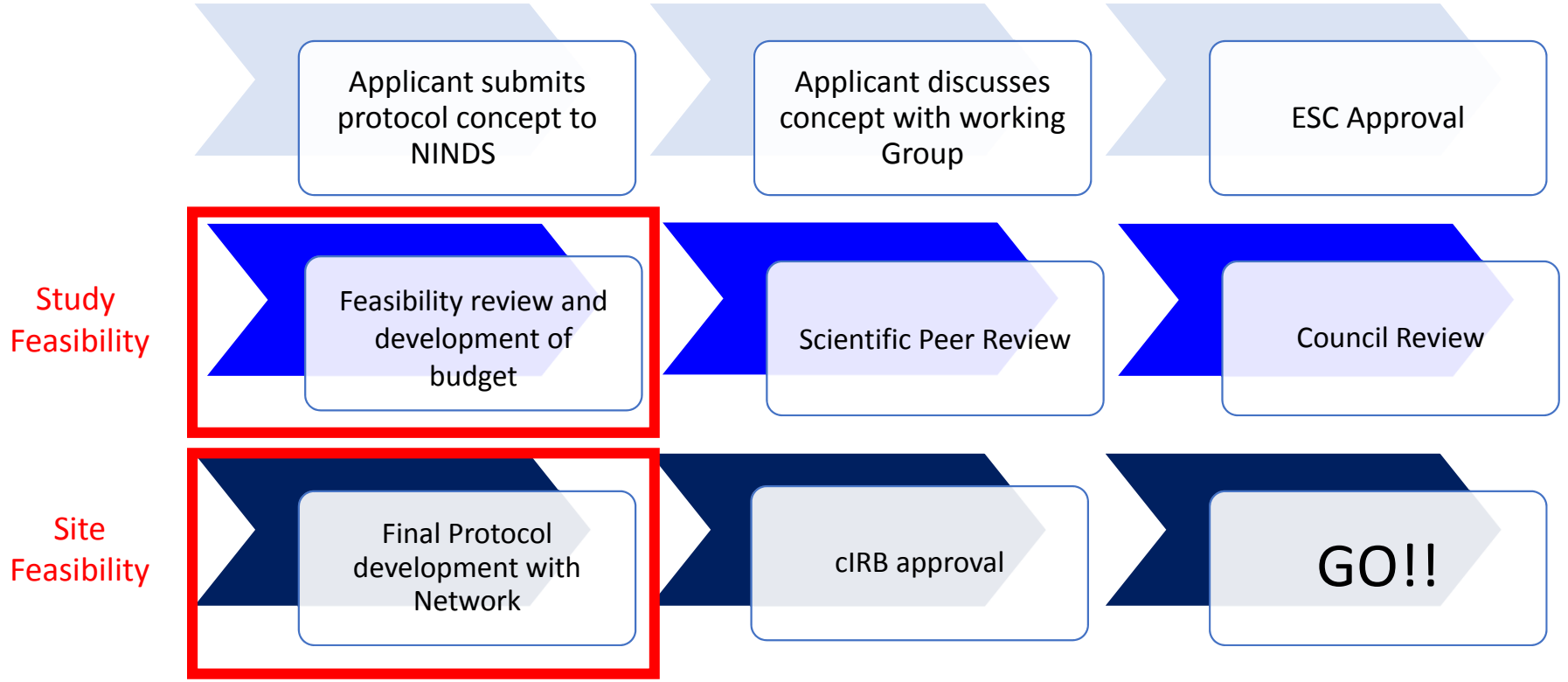
NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

Big Picture


Applicant submits protocol concept to NINDS
Applicant discusses concept with working Group
ESC Approval
Feasibility review and development of budget
Scientific Peer Review
Council Review
Final Protocol development with Network
cIRB approval
GO!!

Big Picture


Applicant submits protocol concept to NINDS
Applicant discusses concept with working Group
ESC Approval
Study Feasibility
Feasibility review and development of budget
Scientific Peer Review
Council Review
Site Feasibility
Final Protocol development with Network
cIRB approval
GO!!

Study Feasibility Assessment (Pre Grant Submission)

- Goal
  - Determine # of sites needed to realistically achieve recruitment numbers over budgeted time period
  - Determine if certain eligibility criteria unnecessarily restrict eligibility
  - Gauge network enthusiasm for the trial (?)
- Three elements
  - StrokeNet survey (+ annual site survey)
  - GCNKSS epidemiological assessment
  - WG recs based on review of survey and epi assessment, followed by EC approval of WG recs

StrokeNet Survey

- First draft by PPIs, input by WG chair, review by WG, programming and dissemination by NDMC
- Approach
  - Ask for objective numbers from registries during specific timeframes
    - WG/Epi assessment (not individual site PIs) to add literature-based decrements in eligibility
  - Understand other issues related to capability (technology, expertise, etc.)
  - Standard enthusiasm questions
    - Does the study meet an unmet need?
    - On a scale from 1-5, with 5 being extremely enthusiastic, please rate your enthusiasm to participate in this study.
    - If this study was funded, would your site be willing to participate?

Epi Assessment

- Population based data on incident strokes during discrete years in five county Greater Cincinnati/ Northern KY region (1993-94, 1999, 2005, 2010, 2015….)
  - Not referral biased
  - Most useful to acute and prevention

WG Synthesis

- Open discussion with PPIs
  - Review survey data
  - Epi eligibility or literature based proportion is then applied to survey total
    - Ex: proportion of diabetics among hospitalized AIS
  - Then reduce numbers based on other subjective factors
    - Consent rates, equipoise issues, competing trials, etc
  - Calculate # sites likely needed
  - If comparable completed/ongoing trials, compare their rates to WG estimate to finalize recommendation
- Recommendations to StrokeNET Executive Committee

Potential Recommendations

Feasible As-Is

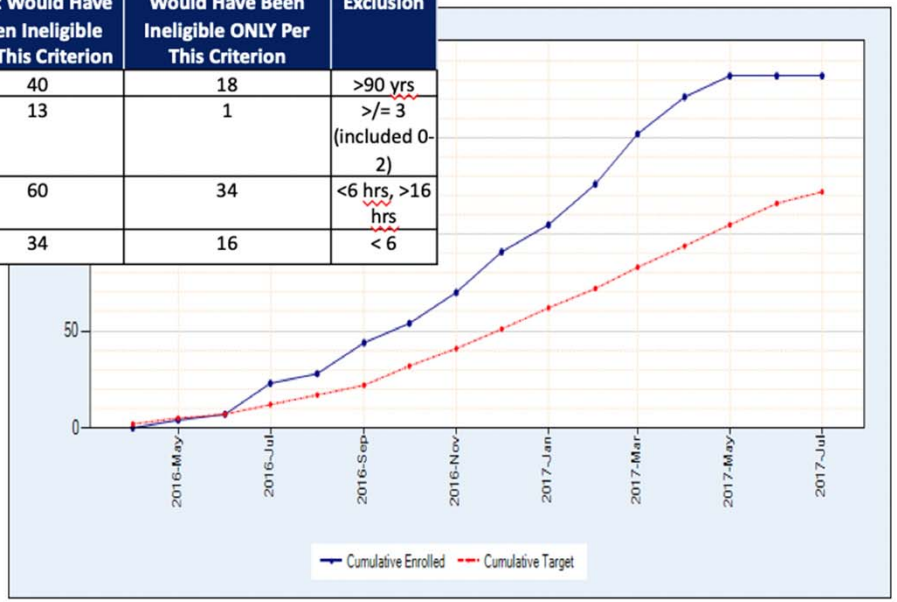
Versus

Recommendations

- **Expand eligibility criteria**
- **Add more sites +/- budget**

DEFUSE III –Feasibility Recommendations Increased Enrollment by More than Half

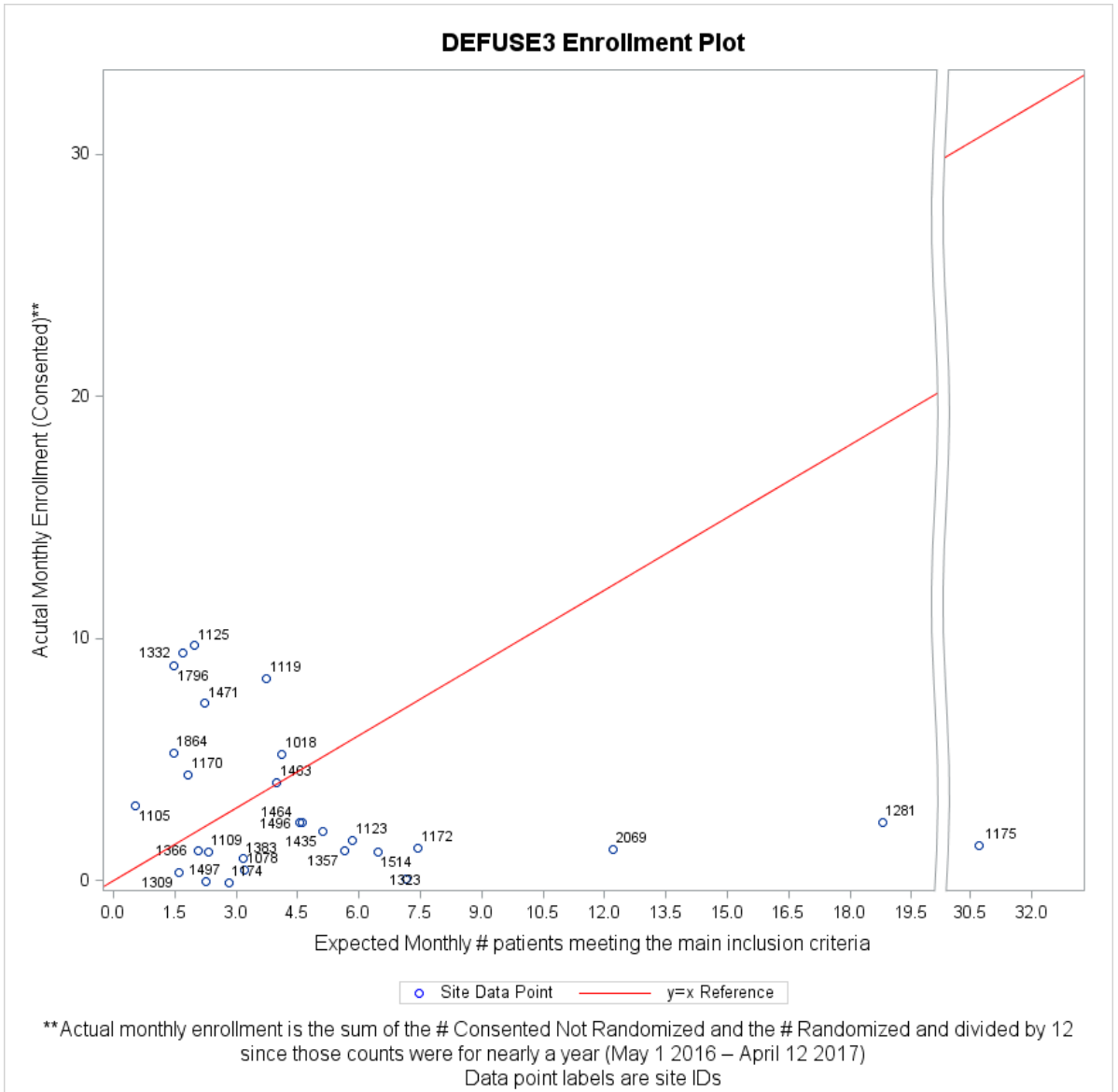
Exclusion Criterion	Initial Exclusion	DEFUSE Patients That Would Have Been Ineligible Per This Criterion	DEFUSE Patients That Would Have Been Ineligible ONLY Per This Criterion	Final Exclusion
Age	>80 yrs	40	18	>90 yrs
Baseline mRS	>/= 2 (included 0-1)	13	1	>/= 3 (included 0-2)
Time since LSN	<6 hrs, >12 hrs	60	34	<6 hrs, >16 hrs
NIHSS	</=8 or > 25	34	16	< 6



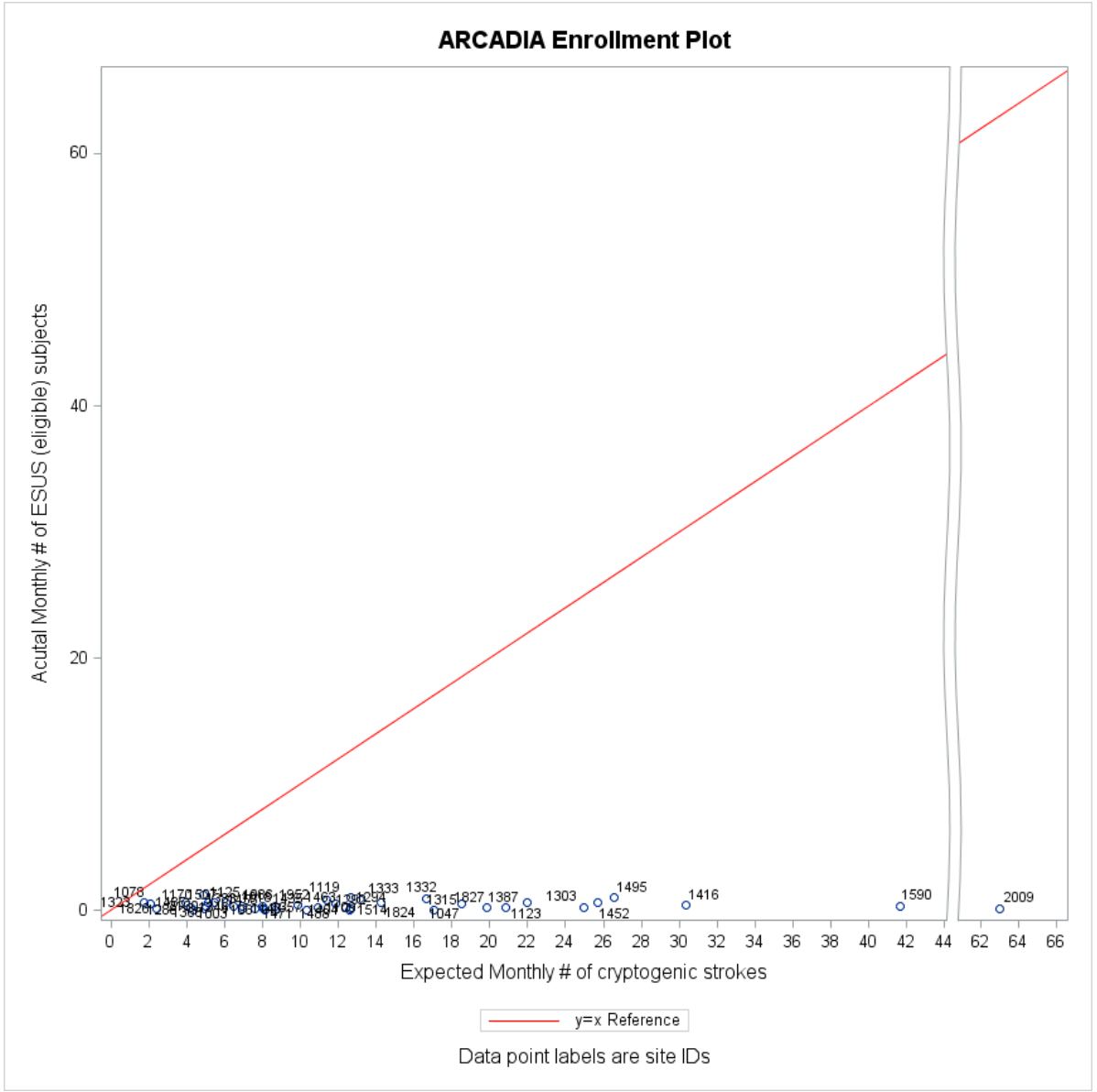
Site Feasibility Survey (After Council Approval)

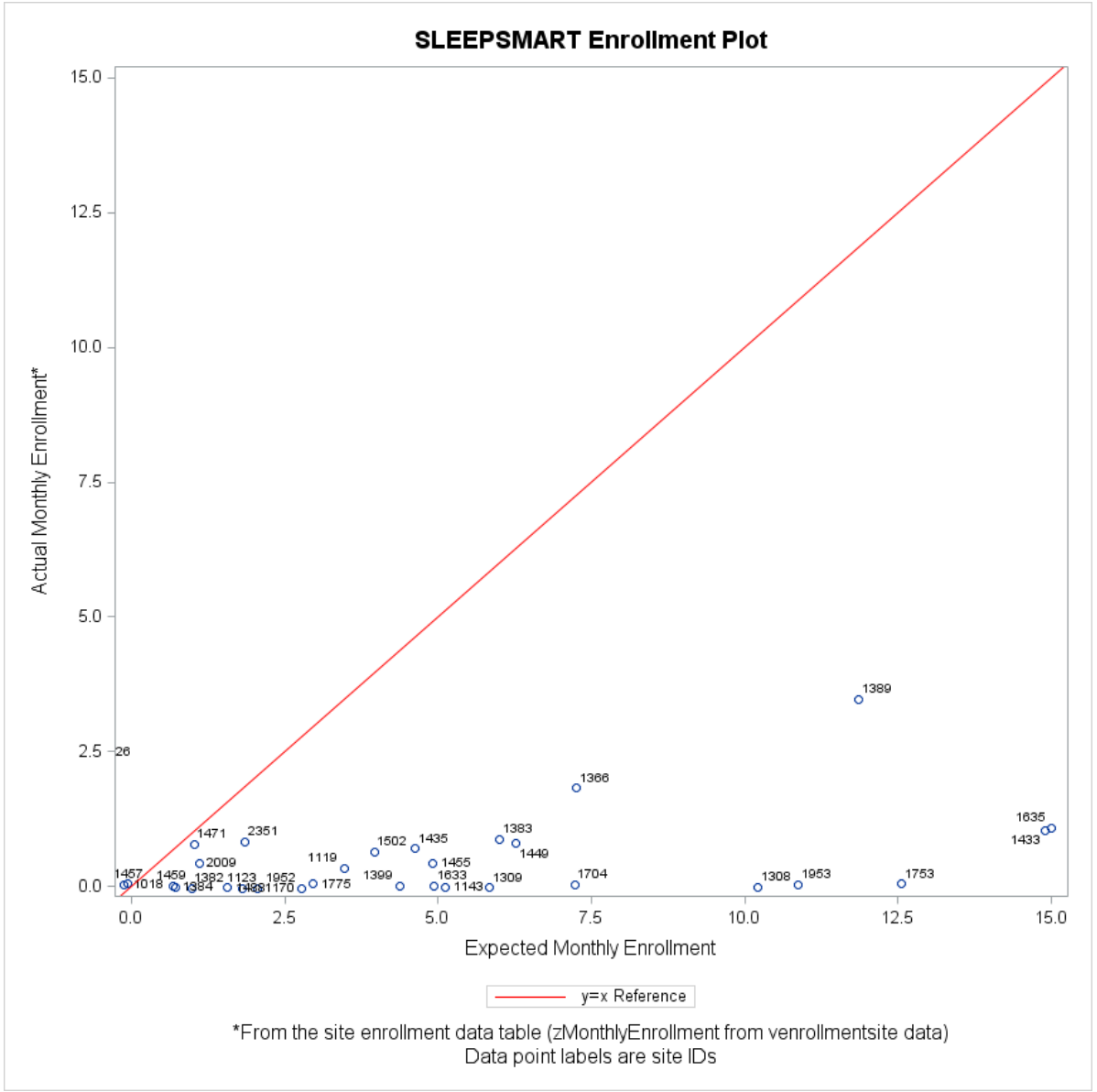
- Once trial is approved by Council, another survey goes out to sites to estimate number that they think that they can enroll and allow PPIs to select specific sites

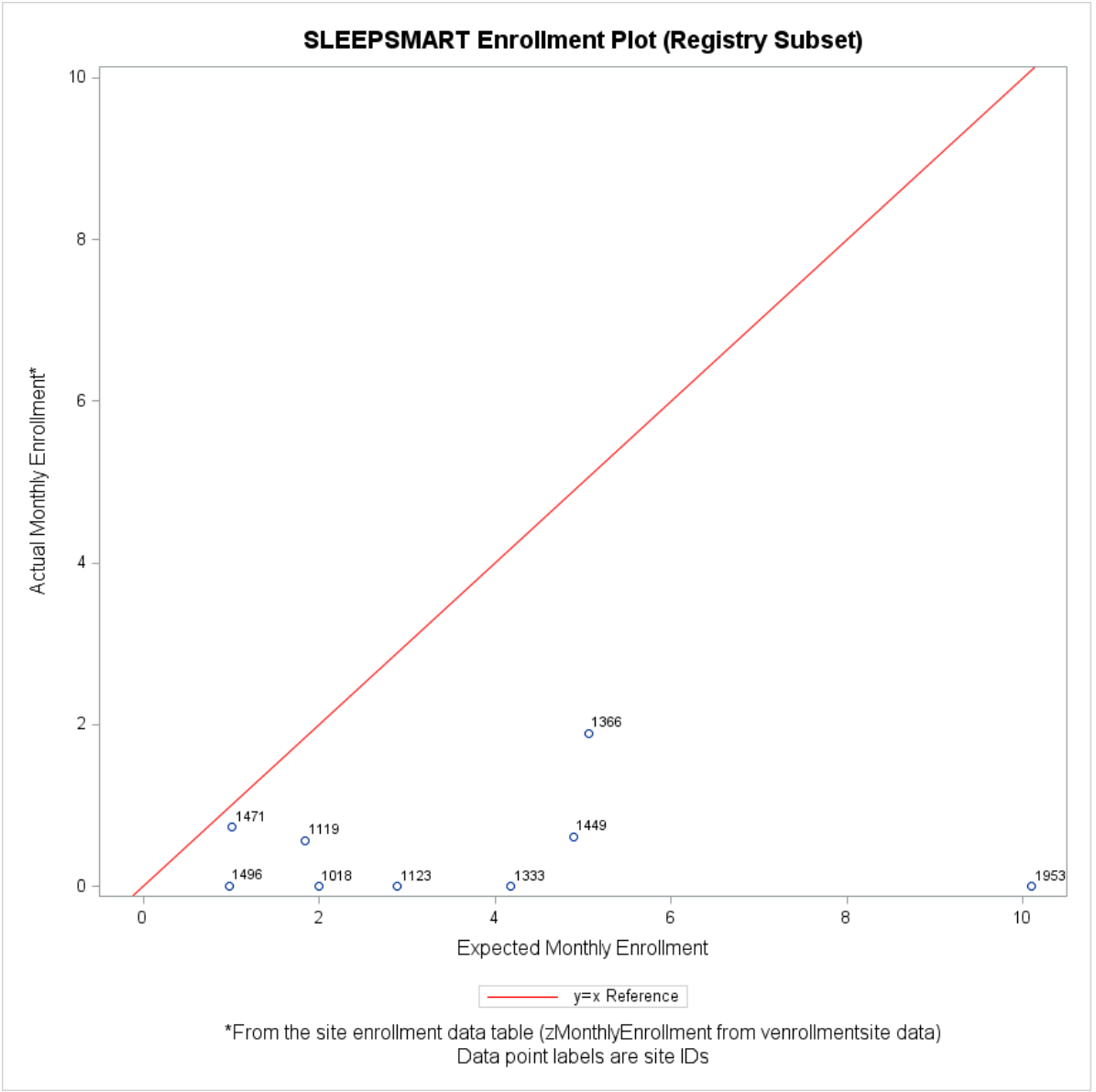
- Jordan Elm will show you actual data of enrollment per site compared to their own estimates



**Actual monthly enrollment is the sum of the # Consented Not Randomized and the # Randomized and divided by 12 since those counts were for nearly a year (May 1 2016 – April 12 2017)
Data point labels are site IDs


ARCADIA Enrollment Plot
Acutal Monthly # of ESUS (eligible) subjects
Expected Monthly # of cryptogenic strokes
y=x Reference
Data point labels are site IDs
0
20
40
60
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 62 64 66
1078
1119
1333
1332
1315
1827
1387
1303
1495
1452
1416
1590
2009
1824
1047
1123


SLEEPSMART Enrollment Plot
Actual Monthly Enrollment*
Expected Monthly Enrollment
0.0
2.5
5.0
7.5
10.0
12.5
15.0
26
1389
1366
1635
1433
1471
2351
1383
1502
1435
1449
1119
2009
1455
1457
1459
1382
1123
1952
1399
1633
1309
1704
1308
1953
1753
1018
1384
1170
1775
1143
y=x Reference
*From the site enrollment data table (zMonthlyEnrollment from venrollmentsite data)
Data point labels are site IDs


SLEEPSMART Enrollment Plot (Registry Subset)
Actual Monthly Enrollment*
Expected Monthly Enrollment
0
2
4
6
8
10
1366
1471
1119
1449
1496
1018
1123
1333
1953
y=x Reference
*From the site enrollment data table (zMonthlyEnrollment from venrollmentsite data)
Data point labels are site IDs

Discussion

Who fills out the feasibility survey for your RCC site?

RCC PI(s)

RCC Coordinator

RCC PI and Coordinator fill out together

Other

Who fills out the feasibility survey for satellite sites?

Site PI(s)

Site coordinator and PI(s)

Combination of Site and RCC personnel fill out

Other

Do you use registry data or estimate to determine projected number of cases?

Registry data (e.g. AHA Get with the Guidelines)

Estimate by PI or key clinician

Both

Other

Do questions in feasibility questionnaire generally represent key elements of study protocol that affect recruitment?

Yes

Definitely yes

Neutral

No

Definitely no

In general, are your enrollment estimates on feasibility questionnaire....?

Overly optimistic

Optimistic

On target

Conservative

Would you prefer enthusiasm question for a trial feasibility questionnaire to be anonymous and separate (for example survey monkey)?

Yes

No

Should enthusiasm and equipoise questions be part of identified survey or separate and deidentified?

Part of feasibility survey

Separate and deidentified

Don't care

Should only registry data be used to give estimates of eligible patients?

Yes

No

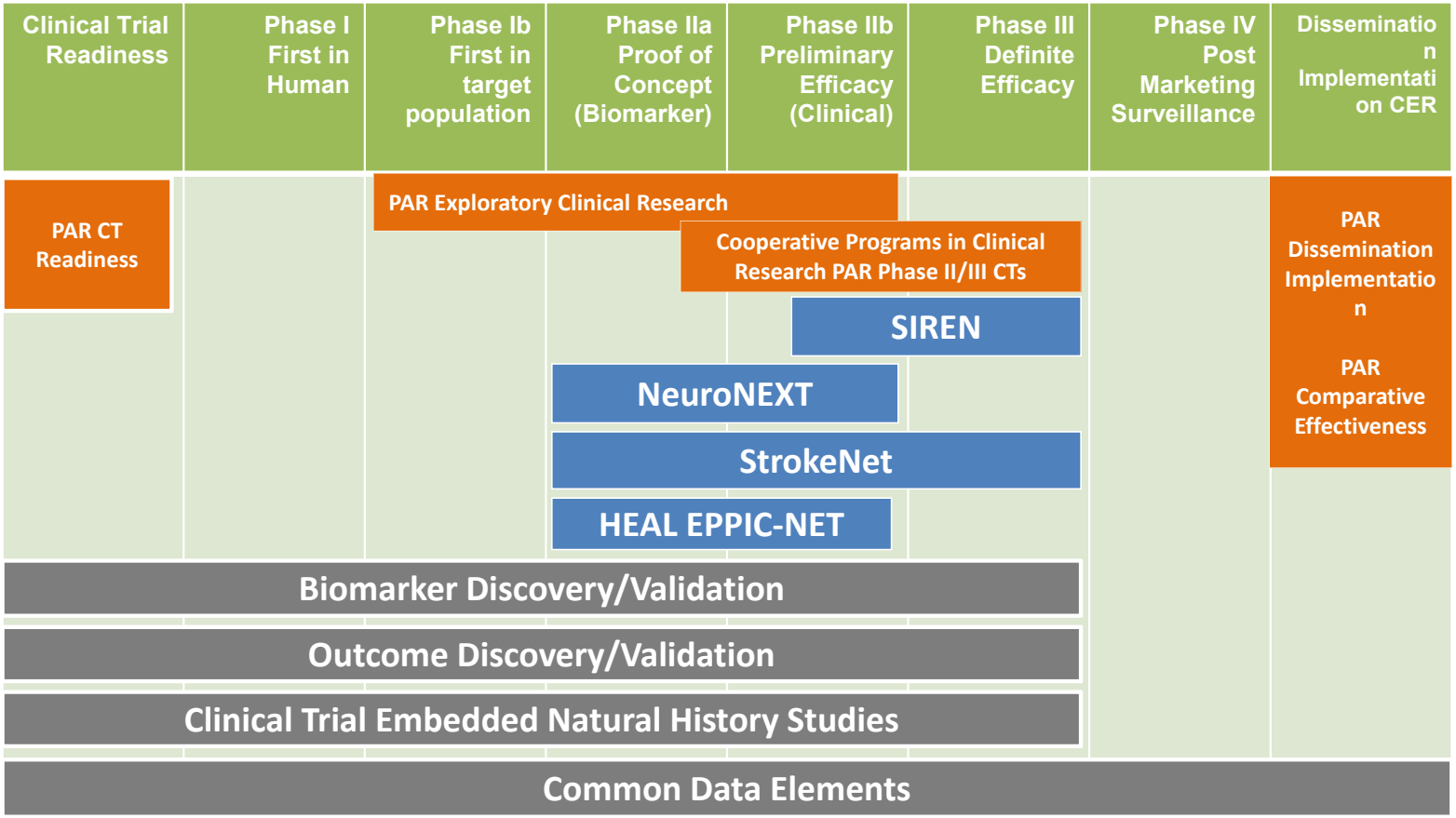
National Institute of Neurological Disorders and Stroke

StrokeNet Investigator Meeting

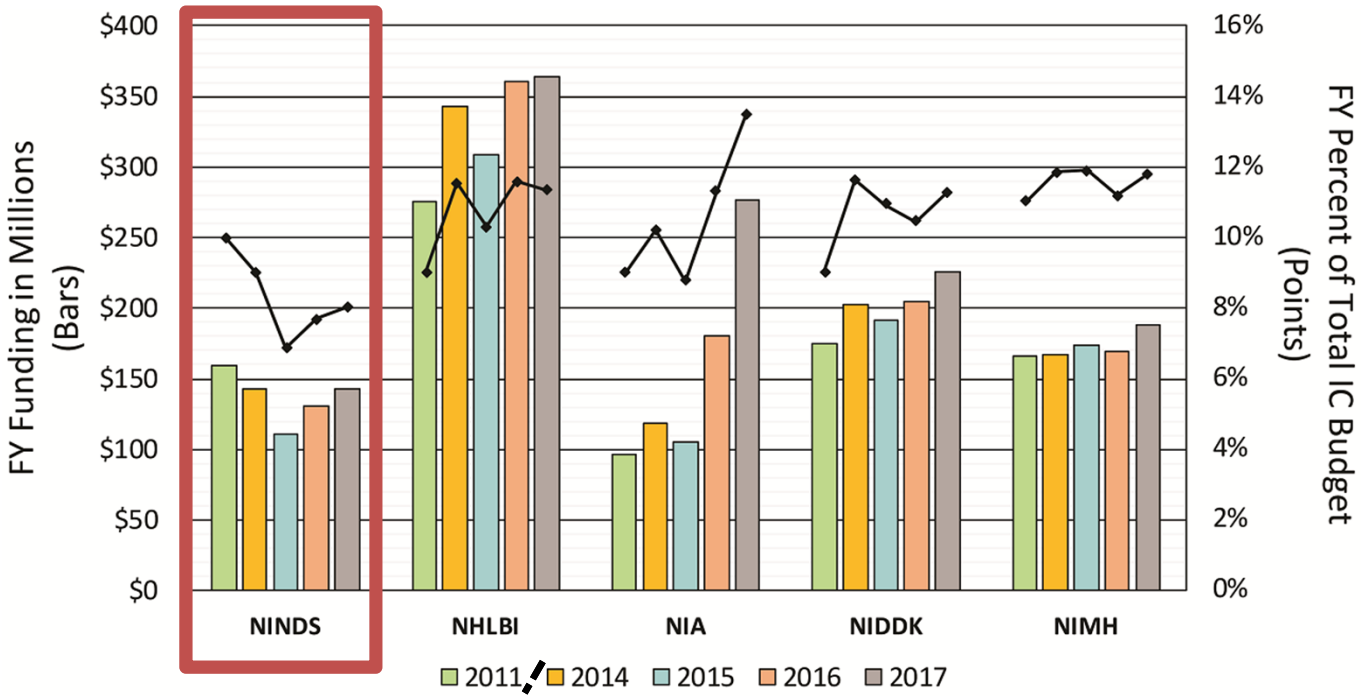
October 29th 2019

Clinton Wright, M.D., M.S.
Director, Division of Clinical Research
Associate Director, NINDS

Division of Clinical Research Programs

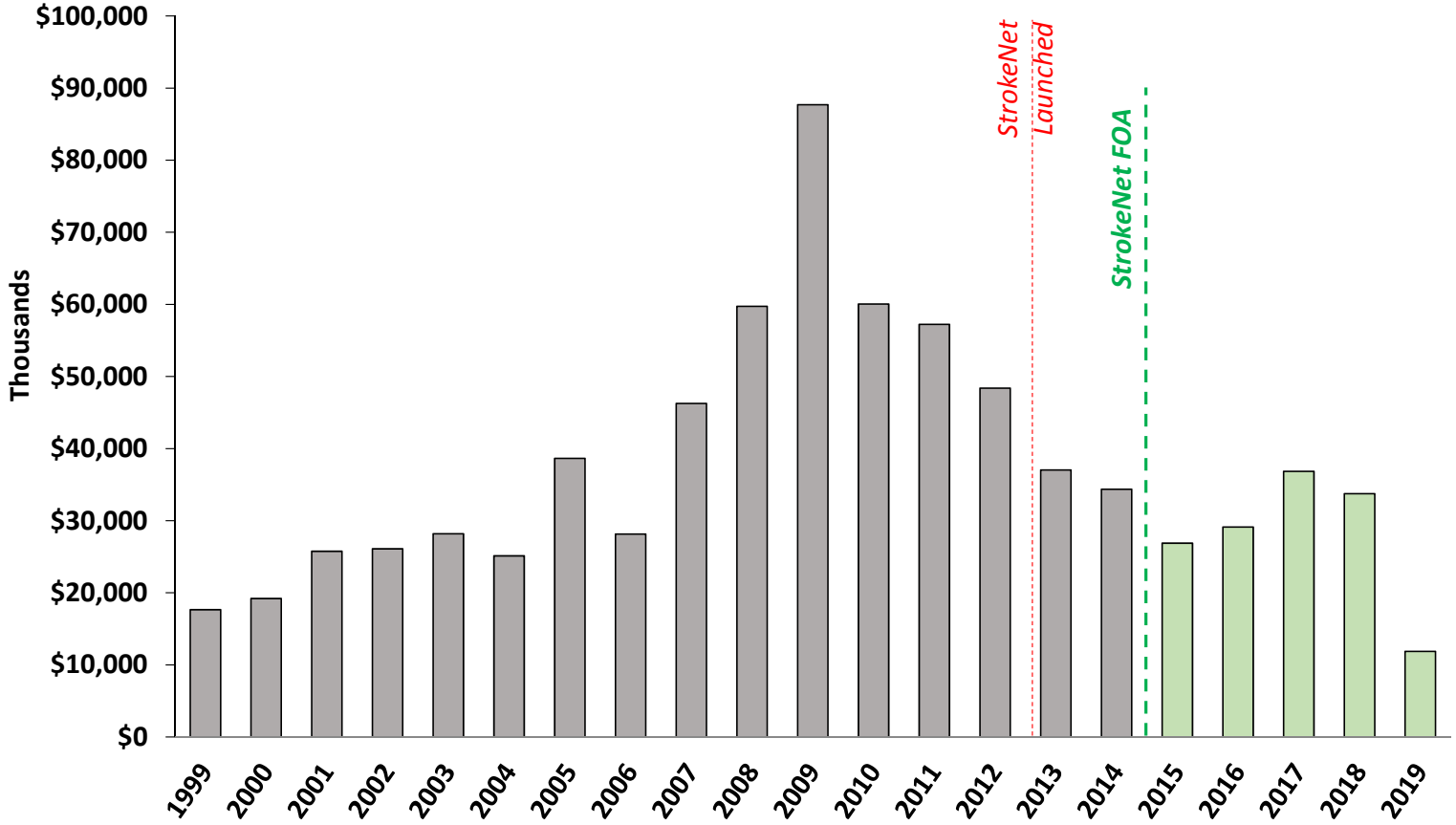


NIH Clinical Trial Funding



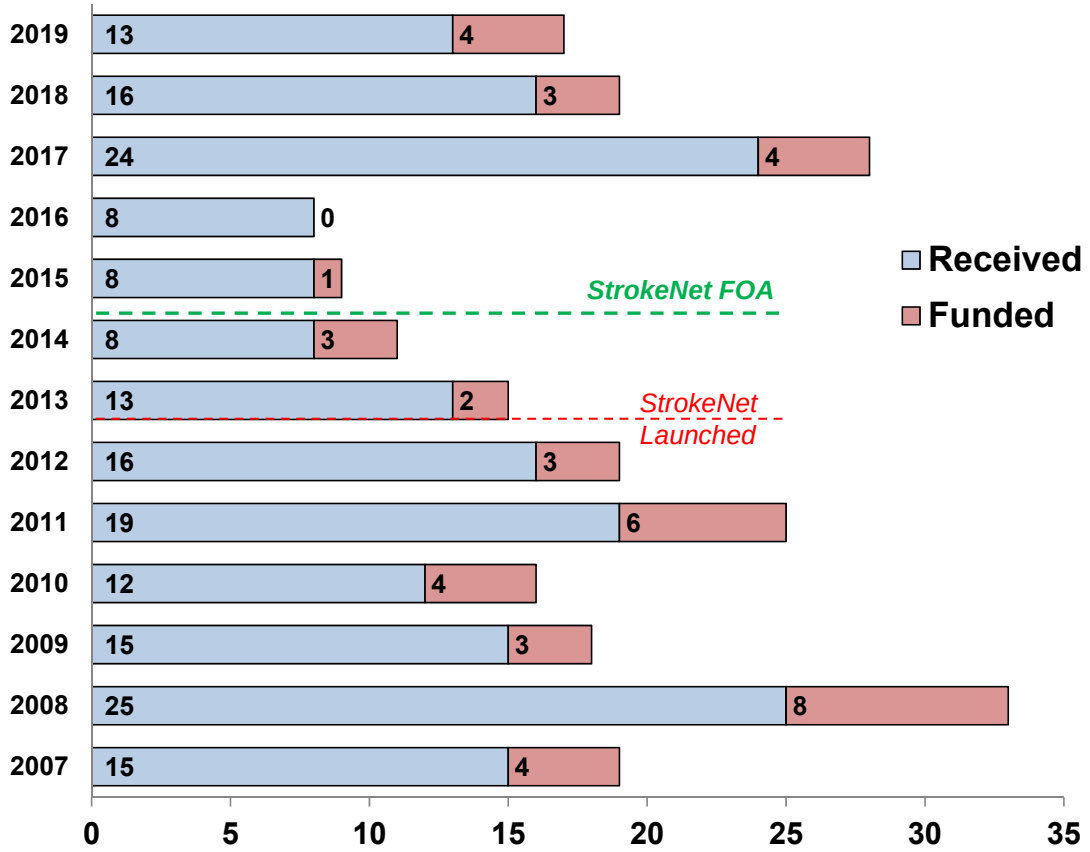
National Institute of Neurological Disorders and Stroke

Stroke Trial Funding per year



National Institute of Neurological Disorders and Stroke

Number of Stroke Trial Applications per year



** Applications includes resubmissions*

National Institute of Neurological Disorders and Stroke

Over to Scott…

NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

NINDS Update

Scott Janis

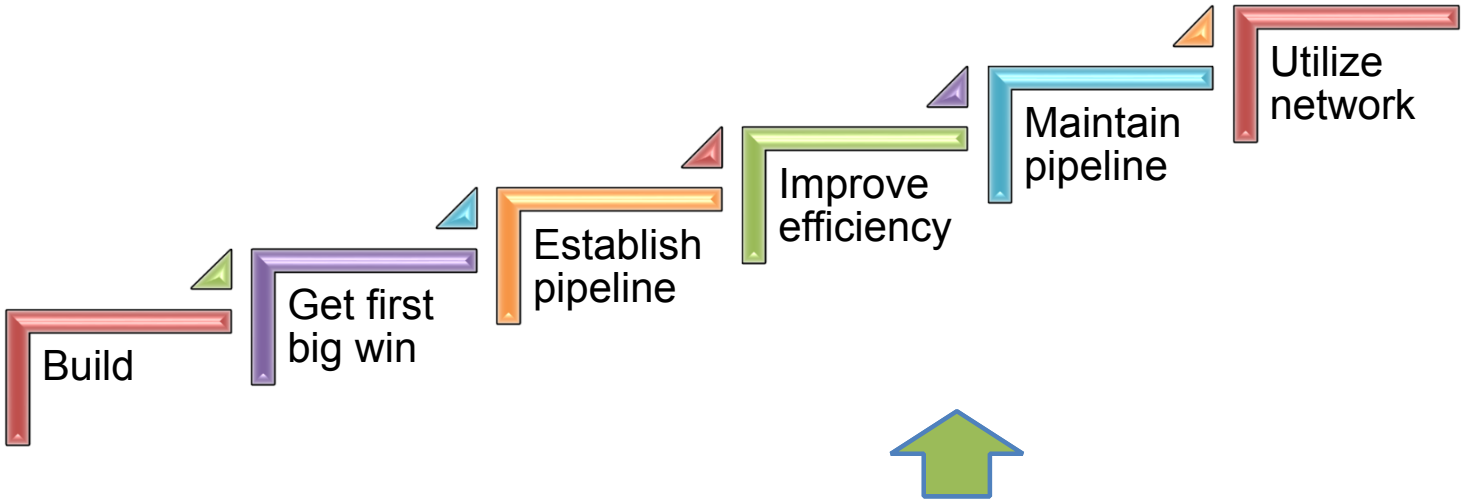
NINDS

October 29, 2019

NINDS team:

Scott Janis
Joanna Vivalda
Claudia Moy
Carlos Faraco
Peter Gilbert
Clint Wright

How are we doing?



StrokeNet Clinical Trials Activity

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY
Funded by a Grant from the National Institutes of Health

Completed:

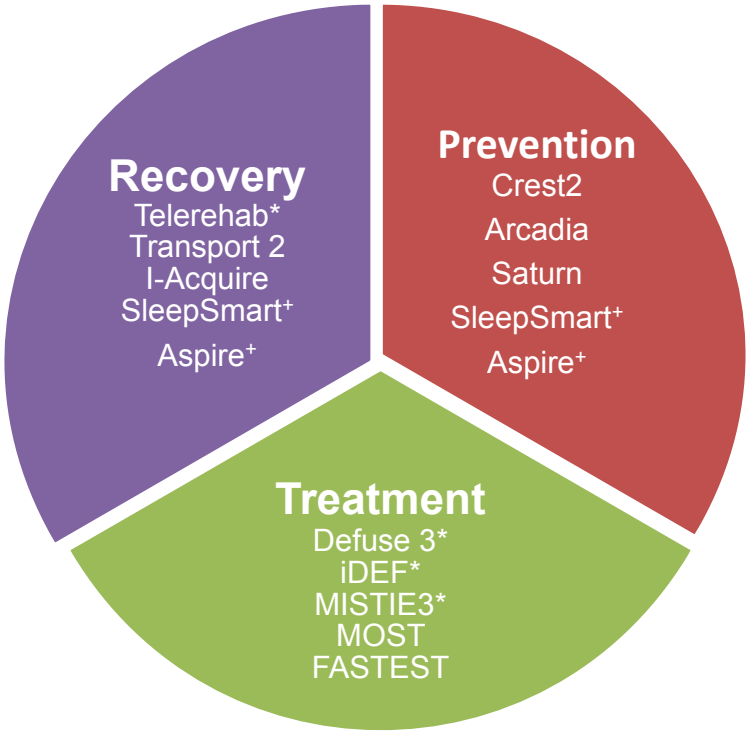
- **MISTIE-3** Minimally Invasive Surgery for ICH evacuation trial (N=500) *
- **i-DEF** Deferoxamine mesylate treatment for ICH trial (N=293) *
- **DEFUSE-3** Delayed endovascular therapy for select patients (N=182)
- **TeleRehab** Home based telerehabilitation stroke recovery trial (N=124)

Ongoing:

- **CREST-2** Carotid revascularization for asymptomatic carotid stenosis (N=1559/2480) *
  - **CREST-H** Hemodynamic impairment ancillary study in CREST-2 (N=114/500)
- **ARCADIA** Atrial cardiopathy and anticoagulation for cryptogenic stroke (N=341/1100)
  - **ARCADIA-CSI** Cognition and silent infarcts in ARCADIA patients (N=500) *in start-up*
- **Sleep-SMART** Sleep for stroke management and recovery (N=91/3062)
- **MOST** Optimization of thrombolysis ischemic stroke trial (N=2/1200)
- **TRANSPORT-2** Transcranial direct stimulation for stroke recovery (N=3/129)
- **I-ACQUIRE** Intensive infant rehabilitation for pediatric stroke (N=5/240)
- **ASPIRE** Anticoagulation for stroke prevention and recovery after ICH (N=700) *in start-up*
- **SATURN** Statin use in Intracerebral hemorrhage patients (N=1456) *in start-up*
- **FASTEST** Early treatment of FVIIa for acute hemorrhagic stroke (N=860) *pending award*

SATURN
Telerehab Trial
SleepSMART
defuse·3
ARCADIA
I-ACQUIRE
iDEF
Intracerebral Hemorrhage Deferoxamine Trial
CREST-2
TRANSPORT2
MOST
ASPIRE
NIH National Institute of Neurological Disorders and Stroke
MISTIE III
CREST-H
ARCADIA•CSI
Cognition & Silent Infarcts

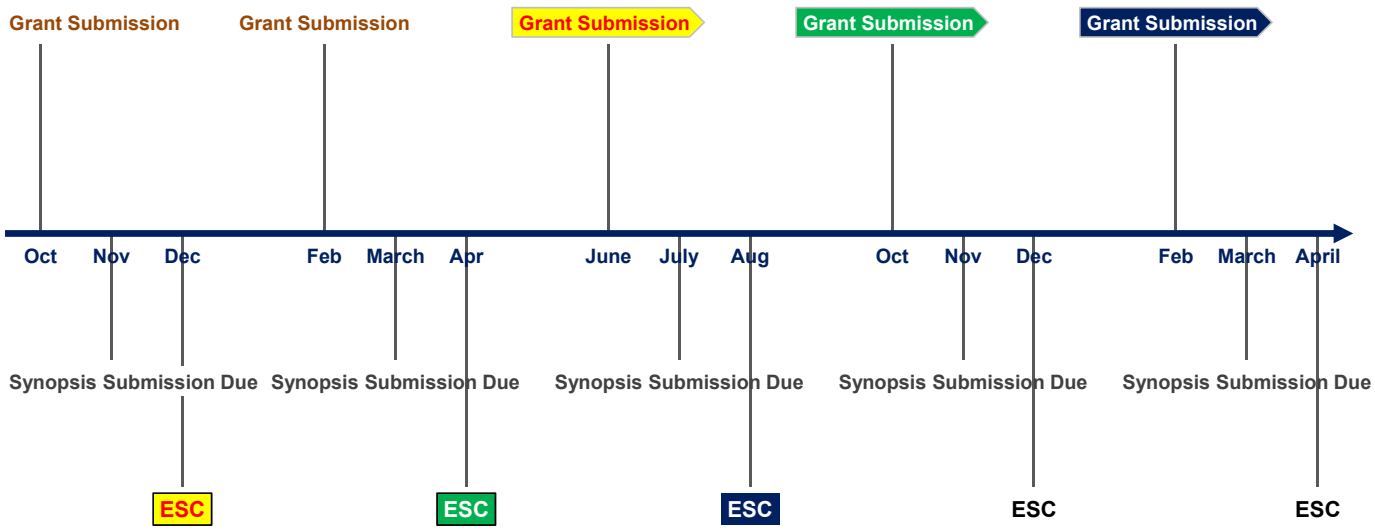
Balance of StrokeNet Trials



Concept Development process – what's changed?

1. Propose concept – notify NINDS
2. Present concept to Working Group
3. Submit final concept with *preliminary budget* to NINDS for ESC review (3 times a year)
4. Conduct Feasibility analysis
   a) Feasibility may be required before final ESC approval
5. Prepare application and final budget with input from NCC/NDMC
6. Submit and wait…

ESC Approval of New Network Projects



Next SN ESC – Jan 24, 2020

StrokeNet Clinical Trials "potential" Activity

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY
Funded by a Grant from the National Institutes of Health

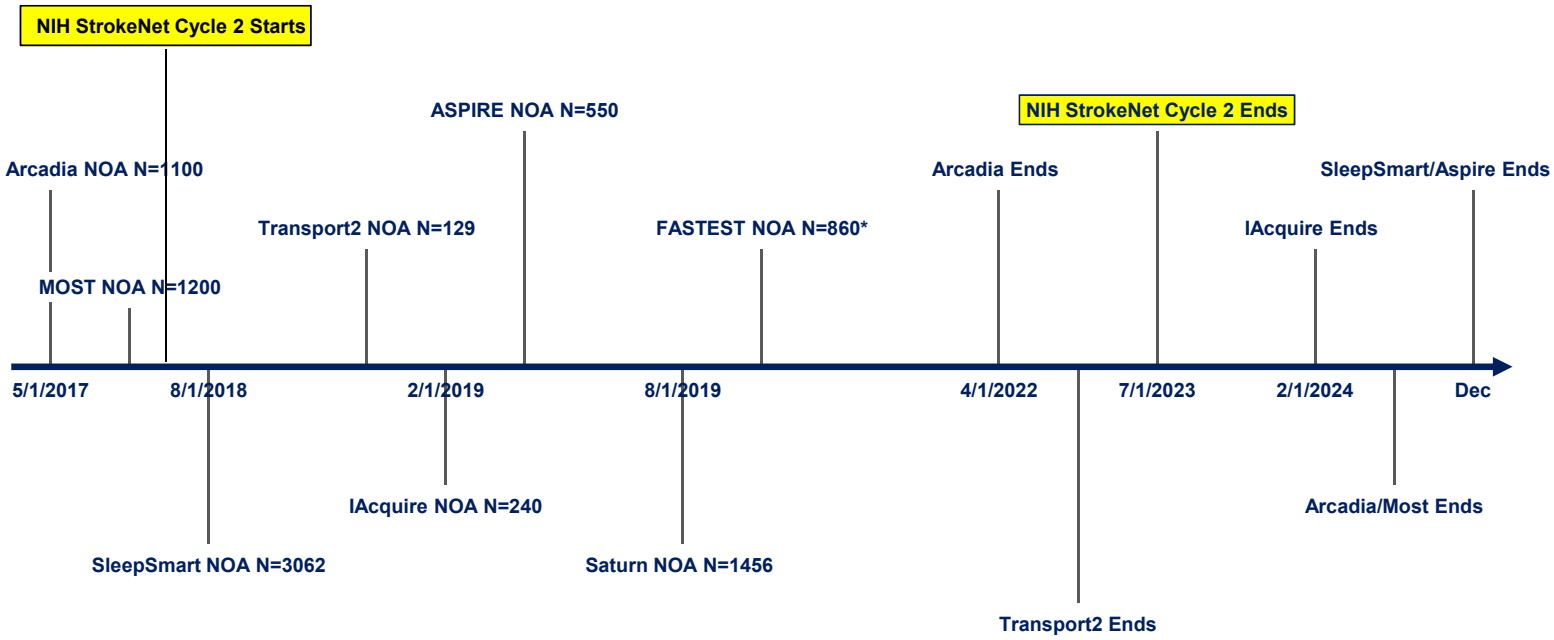
In-review:

- **ALISAH** Human albumin for Sub Arachnoid hemorrhage (N=400)
- **PreLimbs** Preconditioning for SAH (N=150)
- **Test of Time** TNK in for wake-up strokes (N=456)

Pending submission:

- **CAPTIVA** Platelet aggregation inhibitor treatment for ICAD (N=1629)
- **PETITE** Ph2 to develop target mismatch biomarker for pediatric EVT (N=90)
- **CASH** Cilostazol for aneurysmal SAH (N=1764)
- **SPLASH** Cerebral spinal fluid drainage for aneurysmal SAH (N=226)
- **Step-Stone** EVT platform (N=400)
- **RHAPSODY 2** 3K3A-APC (recom prot C) for acute ischemic stroke (N=1700)
- **PERFUSE ICAS** Imaging biomarker for intracranial stenosis (N=300)
- **ERSAIS** EDAS surgery for intracranial stenosis (N=496)
- **COAT** Rivaroxaban for carotid stenosis (N=1140)
- **FOCUS** Corticosteriods for pediatric arterial ischemic stroke (N=65)
- **VERIFY** Recovery biomarker validation study (N=657)

StrokeNet timeline (Oct 2019)



National Institute of Neurological Disorders and Stroke

Looking Forward

- Council evaluation of the program (yr 8 ~2020)
- Explore creative opportunities to tackle administrative challenges (e.g., contracting, IRB, etc.)
- NINDS is creating an open forum with trial PI's to enhance communication
- Expand opportunities for career enhancement (i.e., training) in the network
- More science-based workshops – tackle Prevention next?
- Continue to expand our global outreach with our international partners

Reminders

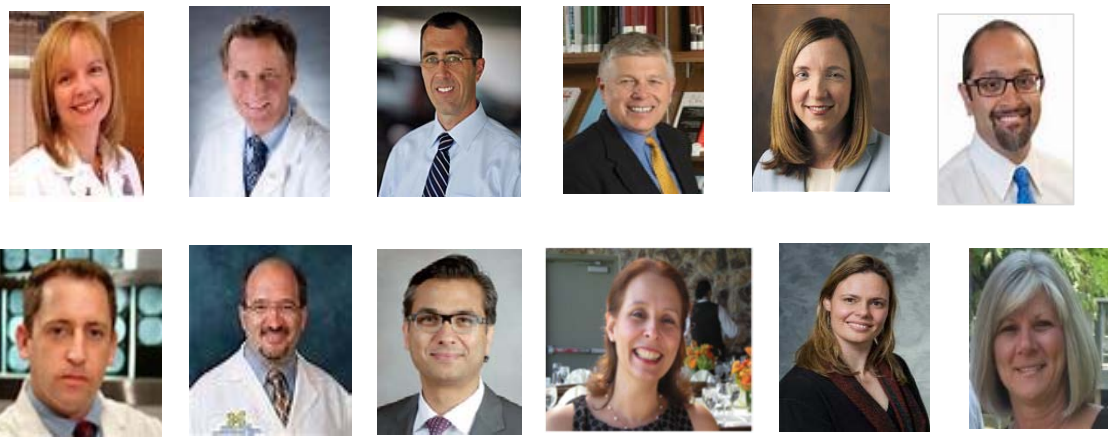
- Timely submission of Progress reports, FSR's, etc. will help ensure flow of resources
- Contact us if you have issues with your awards, projects, etc.
- NIH system is currently down for audit. Expected re-start this week
  - outstanding actions (release restrictions, carryover, etc.)

NIH StrokeNet Training and Education Core

Dawn Kleindorfer, MD

10/19

2019-2020 NIH StrokeNet Training Core Members



2019-2020 Trainee Core Members

Pictured from left to right:
Dawn Kleindorfer, Chair, UC, Randy Marshall, Co-Chair, Columbia, Scott Janis, Project Scientist, NINDS, Harold Adams, Faculty, Iowa, Lori Jordan, Faculty, Vanderbilt, Shyam Prabhakaran, Faculty, Northwestern, David Liebeskind, Faculty, UCLA, Cemal Sozener, Former Trainee, Michigan, Farhaan Vahidy, Former Trainee, UTH, Iszet Campo-Bustillo, Coordinator, Miami, Stephanie Wilbrand, Coordinator, Wisconsin, Jeanne Sester, Coordinator, UC, Trainees: Christine Tschoe, Wake Forest, James Giles, MD, PhD, Washington University, St. Louis

Current Trainees

- 25 trainees, 40% female
- 4 Minority/Underrepresented
- 5/25 are faculty members
- Degrees
  - MD 13
  - MD, PhD 4
  - PhD 3
  - PhD, CCC-SLP 1
  - PhD, MSCI 1
  - PhD – MSCR 1
  - DO 1
  - DPT 1

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Level of Trainees

• Junior Faculty	4
• Fellow	19
• Associate Professor	1
• Post Doc Fellow	1

Disciplines of Trainees

• Neurology	13
• Vascular Neurology	6
• Physical Medicine & Rehabilitation	2
• Speech Language Pathologist	1
• Rehabilitation Medicine / Physical Therapy	1
• Neurosurgery	1
• Pulmonology / Pulmonary Care & Critical Care	1

Activities of Training Core

Activities of the Training Core

- Serve as a resource for trainees and mentors
  - Maintain contact info for current and past trainees
  - Post training opportunities, such as NINDS Clinical Trials Workshop
  - Job postings
  - Assist with finding mentors for trainees off-site
    - Away rotations

Other Activities of the Training Core

- Supervision of the RCC Training Programs
  - Ensure that adequate focus on stroke research
  - Education plans with milestones for progress due prior to trainee arrival
    - We really do read these!
  - Final Progress Report
    - Including information about their next position and success in research so far, contact information
    - We read these too….please ensure that these are filled out adequately. Trainees should participate in the process.

Learning Communities

- To improve networking within the trainees, career mentorship and research mentorship with experts external to the home RCC site
  - Divided trainees by research interest
  - Assigned RCC mentors to each group by research area of expertise
- Monthly video conference calls
  - Agenda and scheduling now driven by mentors
  - Discuss research ideas, career questions, get to know each other, journal clubs

StrokeNet Webinars

Grand Rounds

- 2015-2016 Average Attendees = **78**
- 2016-2017 Average Attendees = **70**
- 2017-2018 Average Attendees = **69**
- 2018-2019 Average Attendees = **55**

Professional Development

- 2015-2016 Average Attendees = **51**
- 2016-2017 Average Attendees = **51**
- 2017-2018 Average Attendees = **38**
- 2018-2019 Average Attendees = **41**

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StrokeNet Grand Rounds

- Process for selecting topics and speakers:
  - All RCC sites are surveyed and asked to name three topics and speakers they would like to hear
  - Training core members review the list and rank their preferences
  - The top scoring topics and speakers are chosen on a Training Core Call

2018 – 2019
StrokeNet Grand Rounds Schedule
All Webinars begin at 4:00PM Eastern Time
https://nihstrokenet.adobeconnect.com/grandrounds/

Date	Topic	Speaker	Institution	Moderator
July 26	Genomics as an Informational Tool in Neurorehabilitation	Steve Cramer, MD	University of California, Irvine	Hal Adams
Aug 30	Cerebral Edema After Acute Brain Ischemia	Kevin N. Sheth, MD	Yale School of Medicine	Cemal Sozener
Sept 27	Community Education in Stroke	Shyam Prabhakaran, MD	Northwestern University	Farhaan Vahidy
Oct 25	Perioperative & Periprocedural Stroke	Steven Messe, MD	UPENN	Cemal Sozener
Nov 29	From Compensation to Recovery in Motor Function Following Stroke: a Never Ending Continuum	John W. Krakauer, MD	Johns Hopkins	Steve Wolf
Jan 31	Blood Pressure Variability and its Effects on Stroke Outcomes	Adam de Havenon, MD	University of Utah	Farhaan Vahidy
Feb 28	Brain Susceptibility to Acute Ischemia: Why White Matter Matters	Natalia Rost, MD	MGH	Shyam Prabhakaran
Mar 21	Gloves Off for Acute Stroke Management; Fellow Case Presentations to Two Stroke Experts	Louise McCullough, MD, PhD Wade Smith, MD, PhD Daniela Zambrano – Fellow Christine Tschoe – StrokeNet Trainee	University of Texas, Houston UCSF Columbia Wake Forest	Randy Marshall
Apr 4	Preconditioning the Brain for Stroke Prevention	Sebastian Koch, MD & Miguel A. Perez-Pinzon, Ph.D.	University of Miami	Dawn Kleindorfer
May 30	Translational Research: Inflammation and Post-stroke Cognitive Decline	Marion Buckwalter, MD, PhD	Stanford	Randy Marshall

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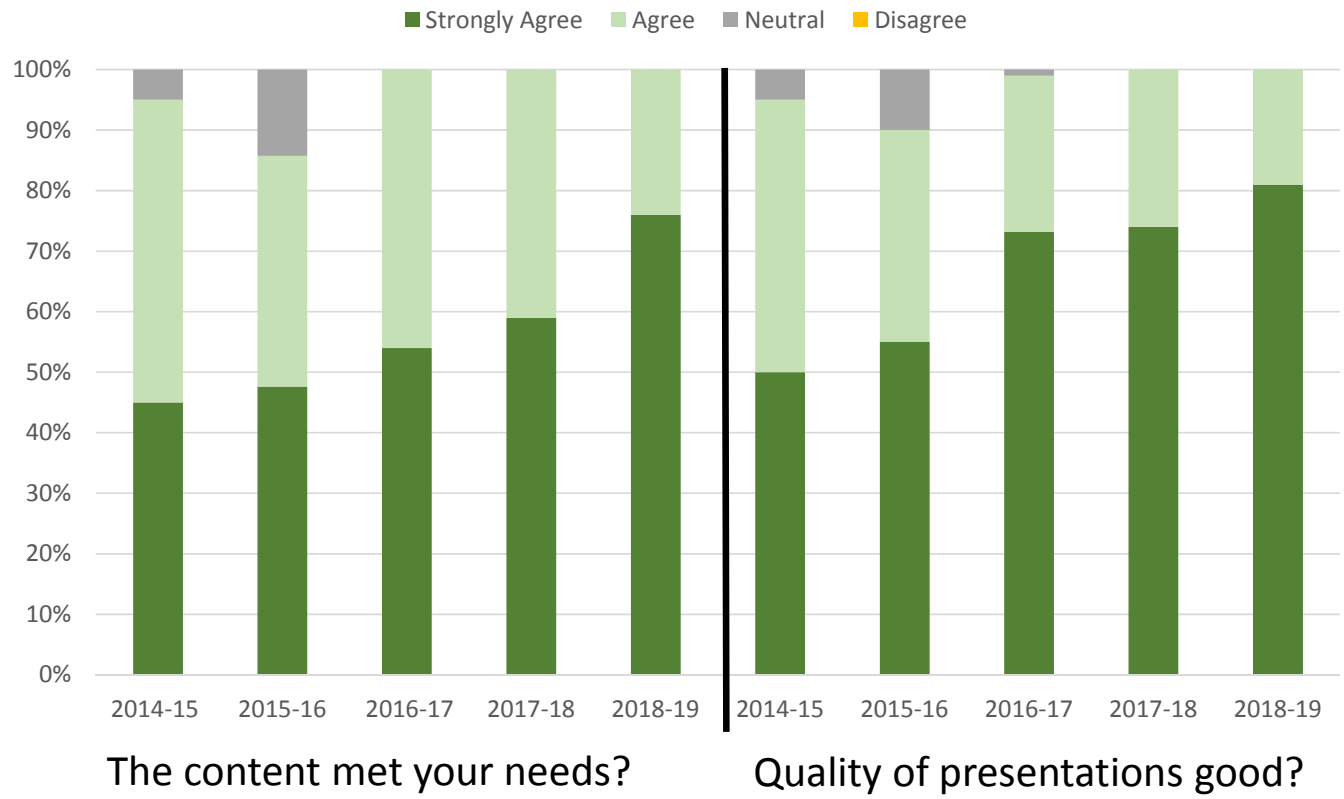
StrokeNet Grand Rounds Evals



NIH StrokeNet Professional Development Webinar Schedule
All Times are Eastern Time
2018 – 2019
https://nihstrokenet.adobeconnect.com/pdw/

Date	Topic	Speaker	Time	Institution	Moderator
Aug 23	How to Present Your Data	Dawn Kleindorfer	2:00 PM	Cincinnati	NA
Sept 24	CV & Biosketch	Lori Jordan	1:00 PM	Vanderbilt	Farhaan Vahidy
Oct 9	Creating a Study Budget	Randy Marshall Stephanie Wilbrand	12:00 PM	Columbia Wisconsin Madison	NA
Dec 4	When & How to Incorporate a Statistician in a Study	Yuko Palesch	1:00 PM	MUSC	Cemal Sozener
Jan - May	Trainee Presentations (TBA)				

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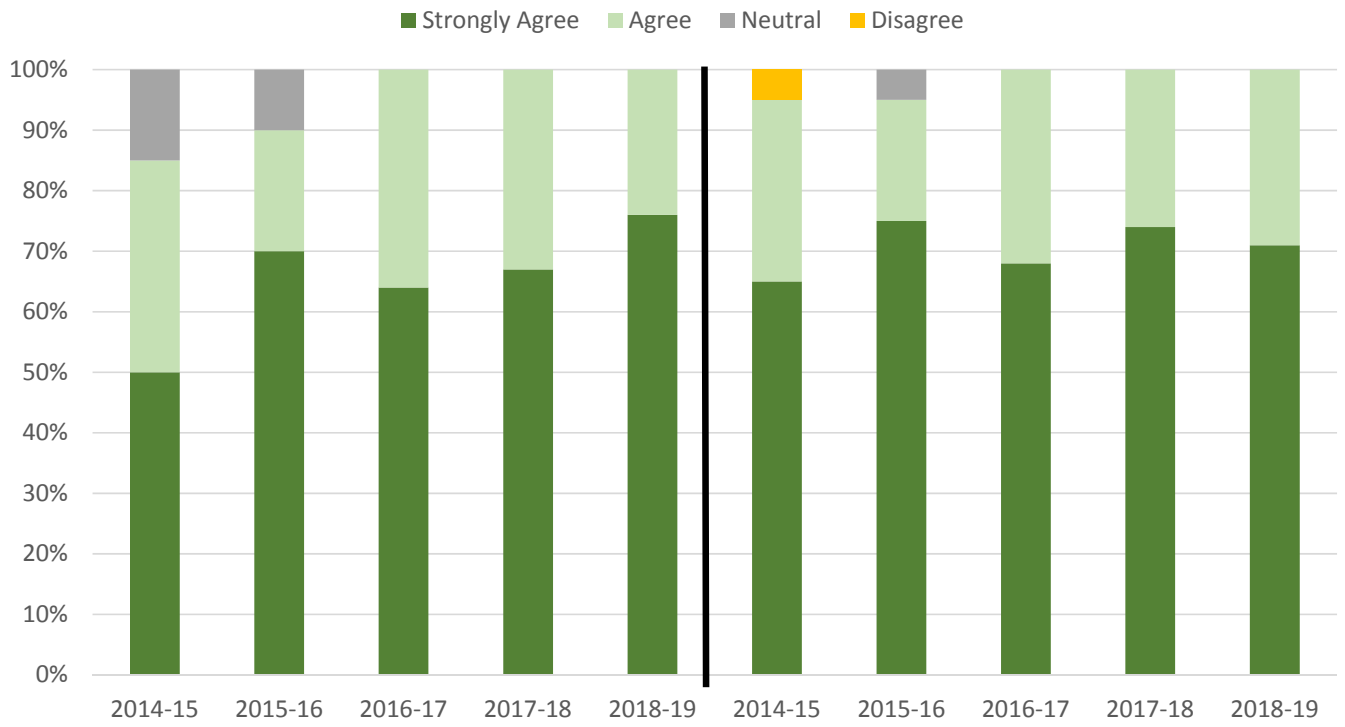
Professional Dev. Webinar Evals

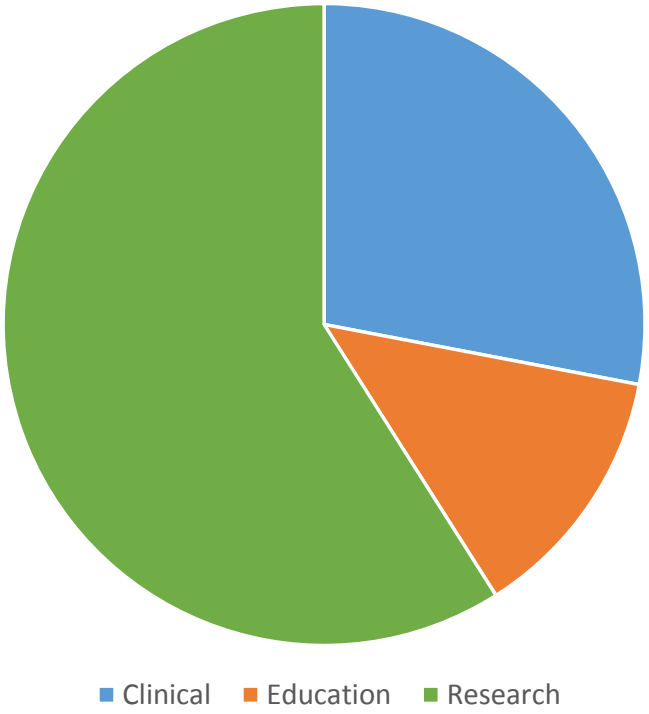


The content met your needs?

Quality of presentations good?

Former Trainee Data

How was your time spent this year?



Trainee Publication Productivity 2018-19

- 20/21 trainees had abstracts or manuscripts

- 66 first-author abstracts
- 40 first-author manuscripts

- 56 secondary author abstracts
- 21 secondary author manuscripts

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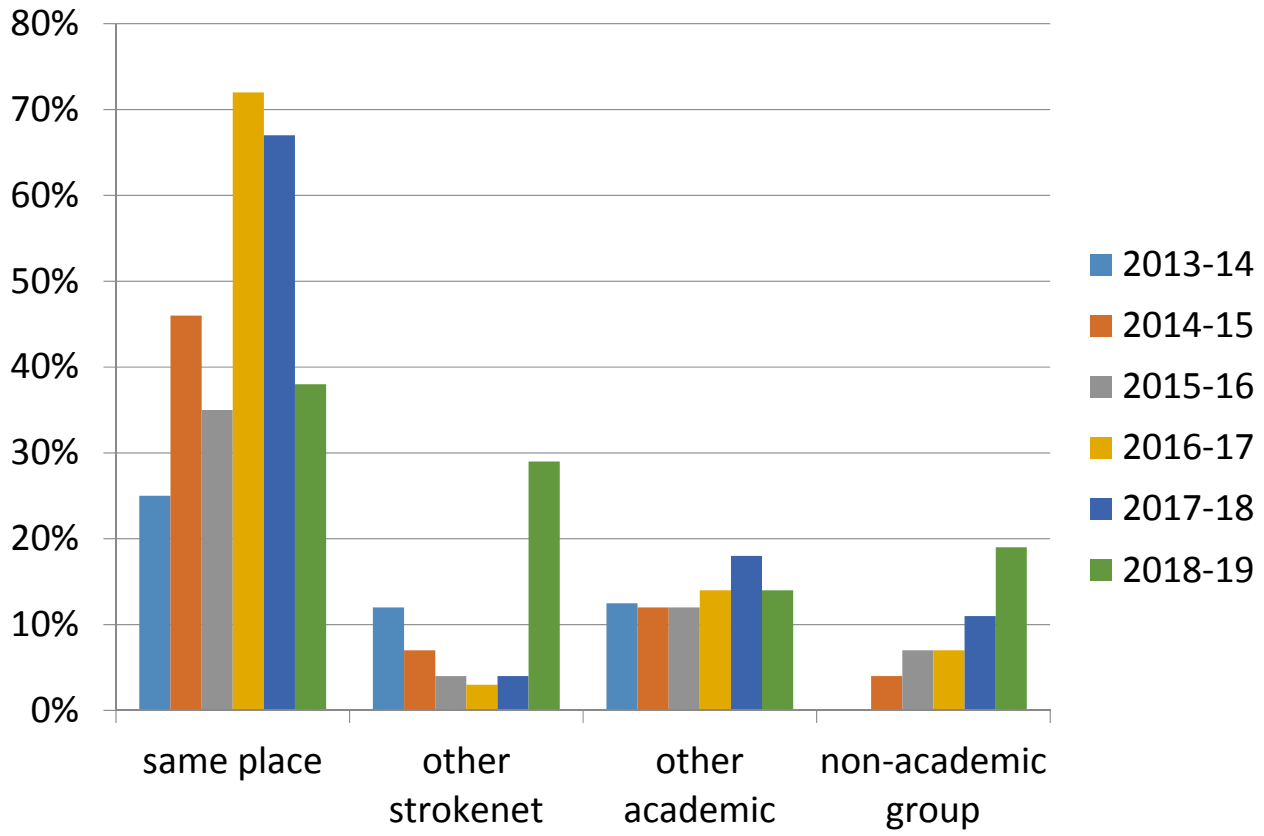
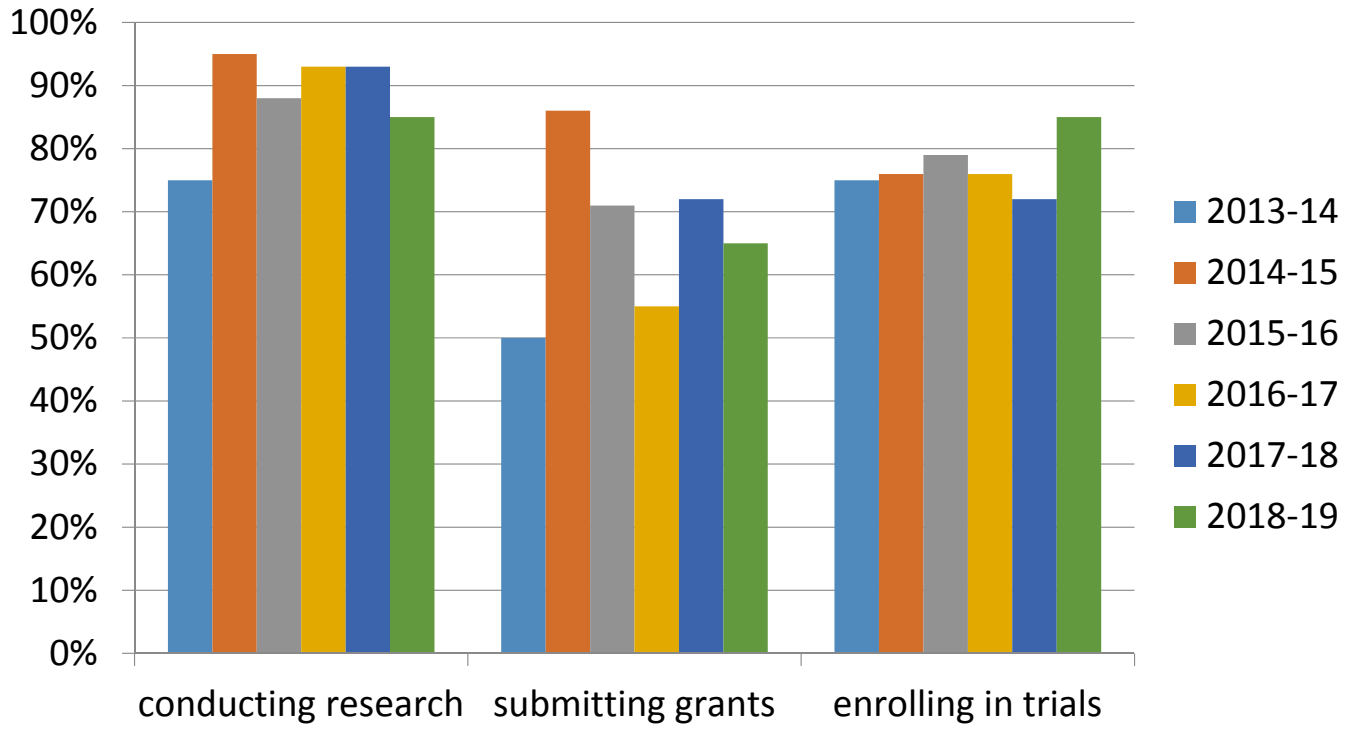
Grant Submissions During StrokeNet Training Period, 2018-19

- **8 trainees submitted 10 grants during the training year**
  - Fogarty International Training Grant
  - K23
  - KL2
  - AHA Mentored Clinical & Population Research Award
  - BMS/Pfizer American Thrombosis Investigator Initiated Research Program (ARISTA-USA)
  - AAN Clinician Scientist Development Award
  - Patterson Trust Mentored Research Award
  - AHA/ASA early career award
  - Center for Clinical and Translational Science (CCTS)

Where do StrokeNet Trainees Go Next?



Outcomes: What are they doing related to research?



Feedback

- Learning communities worked variably well
  - Several really enjoyed them
  - Challenging to schedule, variable engagement
  - More networking with peers still #1 request
- Wanting more interaction with network faculty
  - Loved the “gloves off” case presentations
- Requesting strokenet trainee grants for funding projects and/or travel funds for meetings

NIH StrokeNet Training Core – Manuscript

- Special Report in journal ‘Stroke’: Led by prior trainees
- Highlights
  - History / Rationale
  - Organizational Structure
  - Training Activities
- Progress
  - Manuscripts: 1,659 (58% during or after NIH StrokeNet Training)
  - Grants:
    - 72 submitted proposals (51.4% under review and 22.2% funded)

ARCADIA Recruitment Update Fall 2019

Hooman Kamel on behalf of the ARCADIA Investigators

ARCADIA

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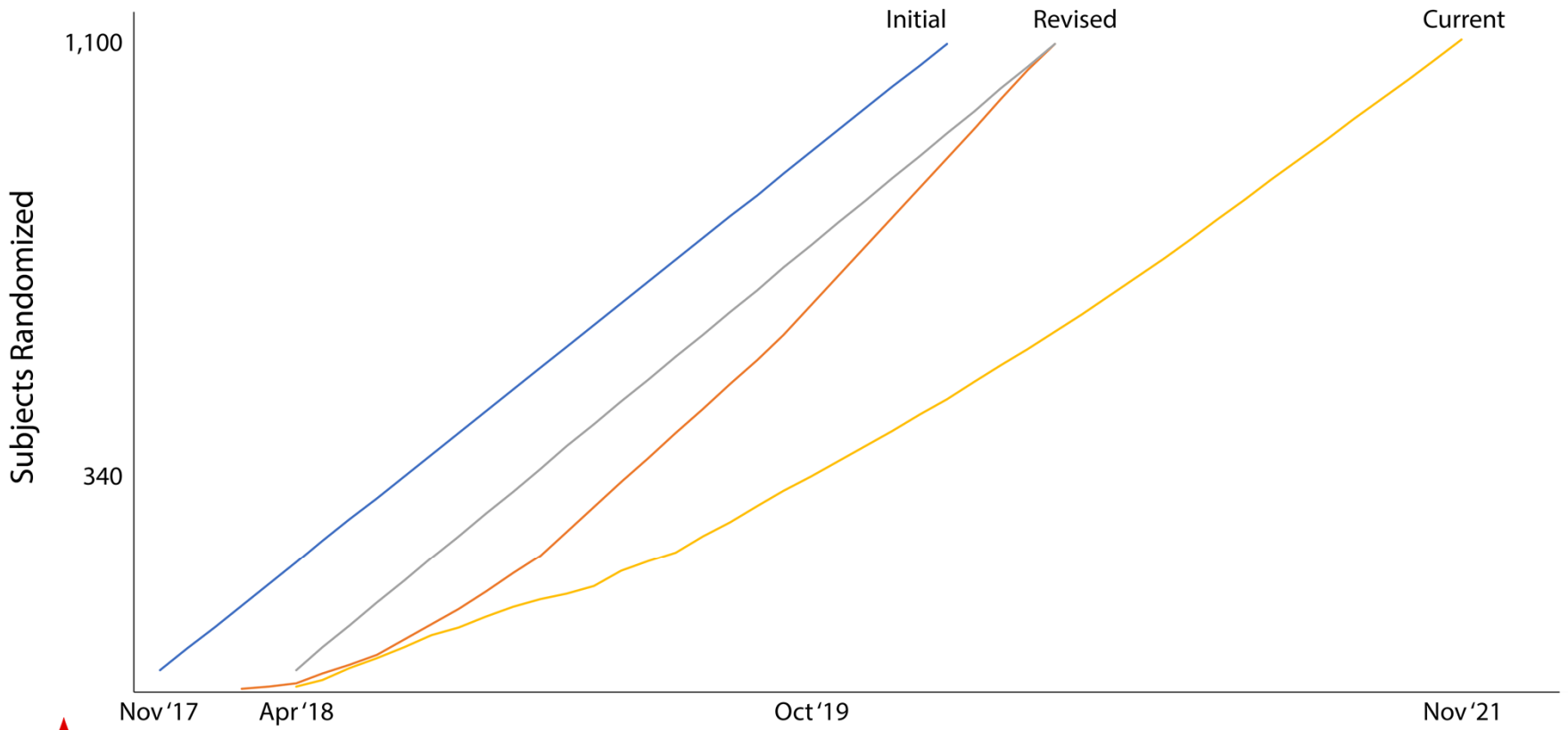
ARCADIA Initial vs Current Recruitment Projections



ARCADIA

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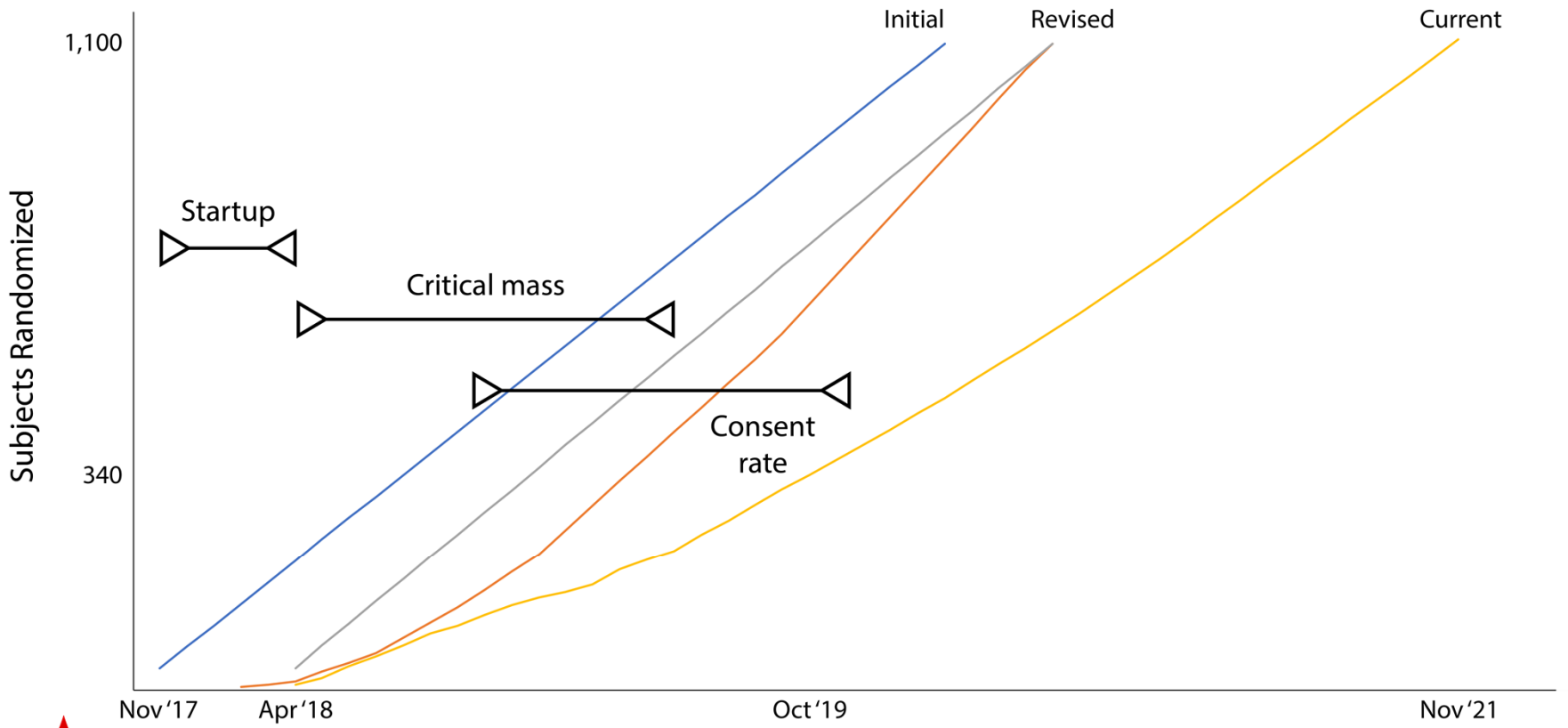
ARCADIA Initial vs Current Recruitment Projections



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Projected versus actual status

	Projected	Actual
Recruitment start date	Nov 2017	Apr 2018
Average number of strokes per site per year	500	
Percent of all strokes -> eligible for consent	20%	
Percent of eligible -> ID'd and agreed to consent	15%	
Percent of consented -> eligible for randomization	35%	
Percent of consented -> randomized	25%	
Randomizations per site per month	0.31	
Number of sites	120	

Projected versus actual status

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Average number of strokes per site per year	500	
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Projected versus actual status

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Percent of consented -> randomized	25%	26%
Randomizations per site per month	0.31	0.19
Number of sites	120	

ARCADIA

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Projected versus actual status

	Projected	Actual
Recruitment start date	Nov 2017	Apr 2018
Average number of strokes per site per year	500	?
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ARCADIA

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Projected versus actual status

	Projected	Actual
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Percent of eligible -> ID'd and agreed to consent	15%	?
Percent of consented -> eligible for randomization	35%	38%
Percent of consented -> randomized	25%	26%
Randomizations per site per month	0.31	0.19
Number of sites	120	128 -> 180

ARCADIA

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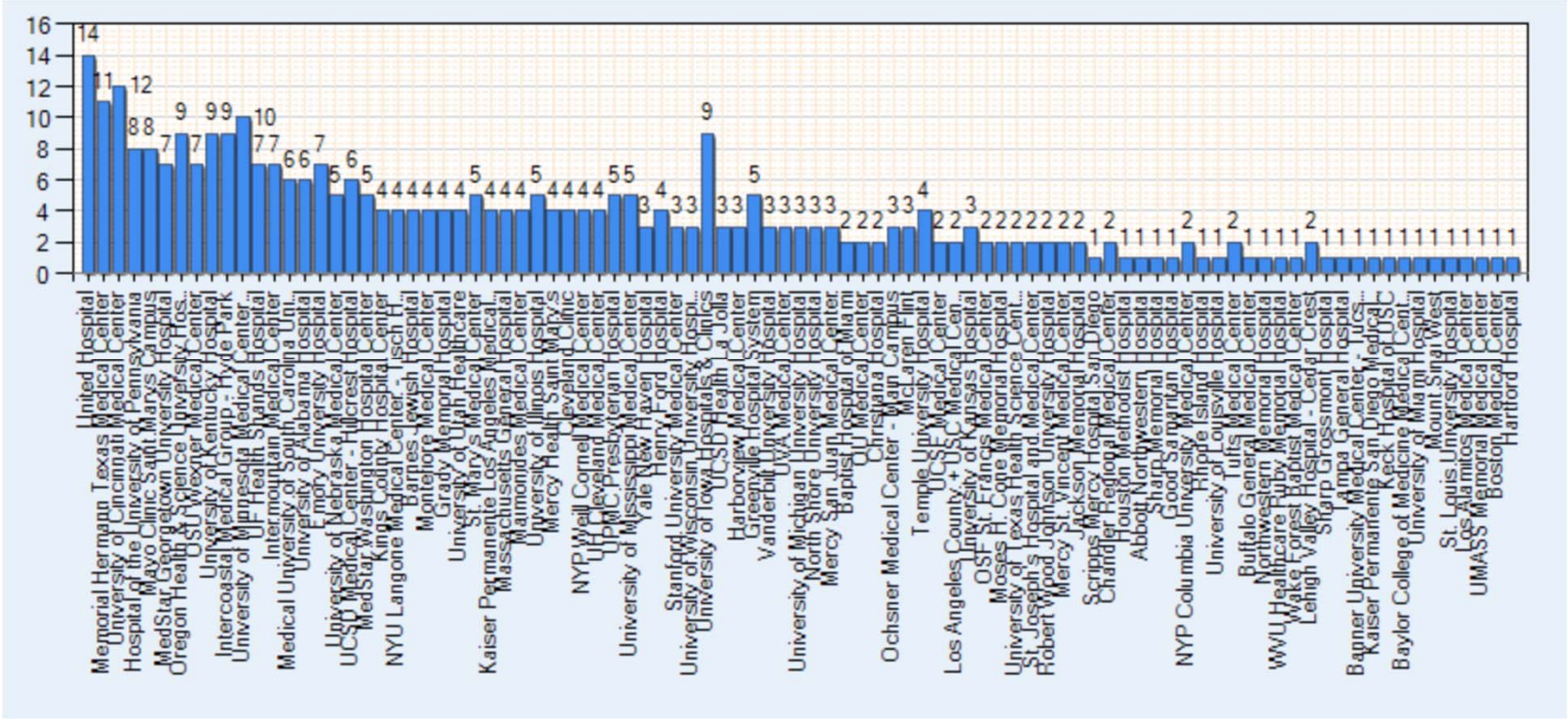
PREVENTION | TREATMENT | RECOVERY



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Highest performing sites - randomizations

Site	Randomized Subjects
United	14
Cincinnati	12
Memorial Hermann	11
Minnesota	10
Iowa	9

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Highest performing sites - consents

Site	Consented Subjects
United	42
Iowa	40
OHSU	37
Cincinnati	36
UPMC	34

Highest performing sites - randomization rate

Site	Randomizations/month
Mississippi	0.93
United	0.78
North Shore	0.71
Emory	0.58
Kentucky	0.58

Highest performing sites - randomization rate

Site	Randomizations/month
Mississippi	0.93
United	0.78
North Shore	0.71
Emory	0.58
Kentucky	0.58
PROJECTION	**0.31**
TRIAL-WIDE AVERAGE	**0.19**

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PREVENTION | TREATMENT | RECOVERY

Highest performing sites - consent rate

Site	Consents/month
Emory	2.6
United	2.3
Moses Cone	2.3
Mississippi	2.2
Iowa	2.1

Highest performing sites - consent rate

Site	Consents/month
Emory	2.6
United	2.3
Moses Cone	2.3
Mississippi	2.2
Iowa	2.1
PROJECTION	**1.2**
TRIAL-WIDE AVERAGE	**0.7**

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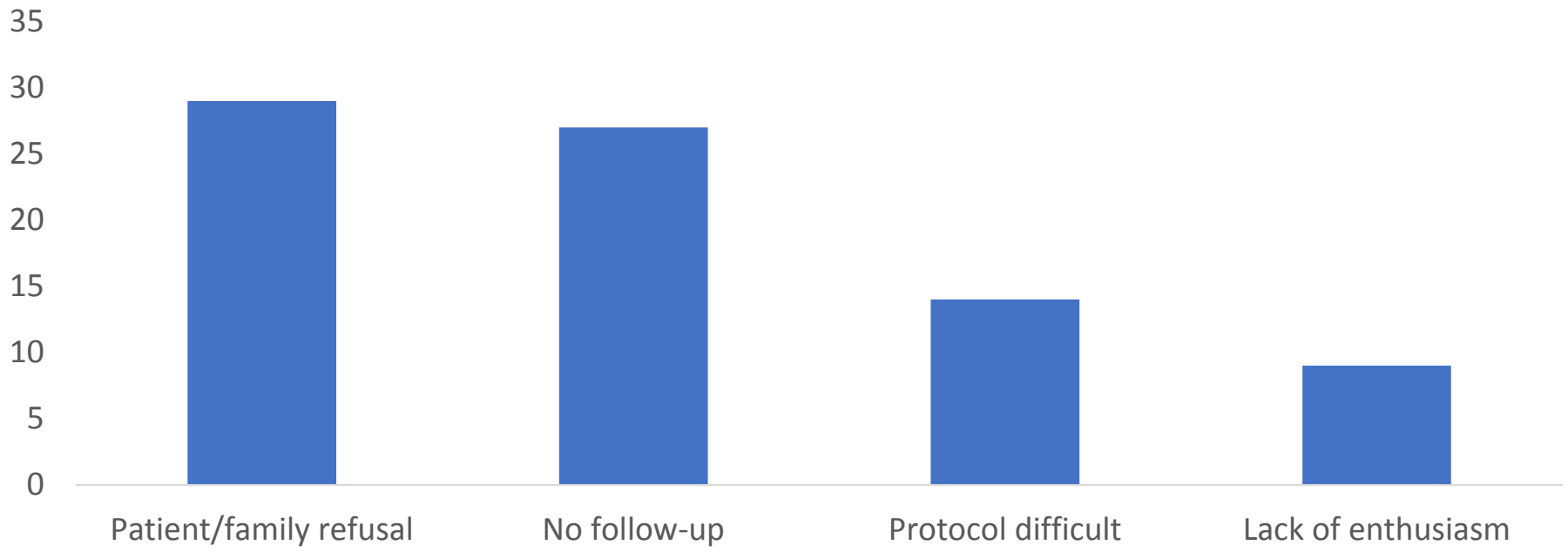
Recipes for success

Presentations by two high-performing sites:

Common barriers to recruitment?

Common barriers to recruitment: your answers



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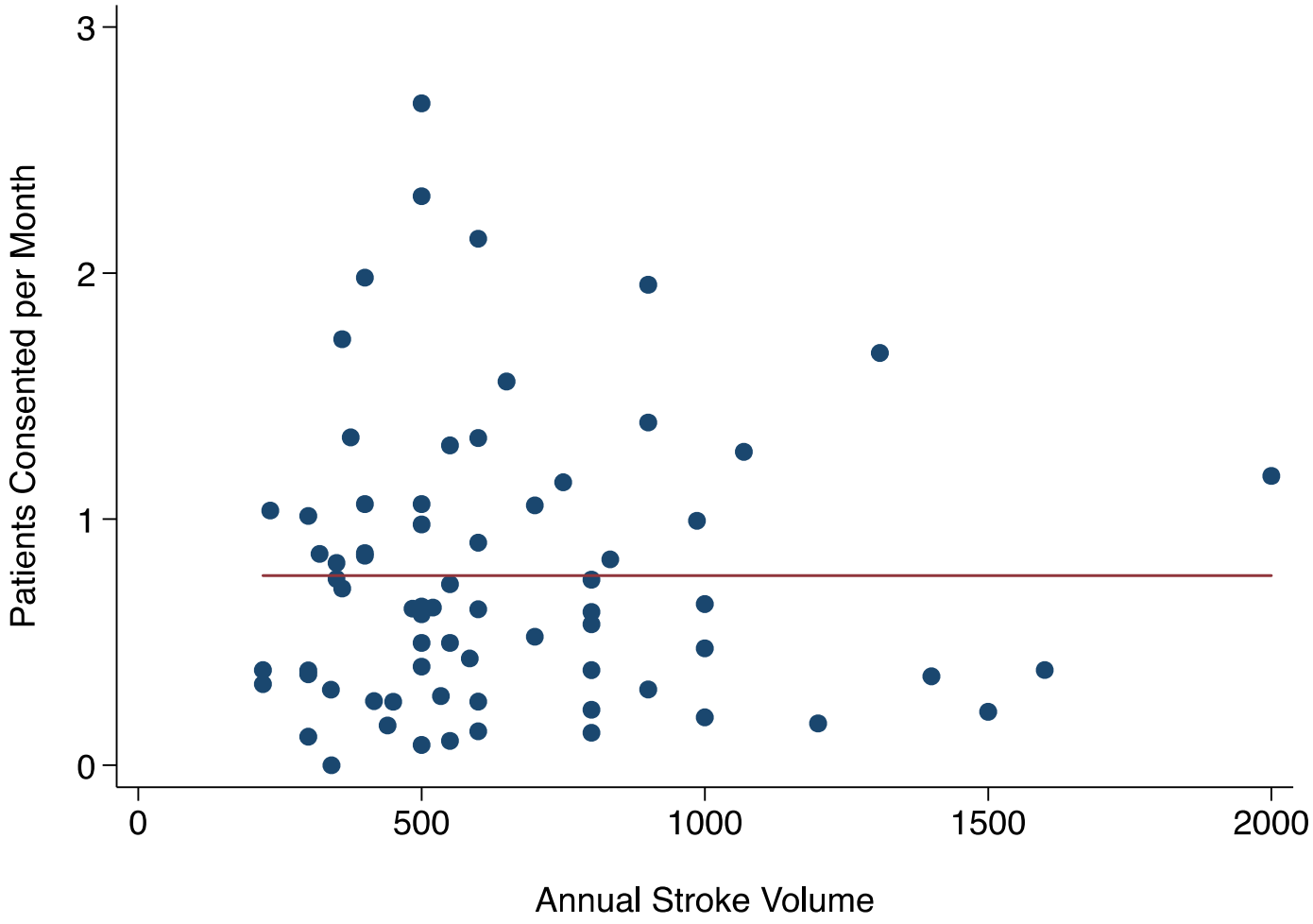

ARCADIA

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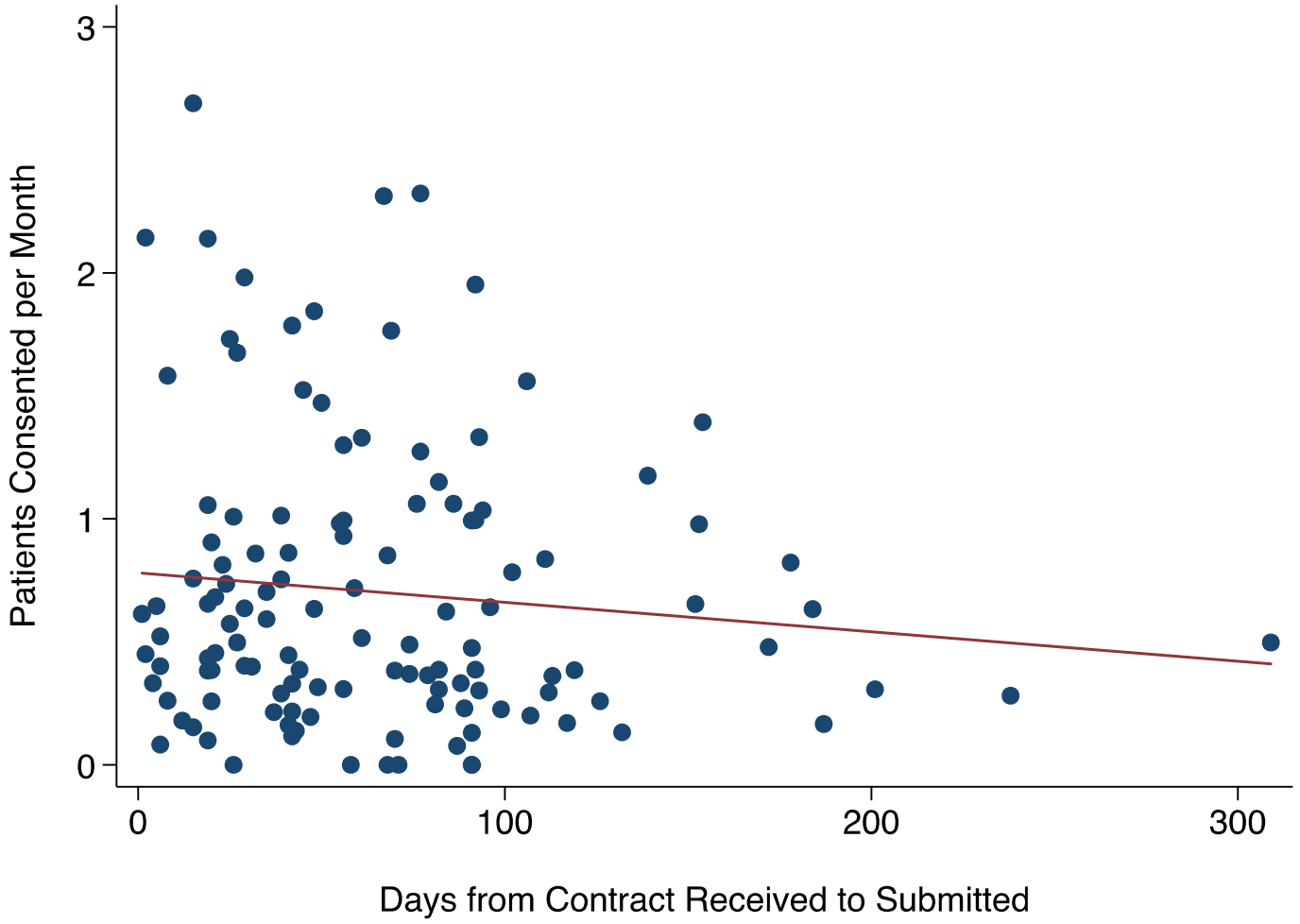
PREVENTION | TREATMENT | RECOVERY



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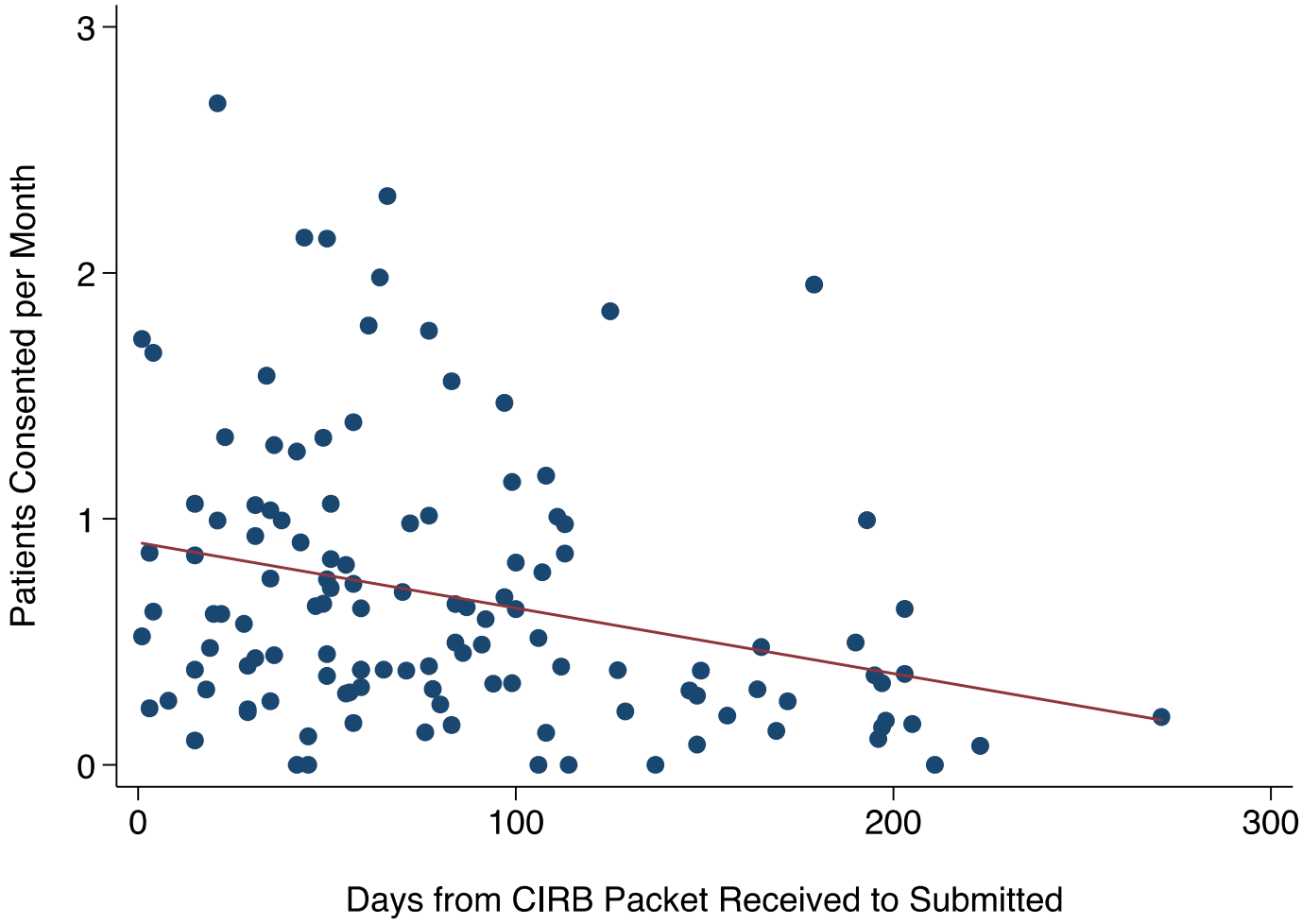
PREVENTION | TREATMENT | RECOVERY



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Plan to increase recruitment

1. Increase recruitment rate
   a. Regular check-in calls to non-enrolling sites -> maintain focus
   b. Patient video -> increase patient/family buy-in
   c. Monthly webinars -> maintain enthusiasm re: scientific importance
2. Increase number of sites
   a. ~20 additional U.S. sites (StrokeNet & non-StrokeNet)
   b. ~30 Canadian sites

Whether patients with cryptogenic stroke who have atrial cardiopathy and are at a high risk for atrial fibrillation could benefit from anticoagulation is being investigated in the ongoing ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs In Prevention after Cryptogenic Stroke).[14]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source

H.-C. Diener, R.L. Sacco, J.D. Easton, C.B. Granger, R.A. Bernstein, S. Uchiyama, J. Kreuzer, L. Cronin, D. Cotton, C. Grauer, M. Brueckmann, M. Chernyatina, G. Donnan, J.M. Ferro, M. Grond, B. Kallmünzer, J. Krupinski, B.-C. Lee, R. Lemmens, J. Masjuan, M. Odinak, J.L. Saver, P.D. Schellinger, D. Toni, and K. Toyoda, for the RE-SPECT ESUS Steering Committee and Investigators*

ARCADIA

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A prospective, randomized clinical trial, ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) sought to answer if OAC therapy compared with daily baby aspirin would prevent recurrent ischemic stroke in patients with cryptogenic stroke who possess at least 1 marker of atrial myopathy: an abnormal P wave, N-terminal pro B-type natriuretic peptide (NT-proBNP) level, and dilated LA on echocardiography (133).

STATE-OF-THE-ART REVIEW

Atrial Myopathy

Mark J. Shen, MD,[a,b] Rishi Arora, MD,[a] José Jalife, MD[c,d]

JACC: BASIC TO TRANSLATIONAL SCIENCE CME/MOC/ECME

ARCADIA

The ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) trial aims to compare apixaban versus aspirin in ESUS patients at high risk of cardioembolism on the basis of atrial cardiopathy detected on 12-lead electrocardiogram abnormalities, left atrium enlargement on echocardiography, or presence of elevated amino terminal pro-B-type natriuretic peptide (83).

THE PRESENT AND FUTURE

JACC SCIENTIFIC EXPERT PANEL

Antithrombotic Therapy to Prevent Recurrent Strokes in Ischemic Cerebrovascular Disease

JACC Scientific Expert Panel

Victor J. Del Brutto, MD,[a] Seemant Chaturvedi, MD,[b] Hans-Christoph Diener, MD, PhD,[c] Jose G. Romano, MD,[a] Ralph L. Sacco, MD, MS[a]

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It seems that the results of ARCADIA are eagerly anticipated

We appreciate your crucial help in making it happen!

Keys to ARCADIA Enrollment: The Emory Experience

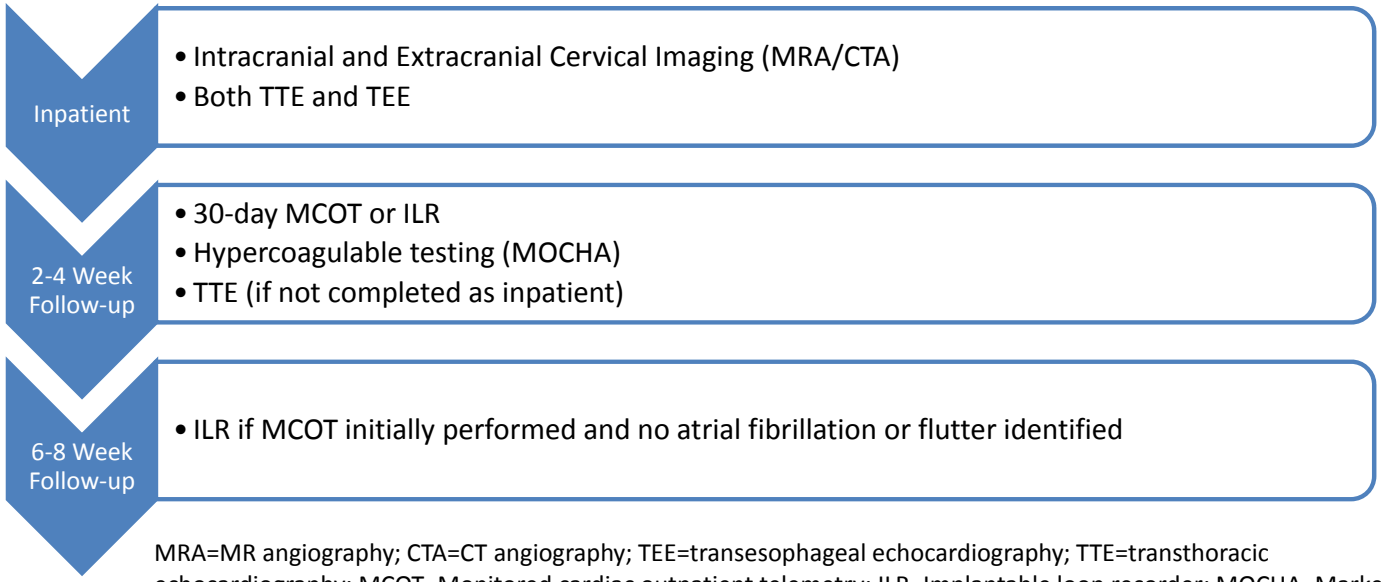
Fadi B. Nahab MD
Associate Professor, Department of Neurology & Pediatrics
Stroke Quality Director, Emory Healthcare

Lori Sutherly
MS, BSN, RN-BC, SCRN, NVRN, CCRC
Clinical Research Nurse II
Emory University School of Medicine

STEP 1: BRING THE PATIENTS TO YOU

- Presentations to the Metro Atlanta health systems:
  - Emory Stroke Conference, Emory Neurohospitalist Conference, Emory Neurology Grand Rounds, Emory **Cardiology** Conference (annually); Emory Medicine Grand Rounds
  - Wellstar **Cardiac**-Cerebrovascular Symposium
  - Northside Women and Stroke Symposium
  - Kaiser Neurology

STEP 2: EMORY CRYPTOGENIC STROKE ALGORITHM



MRA=MR angiography; CTA=CT angiography; TEE=transesophageal echocardiography; TTE=transthoracic echocardiography; MCOT=Monitored cardiac outpatient telemetry; ILR=Implantable loop recorder; MOCHA=Markers of Coagulation and Hemostasis Activation (fibrin monomer, prothrombin fragment 1.2, thrombin-antithrombin complex, d-dimer)

Ellis D, et al. Medicine 2018;97:e13830.

STEP 3: PRIORITIZE EARLY POST-DISCHARGE FOLLOW-UP INTO EMORY STROKE CLINIC

- Inpatient Emory neurohospitalists throughout the Emory Healthcare system directly message our stroke clinic schedulers prior to patient discharge and cc ARCADIA PI (Fadi Nahab) for cryptogenic stroke patients
  - Target for Emory Stroke Clinic is all stroke/TIA post-hospital discharge clinic follow-ups to be seen within 2-4 weeks by Stroke NP.
  - We do not approach and consent anyone during their inpatient stay; showing up to their 1st stroke clinic follow-up visit is a very important sign of patients being a good study patient.
    - No patients to date have consented, been eligible for randomization, and not returned for randomization

STEP 4a: ARCADIA PI HAS CONSENT DISCUSSION WITH ALL ELIGIBLE PATIENTS

- Highlights of patient discussion:
  - Cryptogenic stroke is caused by a heart or blood clotting issue in most patients
  - Your left atrial size is not normal (LA diameter ≥4.0cm or LAVI ≥29) and this has been associated with development of AFib in the future.
    - Patients with normal LA size but with PFO are also included in discussion for enrollment consideration
  - We will evaluate for a clotting issue with our Emory coagulation testing (MOCHA profile) and there is an opportunity for you to participate in a national NIH funded study to evaluate for heart related issues using a unique blood test (e.g. nt pro-BNP) paid by the study as well as experts to review your ECG and heart ultrasound.

STEP 4b: ARCADIA PI (ME) HAS CONSENT DISCUSSION WITH ALL ELIGIBLE PATIENTS

- Highlights:
  - The study will help to assess whether you are high risk or low risk for developing AFib in the future
  - While aspirin is standard of care, patients found to be at high risk for developing AFib based on the study tests will have the opportunity to be randomly assigned (I don't choose, you don't choose) to aspirin (standard of care) or to Eliquis
  - Eliquis is proven to be more effective than aspirin if you have AFib but is unproven if AFib hasn't been diagnosed
  - Pull out the consent and go to page 9 table

Table of Serious Risks

	Risk	
Complication	Apixaban	Aspirin
Major bleeding **(see additional information below)**	Occurs in 4 out of 100 individuals per year	Occurs in 3 in out of 100 individuals per year
Abnormal liver function tests **(indicates possible liver damage)**	Occurs in 1-2 out of 100 individuals per year	Occurs in 1-2 out of 100 individuals per year
Allergic reaction to medication **(skin rash or allergic swelling)**	Occurs in less than 1 out of 100 individuals	Occurs in less than 1 out of 100 individuals
Asthma worsening	Not reported	Occurs in 5-10 in 100 individuals with asthma
Ringing in the ears	Not reported	Depends on dose, but occurs in less than 1 out of 100 individuals for doses in this study

Highlights:

1. Aspirin and Eliquis have similar major bleeding risks, similar low risks of liver problems and allergies but eliquis doesn't have side effects on asthma and ringing in ears like aspirin can have.

STEP 4c: ARCADIA PI (ME) HAS CONSENT DISCUSSION WITH ALL ELIGIBLE PATIENTS

- Educated patient replies: “Well why not put me on Eliquis then?”
- PI Reply:
  - #1 it’s unproven where Eliquis is more effective than aspirin in your current situation
  - #2 you have not been found to have AFib
  - #3 Eliquis can be expensive for most people and I don’t feel comfortable for any of my patients to pay high costs for medicines that are unproven
  - #4 I would recommend participating in this study if you were my own family member (TRUE statement)
  - #5 If you are found to be at high risk and on the study medication, I recommend all patients get a continuous monitor of your heart rhythm (e.g. loop recorder) and if at any point in time you are found to be in AFib, we will contact you immediately and take you off the study medication to place you on Eliquis. While the study does not pay for or require the loop recorder, I would recommend it if you were my own family member.
  - #6 If you are found to be at low risk based on the study, it does not mean you are at 0 risk for AFib and I would still recommend you have the loop recorder placed.
  - #7 If you consent today, we can draw your blood now and have the results back to you within 2-3 business days.
  - #8 The minimum requirement for us to follow you in the study is 18 months and we see you at 3,6,9,12 and 18 mos just like we routinely follow-up all patients; if you’re part of the study we will schedule the visits on days/times that will accommodate your schedule
  - #9 Please spend time reading the consent while I step out of the room and I’ll be back to answer questions; (PI steps out of room to contact clinicial research nurse to come for blood draw)

STEP 5: 95+% CONSENT IMMEDIATELY

- Within 2-3 business days, we get back the ARCADIA results, the MOCHA coagulation profile and notify patient
- Emory Markers of Coagulation and Hemostatic Activation (MOCHA) Profile:
  - D-dimer (normal <500 ng/mL)
  - Fibrin monomer (normal <7 mcg/mL)
  - Prothrombin fragment 1.2 (normal 65-288 pmol/L)
  - Thrombin-Antithrombin complex
    (normal 1.0-5.5 mcg/L)
- Patients who have ≥ 2 elevated MOCHA have never qualified for ARCADIA randomization since Emory began enrollment in ARCADIA
  - Pre-ARCADIA Emory study results (in revision for journal Neurology) highlight that cryptogenic stroke patients with abnormal MOCHA (≥ 2) go on to have occult cancer, occult VTE, or occult hypercoagulable disorder in up to 50% of cases.

Ellis D, et al. Medicine 2018;97:e13830.

Nahab F, et al. Neurology 2019; under revision

STEP 1-5 REQUIREMENT

- Have an outstanding clinical research nurse who is kind, pleasant for patients and staff to work with, knowledgeable and organized.
  - That's you Lori!

Thanks!

Fadi Nahab
fnahab@emory.edu

Lori Sutherly
l.j.sutherly@emory.edu

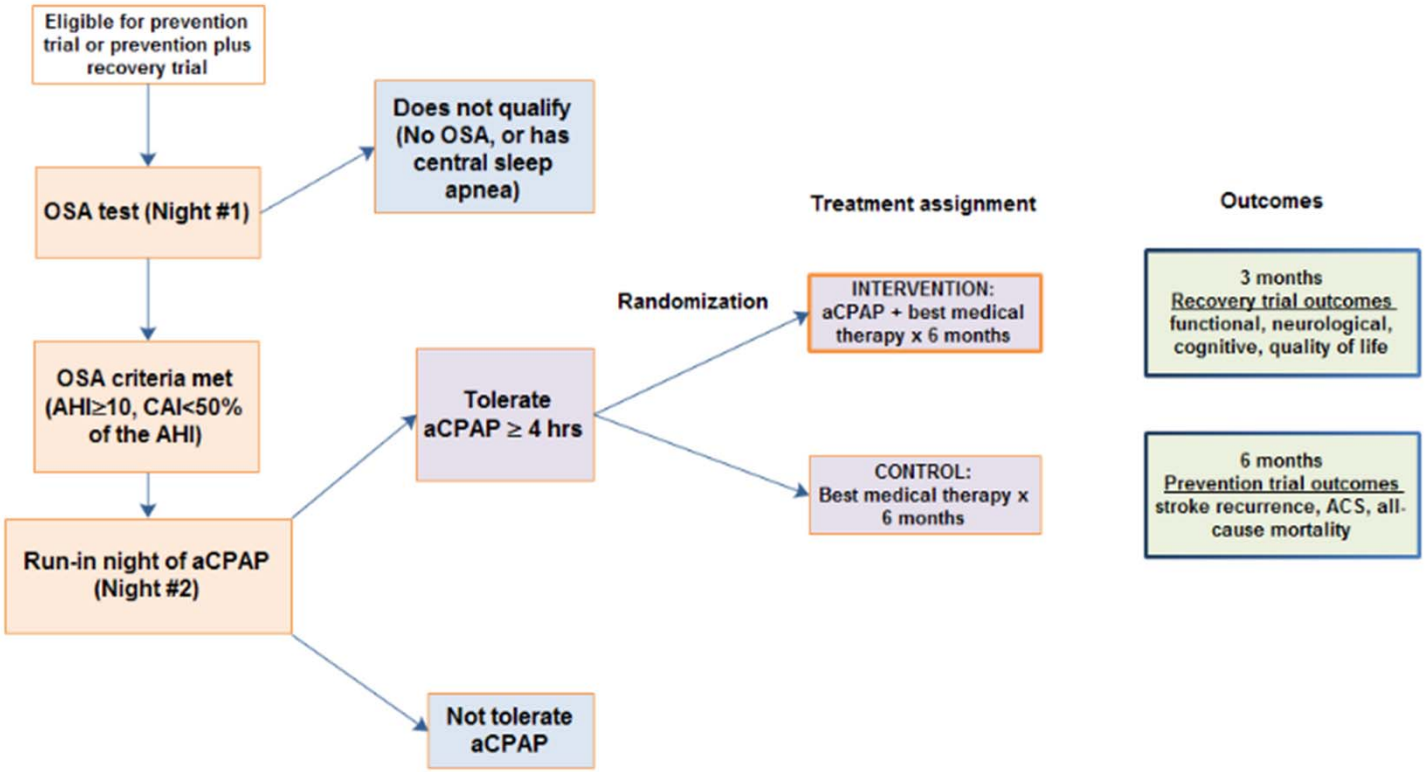
SleepSMART

Sleep for Stroke Management And Recovery Trial

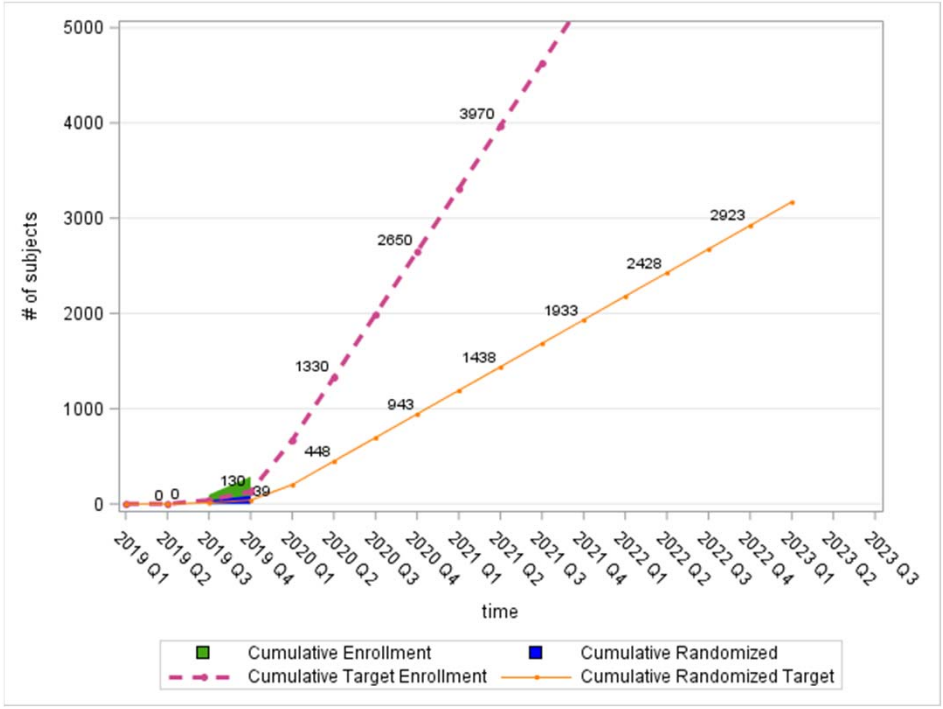
StrokeNet Meeting

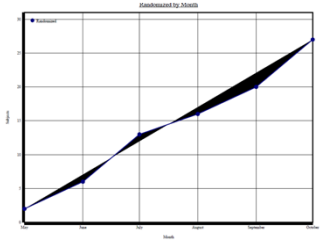
October 29, 2019

Flow


Eligible for prevention trial or prevention plus recovery trial
Does not qualify (No OSA, or has central sleep apnea)
OSA test (Night #1)
OSA criteria met (AHI≥10, CAI<50% of the AHI)
Run-in night of aCPAP (Night #2)
Tolerate aCPAP ≥ 4 hrs
Not tolerate aCPAP
Randomization
Treatment assignment
INTERVENTION: aCPAP + best medical therapy x 6 months
CONTROL: Best medical therapy x 6 months
Outcomes
3 months
Recovery trial outcomes
functional, neurological, cognitive, quality of life
6 months
Prevention trial outcomes
stroke recurrence, ACS, all-cause mortality

Overall and Expected Enrollment and Randomization

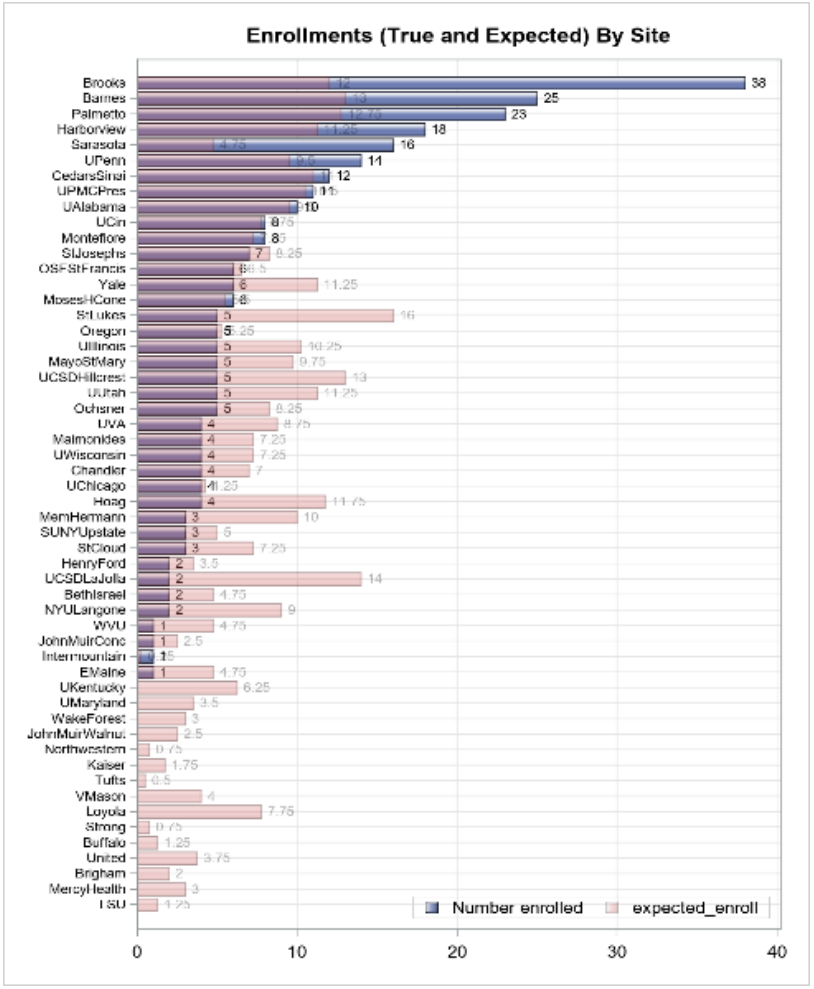




Expected assumptions:

- 2.5 enrollments/site/month
- 30% of enrollments are randomized

Enrollments (True and Expected) By Site



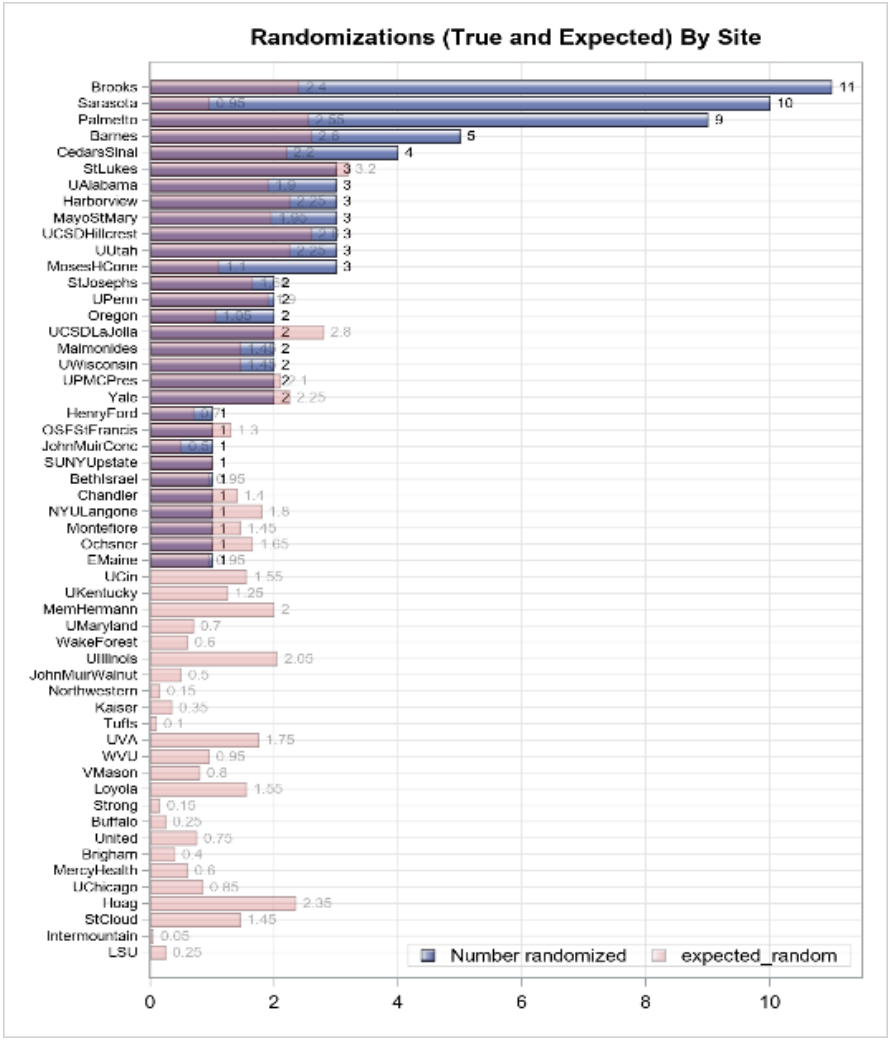
Top 5: enrolling sites

Site name	Number enrolled
Brooks Rehabilitation Hospital, Jacksonville, FL	38
Barnes Jewish Hospital, St. Louis, MO	25
Palmetto Health Richland, Columbia, SC	23
Harborview Medical Center, Seattle, WA	18
Sarasota Memorial Hospital, Sarasota, FL	16

Top 5 sites: rate of enrollment

Site name	Average enrollments per month	Number enrolled	Months released to enroll
Intermountain Medical Center, Murray, UT	10.0	1	0.1
Sarasota Memorial Hospital, Sarasota, FL	8.4	16	1.9
Brooks Rehabilitation Hospital, Jacksonville, FL	7.9	38	4.8
Barnes Jewish Hospital, St. Louis, MO	4.8	25	5.2
Palmetto Health Richland, Columbia, SC	4.5	23	5.1

Randomization by site



Randomizations: 88 total/3062

- 55 sites currently released
- Average per month randomizations: 0.6 overall
- Original goal: one randomization/site/month

Top 5: randomizing sites

Site name	Number randomized
Brooks Rehabilitation Hospital, Jacksonville, FL	11
Sarasota Memorial Hospital, Sarasota, FL	10
Palmetto Health Richland, Columbia, SC	9
Barnes Jewish Hospital, St. Louis, MO	5
Cedars-Sinai Medical Center, Los Angeles, CA	4

Top 5 sites: rate of randomizations

Site name	Average randomizations per month	Number randomized	Months released to enroll
Sarasota Memorial Hospital, FL	5.3	10	1.9
Brooks Rehabilitation Hospital, FL	2.3	11	4.8
Palmetto Health Richland, SC	1.8	9	5.1
Moses H. Cone Memorial Hospital, NC	1.4	3	2.2
Barnes Jewish Hospital, MO	1.0	5	5.2

Top 5 randomizers

- Brooks Rehabilitation Hospital (Jacksonville, FL) – 11
  - Parag Shah, MD, Taisiya Matev
- Sarasota Memorial Hospital (Sarasota, FL) – 10
  - Mauricio Concha, MD, Jeanette Wilson
- Palmetto Health Richland (Columbia, SC) – 9
  - Souvik Sen, MD, Phil Fleming
- Barnes Jewish Hospital (St. Louis, MO) – 5
  - Erin Landsness, MD, Will Holt
- Cedars-Sinai Medical Center (Los Angeles, CA) –4
  - Oana Dumitrascu, MD, Vicki Manoukian

Recommendations from most successful sites:

- **Engage:** Respiratory therapists and nurses are a must!!!!! If they helped enroll a subject, be sure to reward their team. Make sure your department and other involved parties are engaged in the trial.
- **Process:** Screening subjects as soon as they come in, screen for patients daily, engage patients/families early, email notifications of a new subject to all team members (especially RT), research team presence always in the hospital, educating patients about the trial and condition
- **Teamwork**: shared mission, collaborative work environment, accountability; coordinator-PI collaboration to screen; create strong relationships with patients

What are the most significant barriers to recruitment in Sleep SMART at your site?

patients consider protocol too complex

study team considers protocol too complex

patients reluctant to use CPAP

patients reluctant to participate in research

lack of coordinator effort/support

lack of physician engagement

patient not approached as anticipated hospitalization too short

competing trials

other

What are the most significant barriers to randomization at your site?

lack of RT/sleep tech support

difficulty operating Nox T3 device

subject unable to tolerate CPAP mask itself

subject unable to use aCPAP for at least 4 hours during run-in night

subject discharged prior to Nox T3 or run-in night

difficulty getting answers to questions from FusionHealth or University of Michigan

other

What can we do to help your site increase recruitment?

What can we do to help your site increase randomizations?

Results of survey - prior to meeting

Interactive questions

1. What are the most significant barriers to recruitment in Sleep SMART at your site? Please select your top 1-3.

Barrier to recruitment	n (%)
Patient not approached as anticipated hospitalization too short	24 (63%)
Patients reluctant to use CPAP	15 (40%)
Patients reluctant to participate in research	10 (26%)
Patients consider protocol too complex	4 (11%)
Study team considers protocol too complex	2 (5.3%)
Lack of coordinator effort/support	1 (3%)
Lack of physician engagement	0 (%)
Competing trials	0 (%)

Questions, cont.

2. What are the most significant barriers to randomization at your site? Please select your top 1-3.

Barrier to randomization	n (%)
Subject discharged prior to Nox T3 or run-in night	22 (59%)
Subject unable to use aCPAP for at least 4 hours during run-in night	15 (40%)
Subject unable to tolerate CPAP mask itself	13 (35%)
Lack of RT/sleep tech support	5 (13%)
Difficulty operating Nox T3 device	2 (5%)
Difficulty getting answers to questions from FusionHealth or University of Michigan	0 (%)

What can we do to help your site increase recruitment? RESPONSES:

- Additional hands-on training
- Allow run-in night out of hospital
- Offer CPAP device to controls at 6 months
- Tasks switch platforms (WebDCU, KOEO)
- Revise study brochure to include photos and clearer info on steps
- Colorful, simplified pamphlet

Sleep SMART Research Study

You can help us find a new treatment to prevent stroke and improve stroke recovery.
Participation is voluntary and your medical care will not be compromised should you decide not to participate. If you might be interested in being part of this important clinical research study or would like more information, please contact a member of the study team listed in this leaflet. Thank you.

SITE PI:

RESEARCH COORDINATOR:

INSTITUTION:

TELEPHONE #:

WEBSITE:

Sleep SMART

SLEEP FOR STROKE MANAGEMENT AND RECOVERY TRIAL

Version: 2018-OCT-01

Grant Number: 1U01NS099043-01A1

What is the study testing?

This study is being done to figure out whether treatment for sleep apnea, in people who have had a stroke or TIA ("transient ischemic attack" or "mini stroke") improves recovery from stroke and helps prevent future stroke, heart problems, and death

Version: 2018-OCT-01

What will happen if I participate?

Part 1: Eligibility

- We will test you for sleep apnea with a sleep apnea test
- The device records your breathing, blood oxygen, pulse, heart rhythm, and movements during the night
- If this test shows you do ***not*** have obstructive sleep apnea (OSA), your participation in the study is over

Part 2: Treatment Period

- If you have significant OSA, you will then proceed to try CPAP for a night to see if you are comfortable using it. If you are, you can proceed to randomization.
- You will be "randomized" into 1 of 2 groups: A group with CPAP and usual medical care or the other group with no CPAP and usual medical care for the next 6 months
- You have an equal chance of being in either group

Who can participate?

- Patients with a stroke or TIA within the last 14 days
- Patients who are over 18 years of age

There are several other criteria that we can review if you are interested in participating

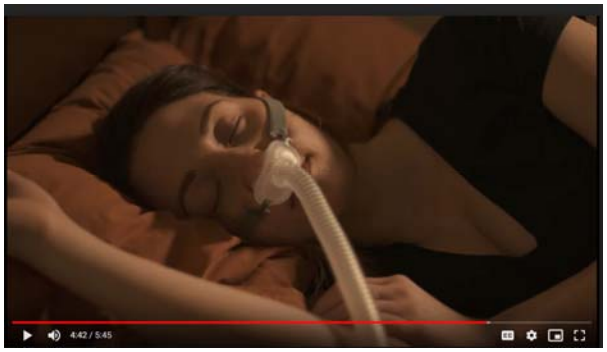
What can we do to help your site increase randomizations? RESPONSES:

- Working on adding rehab as a site
- Allow 2nd run-in night
- Provide more info about frequency of FH's interactions so sites can reassure intervention subjects of support

Enhancement of recruitment

- Recruitment introductory video (English and Spanish)
- Printed brochures (English and Spanish)
  - Plan to revise based on site feedback
- Recruitment challenges and responses document
- Instituting randomization awards for top 5% to show gratitude to sites
- Feature coordinator of the month
- Compiling a list of attractive features of Sleep SMART highlighted by sites
- Considering additional videos about research in general and CPAP
- Altered protocol to allow for readmission to sleep lab, research unit…

Survey about recruitment video

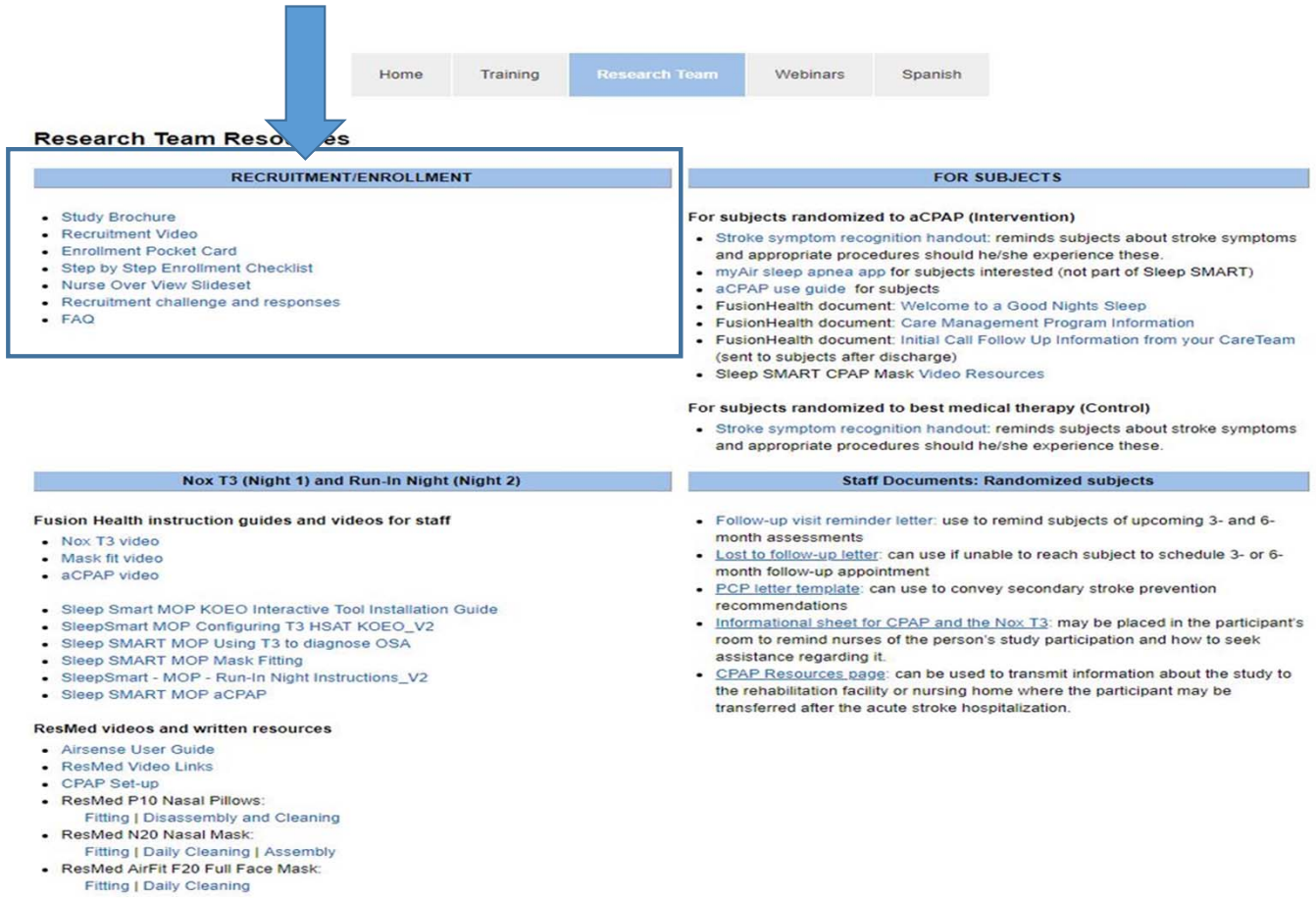


- 22 respondents
  - 24% - never use (average 1 randomized)
  - 14% - use 25% of the time (average 3 randomized)
  - 14% - use 50% of the time (average 4 randomized)
  - 10% - use 75% of the time (average 3 randomized)
  - 38% - use 100% of the time (average 3 randomized)
- All but one who have used it found it to be useful
- 4 noted no device on which to play it
- Separate video about CPAP - 86% would use
- Separate video about research – 59% would use

Equipoise

- NINDS peer review, CIRB, DSMB approved
- No definitive RCT data that any stroke outcome is improved by CPAP
- CPAP may improve, worsen, or have no effect on post-stroke outcomes
- Randomization to a no CPAP arm has been considered ethical in trials that enroll high risk CVD patients
  - Pilot stroke trials
  - SAVE, RICCADSA, and CERCAS
  - APPLES (NIH funded) randomized >1,000 patients with a mean AHI of 40 (severe OSA) to 6 months of sham CPAP
- Even in the general OSA population, the 2017 US Preventive Task Force reported no established benefit of CPAP for any health outcome aside from a modest improvement in sleep-related quality of life
- No evidence that CPAP started 6 months after stroke (or any time after stroke) is effective for stroke outcomes
  - Trial provides free OSA testing - facilitate referral to sleep medicine for CPAP, if desired.
  - Without enrollment, most patients would not know that they have OSA - screening is not part of standard of care.
  - Insurance should cover the costs of CPAP for stroke patients with OSA

nihstrokenet.org/sleep-smart-trial



Home | Training | Research Team | Webinars | Spanish

Research Team Reso…es

RECRUITMENT/ENROLLMENT

- Study Brochure
- Recruitment Video
- Enrollment Pocket Card
- Step by Step Enrollment Checklist
- Nurse Over View Slideset
- Recruitment challenge and responses
- FAQ

FOR SUBJECTS

For subjects randomized to aCPAP (Intervention)

- Stroke symptom recognition handout: reminds subjects about stroke symptoms and appropriate procedures should he/she experience these.
- myAir sleep apnea app for subjects interested (not part of Sleep SMART)
- aCPAP use guide for subjects
- FusionHealth document: Welcome to a Good Nights Sleep
- FusionHealth document: Care Management Program Information
- FusionHealth document: Initial Call Follow Up Information from your CareTeam (sent to subjects after discharge)
- Sleep SMART CPAP Mask Video Resources

For subjects randomized to best medical therapy (Control)

- Stroke symptom recognition handout: reminds subjects about stroke symptoms and appropriate procedures should he/she experience these.

Nox T3 (Night 1) and Run-In Night (Night 2)

Fusion Health instruction guides and videos for staff

- Nox T3 video
- Mask fit video
- aCPAP video

- Sleep Smart MOP KOEO Interactive Tool Installation Guide
- SleepSmart MOP Configuring T3 HSAT KOEO_V2
- Sleep SMART MOP Using T3 to diagnose OSA
- Sleep SMART MOP Mask Fitting
- SleepSmart - MOP - Run-In Night Instructions_V2
- Sleep SMART MOP aCPAP

ResMed videos and written resources

- Airsense User Guide
- ResMed Video Links
- CPAP Set-up
- ResMed P10 Nasal Pillows:
  Fitting | Disassembly and Cleaning
- ResMed N20 Nasal Mask:
  Fitting | Daily Cleaning | Assembly
- ResMed AirFit F20 Full Face Mask:
  Fitting | Daily Cleaning

Staff Documents: Randomized subjects

- Follow-up visit reminder letter: use to remind subjects of upcoming 3- and 6-month assessments
- Lost to follow-up letter: can use if unable to reach subject to schedule 3- or 6-month follow-up appointment
- PCP letter template: can use to convey secondary stroke prevention recommendations
- Informational sheet for CPAP and the Nox T3: may be placed in the participant's room to remind nurses of the person's study participation and how to seek assistance regarding it.
- CPAP Resources page: can be used to transmit information about the study to the rehabilitation facility or nursing home where the participant may be transferred after the acute stroke hospitalization.

Rehab sites?

- Provide site selection survey to any rehab sites?

Thank you!

NIMICT
NATIONAL INITIATIVE FOR
MINORITY INVOLVEMENT IN
NEUROLOGICAL CLINICAL TRIALS

CREST-2

Inclusion of Women and Minorities in CREST-2

Thomas Brott, MD
Bernadette Boden-Albala, MPH, DrPH

CREST-2

UNIVERSITY of MARYLAND MEDICAL CENTER

MAYO CLINIC

UAB

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Background

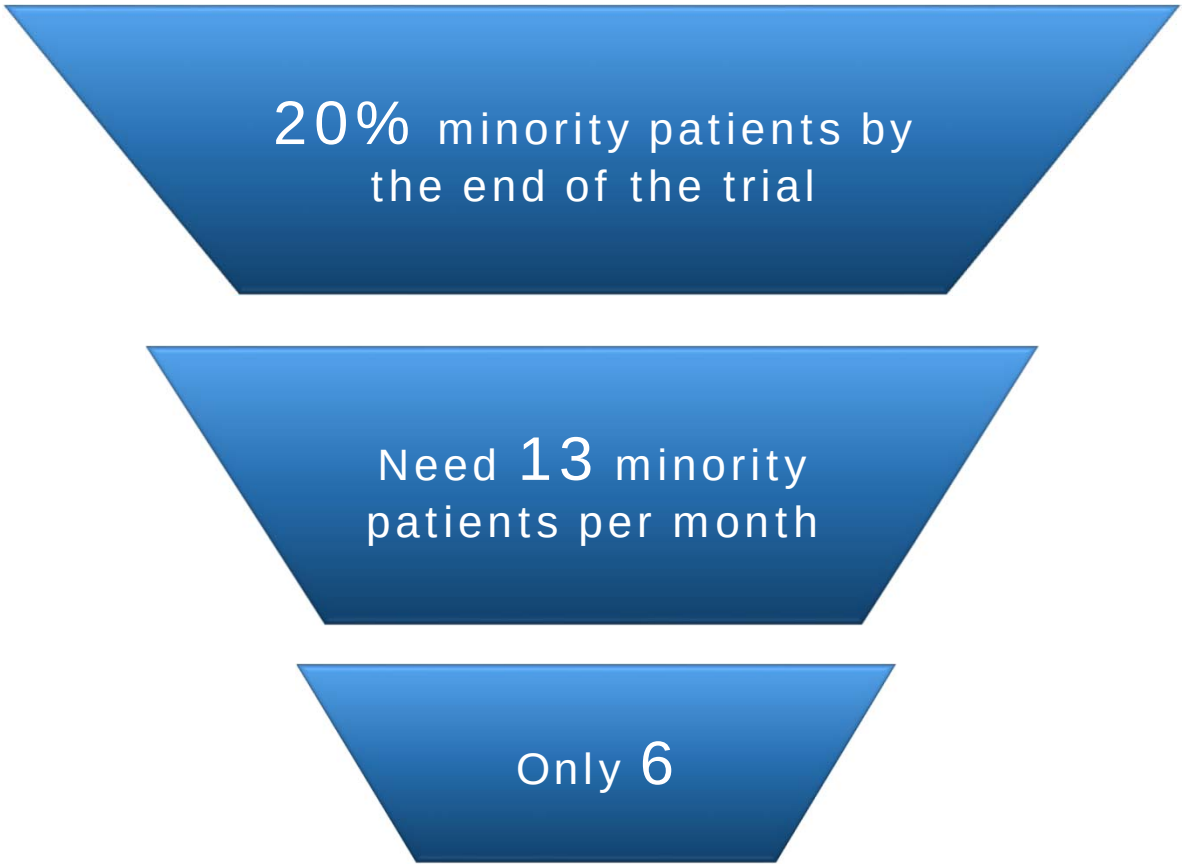
Inclusion of Women, Minorities, and Children

By law, Women and Minorities must be included in clinical research studies; in Ph III CT in numbers adequate for valid analysis

By NIH policy, children should also be included in human subjects research unless scientific/ethical reasons (NOTE: Children are < 21 years)

NOTE: difference between children according to HS regulations and children according to inclusion policy

CREST-2 Minority Recruitment Goal



CREST-2 Enrollment of Women and Under-represented Minorities

- In CREST-2, of 1545 patients*
  - 39% Women
  - 14% Minority
    - 7% African American/black
    - 5% Hispanic/Latino
    - 2% Asian

*data as of October 2019

Overall Challenges to Inclusion

1) Enhancing the screening pool

2) Converting eligible to enrolled

3) Retaining enrolled participants

NIMICT

NATIONAL INITIATIVE FOR MINORITY INVOLVEMENT IN NEUROLOGICAL CLINICAL TRIALS

Specific Aim 1: Enhance screening procedures to increase the pool of women, black, and Hispanic patients.

…we will refine existing screening procedures to address these barriers by linking sites to targeted resources and by conducting quarterly webinars focused on overcoming identified barriers. Our data suggest that this will lead to a 20% increase in women and minority patients in the CREST-2 screening pool.

Specific Aim 2: Identify and target sites with high potential for increasing women and minority patient enrollment and work with them individually to tailor a plan and implement best practices for recruitment and retention.

…[prioritize] 35 sites to enhance screening and enrollment by promoting and incentivizing adoption of best practices. …We predict this approach and collaboration with the CREST-2 team will lead to an approximately 120% increase in African American and Hispanic participants and 7% increase in women participants over the next three years of recruitment.

Specific Aim 3: Across all sites we will elevate procedures to support moving patients from eligible to enrolled and to support participant retention.

All CREST-2 sites will be given access to NIMICT's web based toolkit, NIMICT.com…will be offered NIMICT's web based Motivational Interviewing training for research staff…We predict these strategies will lead to an approximately 30% increase in African American and Hispanic participants and 3% increase in women participants over the next three years of recruitment.

NIMICT Timeline

Table 1. CREST-2 and NIMICT Partnership Timeline					
Activity	Year 1				
Diagnose barriers to women and minority enrollment	X	X			
Enhance recruitment materials and study website to be health literate, and culturally appropriate	X	X	X	X	
Work with high potential sites to create tailored plans to improve screening pools		X	X	X	
In-service CREST-2 coordinators to online toolkit, NIMICT.com	X	X			
Implement NIMICT's online MI training with interested CREST-2 coordinators		X	X		
Identify and work with 35 high priority sites to promote and incentivize best practices	X	X	X	X	
Pilot protocol for engaging with local infrastructure, i.e. primary care centers and clinics	X	X	X	X	
Monitor high priority sites to aid in implementing best practices and track progress			X	X	
Participate in monthly Women and Minority Recruitment Committee calls	X	X	X	X	
Hold quarterly calls for CREST-2 and NIMICT teams to review performance goal progress and create contingency plans as needed	X	X	X	X	
Host 2 web-based workshops	X	X	X	X	

Coordinator Survey Results

Main barrier reported to enrolling minority populations in CREST-2:

- **Not receiving referrals or seeing minority patients in their practices**

Lunch & Learns at Primary Care Practices

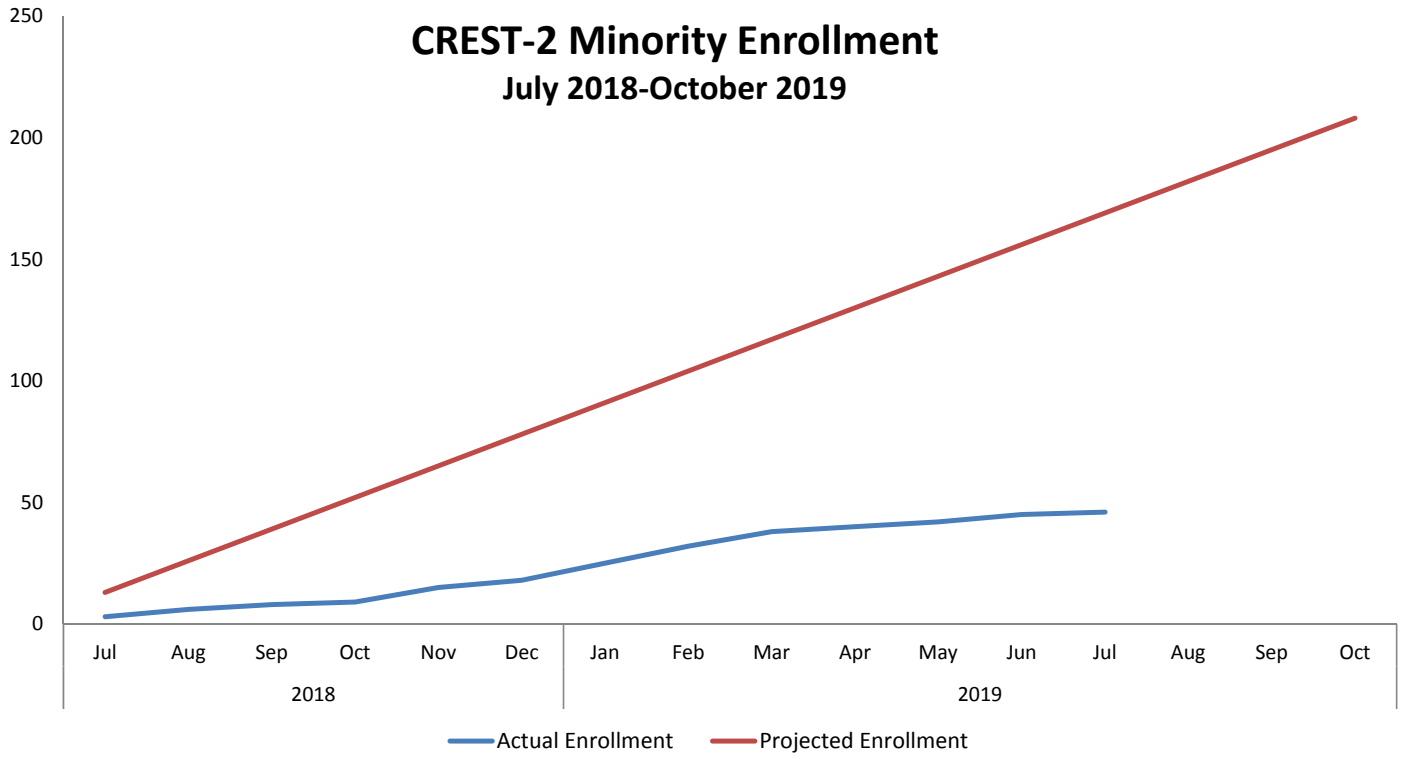
What is a Lunch and Learn? Informal outreach events hosted by a CREST-2 site PI and coordinator at clinics surrounding their practice.

Goal: to meet and share trial information in order to encourage patient referrals to the study.

Format: brief (10-15 minute) slide presentation during lunch, followed by questions and discussion.

- **All lunch costs fully reimbursed**
  - **PIs reimbursed for time**
  - **Coordinators receive a gift card**

Minority Enrollment



Physician Involvement

Barbara Tilley, Ph.D

LOCATION, Location, location

Top Sites: Minority Enrollment

- Navdeep Sangha, MD, Kaiser **LA**
- Charles Sternbergh, MD, Ochsner, **New Orleans**
- Randy Marshall, MD, Columbia, **New York City**
- Robert Beasley, MD, Mt. Sinai Medical, **Miami**
- Fayaz Shawl, MD, Washington Adventist, **DC**
- Joseph Zabramski, MD, Barrow, **Phoenix**
- Warren Strickland, MD, **Huntsville** Hospital, AL

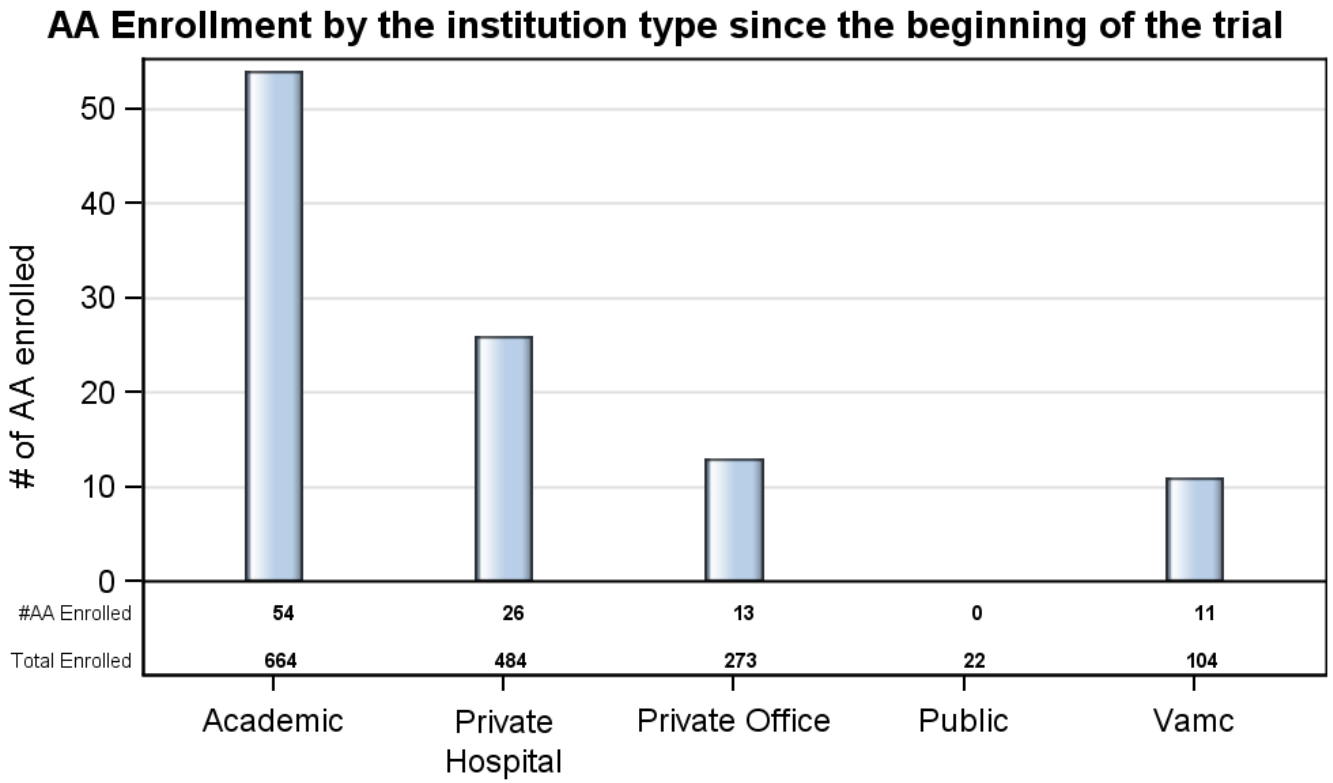
Top Sites: Minority Enrollment

Kaiser Permanente, Los Angeles, California

Ochsner Health System, New Orleans, Louisiana

Columbia Medical Center, New York City, New York

CREST-2 Enrollment of African Americans by Institution



CEAs by Race
University of Cincinnati

Race	Symptomatic
White	62
Black	13
Other	1
Total	76

Race	Asymptomatic
White	14
Black	2
Hispanic	1
Total	17

Total in the past 2 years: 93

We are still trying

CREST-2 Women & Minority Committee

Warren Strickland, MD,
CREST-2 Principal Investigator
at Huntsville Hospital, CREST-2
Women & Minorities Committee
Chair

CREST-2

CREST-2 Women & Minority Committee Members

Thomas Brott, MD, CREST-2 Principal Investigator

Kevin Barrett, MD, FAAN, CREST-2 Director of Recruitment, CREST-2

Cheryl Bushnell, MD, MS, CREST-2 Principal Investigator at Wake Forest

Bernadette Boden-Albala, MPH, DrPH, National Initiative for Minority Involvement in Neurological Clinical Trials

Claudia Moy, Ph.D, National Institute of Neurological Disorders and Stroke

Virginia Howard, Ph.D, CREST-2 Statistical and Data Coordinating Center

Linda Breathitt, RN, CREST-2 nurse research coordinator at Baptist Health Lexington

Noa Appleton, MPH, National Initiative for Minority Involvement in Neurological Clinical Trials

Kassondra Guzman, BS, CREST-2 Recruitment

Women and Minorities Committee

NIMICT and Other Efforts

- Administered and analyzed survey of 90+ CREST-2 coordinators
- Developed a 'Lunch and Learn' program to engage primary care physicians in CREST- 2 screening
- Enhanced recruitment and retention resources on CREST-2 website 'Women and Minorities' tab
- Creating additional recruitment videos and scripts for PIs and coordinators
- Speaking with individual sites to troubleshoot barriers and promote best practices
- Contracted with Life Line screening to increase referrals to CREST-2

All of us need ideas for improvements

CREST-2 Partnership with Life Line Screening

NIH StrokeNet Network Meeting

James Meschia, MD
Department of Neurology
Mayo Clinic, Jacksonville, FL

How Life Line Works

Event Promotion
Screening events are confirmed and promoted to relevant audience

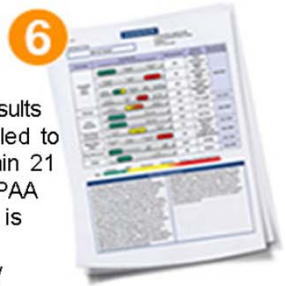
Registration
Life Line Screening Response Center registers patients for event by appointment

Patient Check-in
Medical history, disclosures and patient chart is created

Complete the Circle of Care
Hospital, Specialist and PCP are now in Sync and a Proper Preventive Care Plan is in Place for the Patient for the Upcoming Year.

Screening
60-90 minute Process to complete all screenings with clinical team

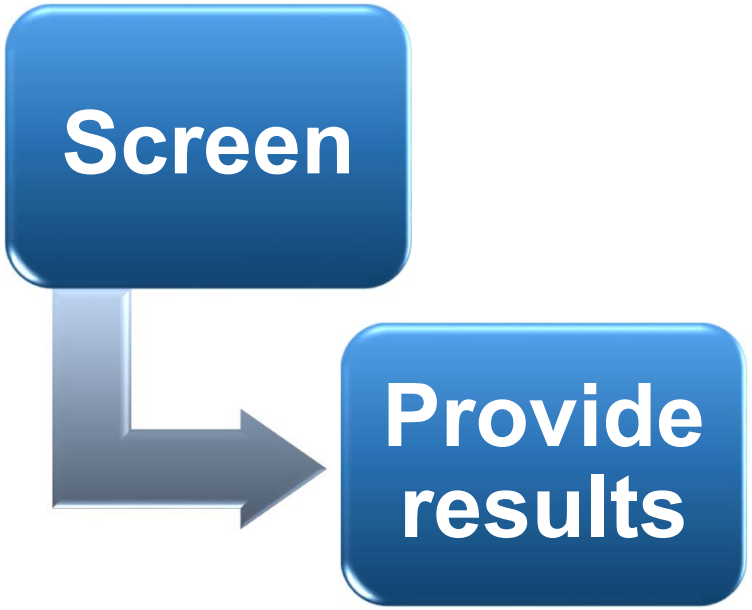
Physician Review
State licensed physician reviews and confirms test results



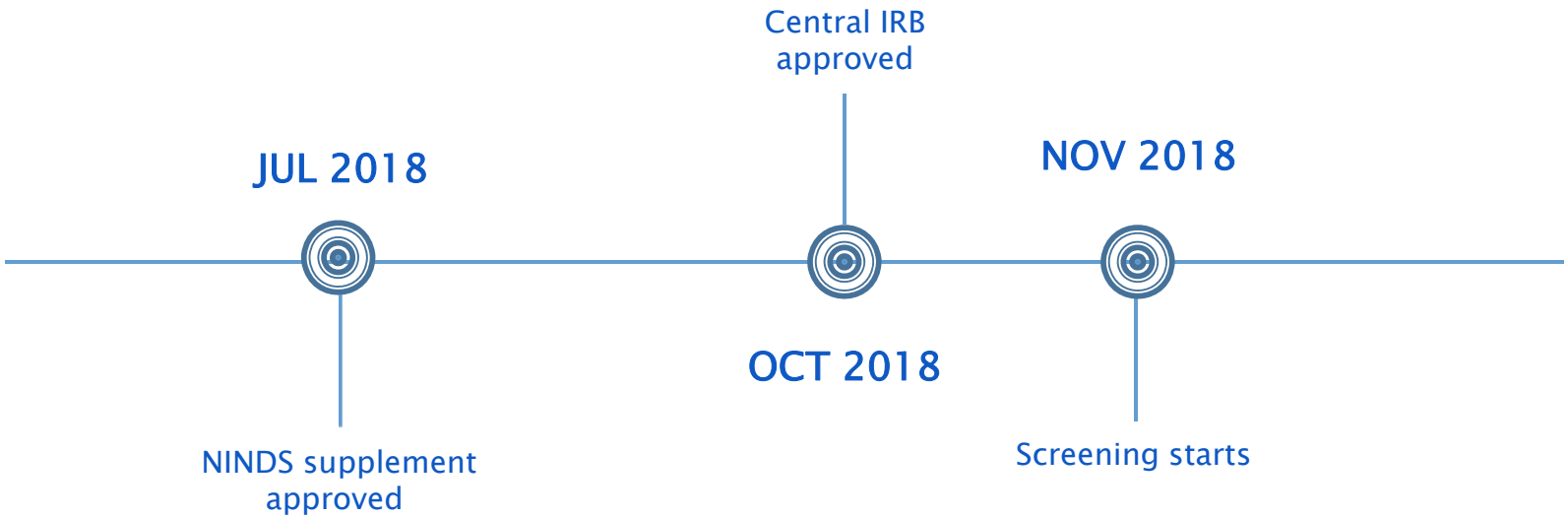
Results
Non Critical Results are mailed/emailed to participants within 21 days and all HIPAA authorized data is provided to the hospital monthly

Abnormal and Critical Result Follow up
Calls should be made by the provider or on their behalf to help facilitate a referral or establish a relationship

Life Line Screening
National Access



- In 2017, 17,000 screening events 49 states
- 1 million people screened


JUL 2018
NINDS supplement approved
Central IRB approved
OCT 2018
NOV 2018
Screening starts

Program Work Flow for PSV 230-299 cm/s

1. Ultrasound data is transmitted to LLS
2. PSV 230-299 cm/s is found
3. Within ~21-days:
    a. Results sent by mail to the screenee
    b. Follow-up phone call made to the screenee by LLS where CREST-2 is introduced and screenee is asked if they are interested in being evaluated for trial
    c. Email sent by LLS with link to sign HIPAA form and link to CREST-2 FAQs
4. Contact information forwarded to U Maryland

Program Work Flow for PSV ≥ 300 cm/s

1. Screenee provided results on-site
2. Results are reviewed by LLS Clinical and a follow-up phone call is made to the screenee within 72 hours of the screening where CREST-2 is introduced and screenee is asked if they are interested in being in trial
3. If screenee agrees, an email is sent by LLS with link to electronically sign a HIPAA form and link to CREST-2 FAQs . The HIPAA form authorizes release of their contact information to U Maryland for referral to a CREST-2 center for formal diagnosis
4. Ultrasound data is transmitted to LLS central office for review over a 21-day period
5. Within ~21-days following screening, formal screening results sent by mail by LLS.

Communication Between LLS-Maryland

- LLS shares screening results of individuals with PSV of 230-299 cm/s and with PSV ≥ 300 m/s with University of Maryland using a HIPAA-compliant, secure electronic channel.

- In accordance with geocoded regions on the country, University of Maryland will contact the nearest CREST-2 center with screenee contact information.

Communication Between Maryland-CREST-2 Center

- CREST-2 center contacts the screenee referred to them by University of Maryland to set up an appointment for formal diagnosis.
- CREST-2 center evaluates the screenee and establishes the diagnosis.
- If found to be eligible for CREST-2, the Center will offer the patient participation in the trial.
- CREST-2 centers update the University of Maryland for tracking purposes:
  - Date patient is seen in the clinic
  - Formal diagnosis results: Carotid ultrasound/CTA/MRA report
  - Treatment recommendation (Medical management/CEA/CAS)
  - Eligibility
  - Randomized into CREST-2

Quarterly Results
April 1st – June 30th, 2019

Race	# of Carotid Screens	% Positive
Caucasian	52,560	0.28
African American	6,936	0.20
Hispanic	3,622	0.11
Asian	1,791	0.28
Native American	298	0.36
Other	2,178	0.51

CREST-2 Lifeline Results
November 15th – October 15th, 2019

- 92 CREST-2 Centers participating
- 117,137 patients screened (November 15th-June 30th)*
- 157 referrals from Lifeline to 61 CREST-2 Centers
- 2 patients randomized
- 0 minority patients randomized
- 0 African Americans randomized

*Through June 30th only

Conclusions

- Ambitious national CREST-2 screening program established in partnership with NINDS.
- Screening goals by total #s accomplished.
- Very modest # of general referrals generated.
- So far, the primary goal of increasing enrollment of minority patients, particularly of African Americans, appears to be unrealistic with the general carotid screening approach.

Thanks

- To Brajesh Lal and the Team at University of Maryland
- To our collegial and “let’s get it done” partners at Lifeline
- To Claudia, Scott, and Clint at NINDS

LLS Screening events over 12 months that were located within a 20-mile radius around a CREST-2 center Top 10 locations ranked by number of carotid stenosis identified.

CREST-2 Center name	City	State	Zip code	Adults with PSV≥230	Women with PSV≥230	Minorities with PSV≥230	Total screening events conducted
Columbia University Medical Center	New York	NY	10032	92	38	46	260
Hackensack University Medical Center	Hackensack	NJ	7601	67	21	38	232
Houston Methodist Hospital	Houston	TX	77030	59	38	33	103
Lankenau Medical Center	Wynnewood	PA	19096	59	33	17	134
University of Washington Harborview Medical Center	Seattle	WA	98104	59	29	4	94
The University of Chicago Medical Center	Chicago	IL	60637	59	25	17	158
UPMC Presbyterian University Hospital	Pittsburg	PA	15213	38	13	4	78
Yale New Haven Hospital	New Haven	CT	6520	29	13	8	40
University of Kansas Medical Center	Kansas City	KS	66160	25	13	4	99
Kaiser Permanente San Francisco	South San Francisco	CA	94115	25	0	13	69

Quarterly Results by Sex
April 1st – June 30th, 2019

Male	
# of Carotid	% Positive
20,804	.36
2,387	.21
1,369	.15
722	.42
105	0
864	.46

Female	
# of Carotid	% Positive
31,756	.23
4,549	.20
2,253	.09
1,069	.19
193	.52
1,314	.53

Tips for hosting Lunch and Learns

1. **Keep it informal**. Give a short and engaging presentation and leave plenty of time for questions
2. **Take materials with you** (posters, brochures, patient handouts, inclusion/exclusion criteria)
3. Coordinators should **follow up over the phone** with nurses or physicians within 2-4 days after each event and can also call every 2-3 weeks to check in
4. **Lunch logistics**: CREST-2 will reimburse for lunch expenses and time spent planning/hosting events

Promoting CREST-2 In Your Community

- Set up a booth at a local **health fair**
- Promote the CREST-2 trial at **local conference**
- Post flyers and leave brochures in nearby clinics or **primary care practice**
- Present at **Community Research Advisory Board** meetings
- Talk to your hospital **CTSI or public/ community relations department** about additional ways to publicize CREST-2 within your hospital and community

What are the barriers to screening in a primary care setting?

- Patient perspective:
  - Continuity of care
  - Insurance concerns
  - Transportation/Convenience
  - Follow-up

- Physician perspective:
  - Continuity of care
  - Concern about randomization to surgical arm
    - Not knowing the interventionist/surgeon who will perform the procedure

Why host Lunch and Learns?

- Primary care doctors can be a key source of patient referrals, but often have little knowledge about CREST-2.
- Can help minority and other underserved populations gain access to top quality care provided by CREST-2
- Meeting face-to-face is key to building relationships.
- Can be a great publicity opportunity for your practice.

Identifying Primary Care Sites for Outreach

- University settings might have a **Referring Physicians Office**
  - This office may have numbers on how many patients have been referred from each practice previously.

- Screening for general population: Who?
  - Bruit – most common reasons PCPs refer patients for dopplers
  - Coronary Disease

Promoting CREST-2 In Your Hospital

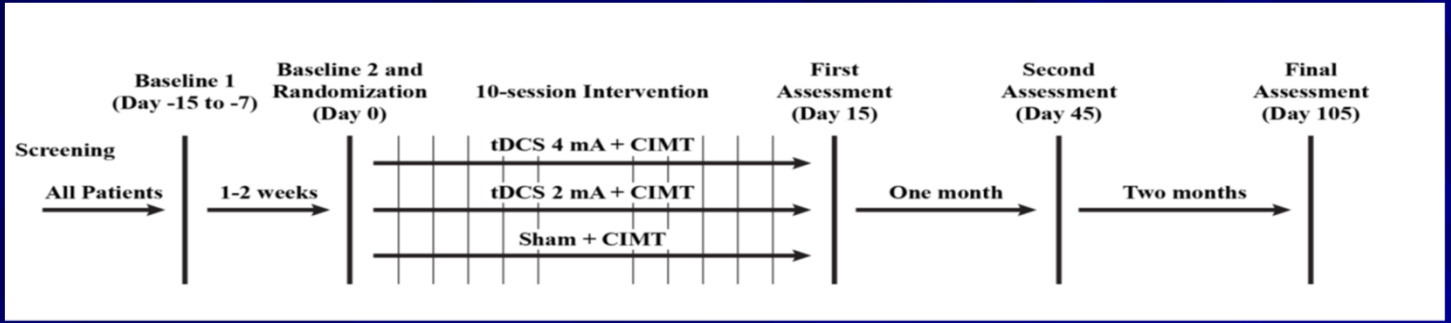
- Present at Departmental or Division **Conferences**
- Host **Grand Rounds** or **CME** meetings
- Post information about CREST-2 on your hospital or **practice website**
- Send reminders in hospital staff **newsletters or email blasts**
- Present at **physician meetings** and calls
- Enter CREST-2 information in your hospital or clinic **'StudyFinder' syste**m
- Post flyers and leave brochures in **ultrasound labs**
- Pass out **inclusion/exclusion cards** to other departments or teams within your hospital system.

TRANSPORT2: Updates

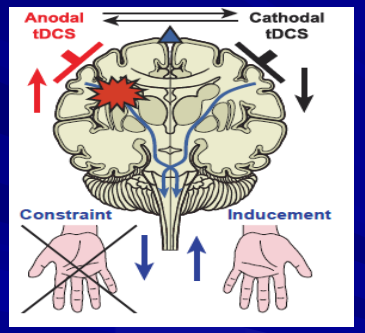
Wayne Feng MD MS
Duke University Medical Center

Gottfried Schlaug MD PhD
BIDMC/University of Massachusetts

TRANScranial direct current stimulation for POst-stroke motor Recovery – a phase II sTudy (TRANSPORT2)



- To determine whether there is an initial overall treatment effect (FM-UE) among 3 dosing groups:
  - sham + mCIMT
  - 2 mA + mCIMT
  - 4 mA + mCIMT
- Efficacy (FM-UE change) is measured at day 15 after the initiation of the 10-day intervention.
  - Both Intent-to-treat and per protocol analysis.

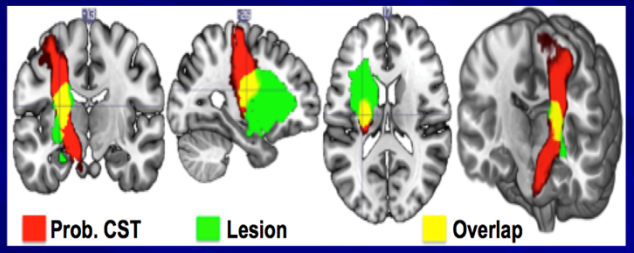


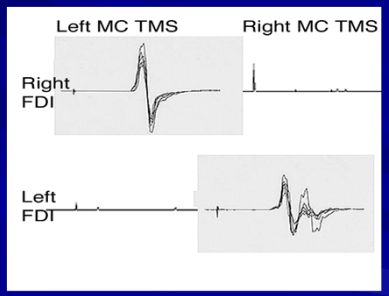
Secondary Aims

- To confirm that the proposed intervention is **safe**, **tolerable**, and **feasible** to administer in a multi-site trial setting
- **Endpoints**
  - Safety: Rate of Adverse Events
  - Tolerability: Visual Analog Scale
  - Feasibility: Intervention Completion Rate

Exploratory Aims

- To examine whether wCST-LL (structural assessment of integrity of descending motor tract) or MEPs (functional assessment of integrity of descending motor tract) or combination of both are correlated with changes in FM-UE scale, and evaluate the utility of these measures as biomarkers for subject selection criteria in the future confirmatory Phase III study
- To examine whether functional or structural changes in motor tracts correlates with changes in impairment and functional motor activity induced by the intervention.





PATIENT SELECTION

Eligibility: Inclusion

- **Each subject must meet <u>all</u> of the following criteria to participate in this study:**
- 1) 18-80 years old; and
- 2) First-ever unihemispheric ischemic stroke radiologically verified and occurred within the past 30-180 days; and
- 3) >10° of active wrist extension, >10° of thumb abduction/extension, and > 10° of extension in at least 2 additional digits; and
- 4) Unilateral limb weakness with a Fugl-Meyer Upper Extremity score of ≤ 54 (out of 66) to avoid ceiling effects; and
- 5) An absolute difference of FM-UE scores between the two baseline assessments that is ≤ 2 points indicating stable motor impairment; if subject is not stable, then he/she will be invited for a reassessment after 2 weeks (but no more than 3 reassessments); and
- 6) Pre-stroke mRS ≤2; and
- 7) Signed informed consent by the subject or Legally Authorized Representative (LAR)

Eligibility: Exclusion

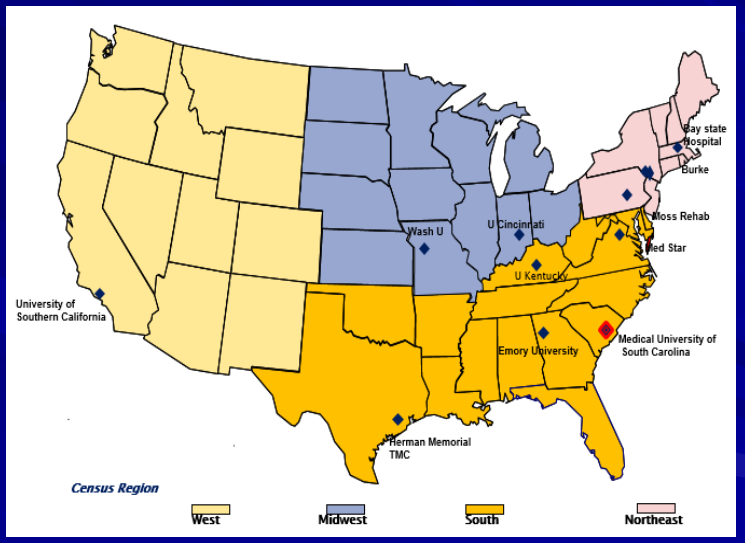
- Each Subject who meets any of the following criteria will be excluded from the study:
- 1) Primary intracerebral hematoma, subarachnoid hemorrhage or bi-hemispheric or bilateral brainstem ischemic strokes;
- 2) Medication use at the time of study that may interfere with tDCS, including but not limited to carbamazepine, flunarizine, sulpiride, rivastigmine, dextromethorphan;
- 3) Other co-existent neuromuscular disorders (pre- or post-stroke) affecting upper extremity motor function;
- 4) Other neurological disorders (pre- or post-stroke) affecting subject's ability to participate in the study;
- 5) Moderate to severe cognitive impairment defined as Montreal Cognitive Assessment (MOCA) score < 18/30;
- 6) History of medically uncontrolled depression or other neuro-psychiatric disorders despite medications either before or after stroke that may affect subject's ability to participate in the study;
- 7) Uncontrolled hypertension despite medical treatment(s) at the time of randomization, defined as SBP≥185 mmHg or DBP≥110 mmHg (patient can be treated, reassessed and randomized later);

Eligibility: Exclusion

- 8) Presence of any MRI/tDCS/TMS risk factors including but not limited to:
  - 8a) an electrically, magnetically or mechanically activated metallic or nonmetallic implant including cardiac pacemaker, intracerebral vascular clips or any other electrically sensitive support system;
  - 8b) a non-fixed metallic part in any part of the body, including a previous metallic injury to eye;
  - 8c) pregnancy (effects of MRI, TMS, and tDCS on the fetus are unknown);
  - 8d) history of seizure disorder or post-stroke seizure;
  - 8e) preexisting scalp lesion under the intended electrode placement or a bone defect or hemicraniectomy;
- 9) Planning to move from the local area within the next 6 months;
- 10) Life expectancy less than 6 months;
- 11) Has received Botulinum toxin injection to the affected upper extremity in the past 3 months prior to randomization or expectation that Botulinum will be given to the Upper Extremity prior to the completion of the last follow-up visit;
- 12) Concurrent enrollment in another investigational stroke recovery study;
- 13) Doesn't speak sufficient English to comply with study procedures;
- 14) Expectation that subject cannot comply with study procedures and visits.

TRANSPORT2 SITES

- **Medical University of South Carolina (Michelle Woodbury PhD)**
  - Kelly Krajeck; Emily Grattan; Scott Hutchison and Will Devries
- **MedStar Health Research Institute (Alexander Dromerick MD)**
  - Shashwati Geed; Juby Matthews; Abigail Mitchell; Preethy Freit & Katie Larson
- **Burke Rehabilitation Institute (Tomoko Kitago MD)**
  - Joshua Silverstein; Marissa Wuennemann ; Katherine Friel & Heather Lane
- **Emory University (Steve Wolf PhD PT)**
  - Michael Borich; Marsha Bidgood; Heather Stewart & Theresa McLaughlin
- **University of Alabama Birmingham (Ling Chen MD)**
  - Tammy Davis; David Morris; Tara Pearce & Rodolphe Nenert
- **University of Southern California (Beth Fisher PT PhD)**
  - Clarisa Martinez; Clare Binley; Tasha Hsu and Jorge Caro
- **University of Kentucky (Lumy Sawaki MD PhD)**
  - Luther Pettigrew; Elizabeth Powell; Patricia Arnold & Cessandra Ginn
- **University of Cincinnati (Oluwole Awosika MD)**
  - Emily Wasik; Emily Goodall; Emily Staggs & Kari Dunning
- **Washington University (Catherine Lang PhD PT)**
  - Jenny Babka; Christine Gordon; Jull Newgent; Maggie Bland & Alex Carter
- **Beth Israel Deaconess MC (Gottfried Schlaug MD PhD)**
  - Michelle Lantaigne; Andrea Norton; Anant Shinde & Sebastein Paquette
- **Moss Rehabilitation Institute (Dylan Edwards PhD PT)**
  - Stephaine Farm
- **Memorial Hermann – TMC (Gerard Francisco MD)**
  - Dory Parker; Erin Edenfield; Yen-Ting Chen & Chad Tremont

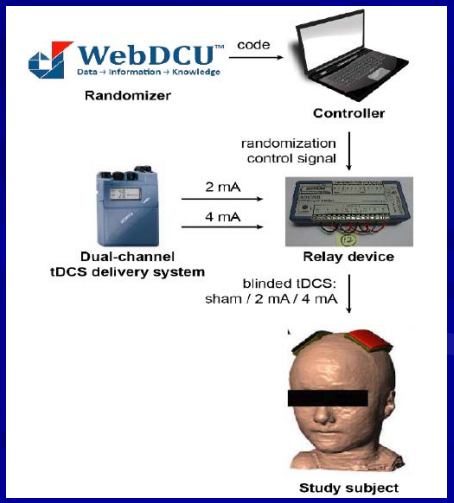


TRANSPORT2 Time Line

- NOA released (08/15/2018)
- cIRB approved (10/29/2018)
- Decide to add a training participant protocol (12/2019)
- First investigator meeting/training workshop in Charleston (02/25-02/26/2019)
- First training participant enrollment (03/30/2019)
  - 27 training participants enrolled
- First study participant enrollment (09/09/2019)
- 3/129 (2.3%) enrolled (as 10/28/2019)
- Initial targeted last patient enrollment is Jan 2022 (27 months, 4.5 participants per month vs. 3.3 participants per month)

Standardization & Quality Control

- TMS protocol
- tDCS protocol
- MRI protocol
- Outcome assessment certification process
  - Fugl-Meyer Upper Extremity scale
    - Online certificate, workshop, self & central assessment
  - Wolf Motor Function Test
    - Workshop, self-central assessment
  - Stroke Impact Scale
    - Workshop, self-central assessment
- Constraint-induced movement therapy (CIMT) certification process



Outcome Assessment Certification Process

Outcome	First Pass	2nd Pass	Third Pass	Not yet pass
Fugl Meyer Upper Extremity Scale	9	4	1	1
Wolf Motor Function Test	5	10	n/a	n/a
Stroke impact scale	8	7	n/a	n/a

* 15 raters submitted certification process

Current Enrollments

#:	Site:	Total Enrolled	In Screening	Being Scheduled	Total Screenfails
1	MUSC			1	1
2	Burke Rehab				
3	Emory	1	1		2
4	Baystate*				
5	MedStar				
6	UAB				
7	USC/Keck				
8	U. Kentucky				
9	TIRR				1
10	U. Cincinnati	2	1		3
11	Barnes Jewish				
12	Moss Rehab			3	2

* Site has not been activated yet

TRANSPORT2 Time Line

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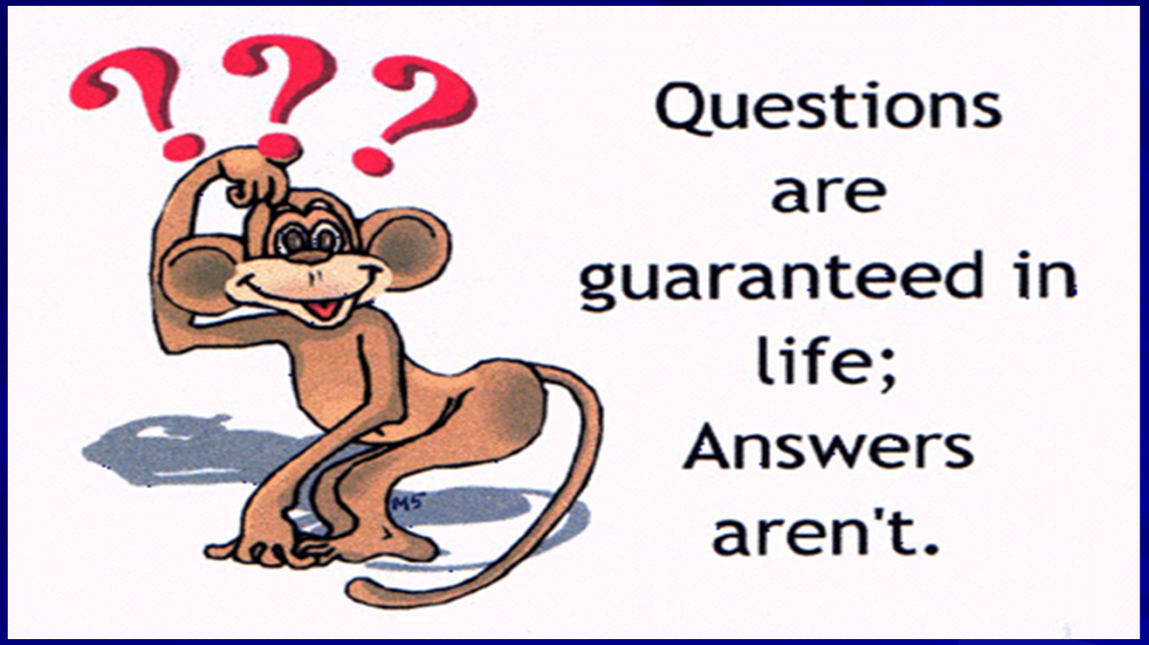
New Barriers & Challenges

- ***The main challenges is to find the eligible participants and put them in the study***
  - Inclusion criteria issues (first-ever stroke, two baseline assessments, imaging & TMS assessments)
  - The initial followed patients turned out to be too good/bad(outcome prediction issue)
  - Patient is still receiving rehab therapy
  - Patient access issue (i.e. Burke)
  - Trial competitions

Solutions?

- Consider to add to 2-3 sites
- Consider to use social media to assist patient enrollment
- More engagement between Transprt2 spoke site with RCC main hub
- All Sites meeting vs. individual site meeting

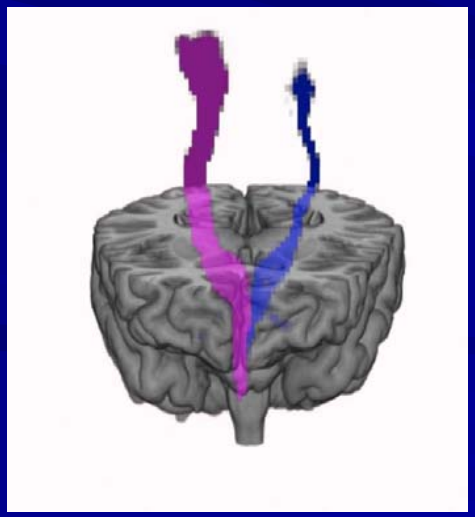
Questions?



Please kindly refer to patients to TRANSPORT2

Wayne.feng@duke.edu

Neuromodulation & Stroke Recovery Lab



By joining ARCADIA-CSI, you will make a big difference with minimal effort !

Investigators, to make ARCADIA-CSI as attractive as possible we have:

1. Maximized study reimbursement
2. Minimized your workload

Participants, ARCADIA-CSI is a simple study that won't take much of your time. If you sign up, you will undergo:

1. Annual cognitive assessments by telephone (22 min)
2. A brief (15 min) MRI at the end of the ARCADIA study

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

MOST

MOST Update

8/28/2019: CIRB approval of protocol amendment to single blind design

10/10/2019: First site released to enroll (4 sites released as of 10/25/2019)

10/15/2019: First subject randomized at Memorial Hermann

1/31/2020: Target 75 sites released to enroll

University of CINCINNATI

MUSC MEDICAL UNIVERSITY of SOUTH CAROLINA

UTHealth The University of Texas Health Science Center at Houston

MEMORIAL HERMANN Texas Medical Center

UNIVERSITY OF IOWA HEALTH CARE

What is your site's biggest barrier to site activation

Training of coordinators and investigators

Pharmacy training and readiness

IRB approval process

Site activation and release

I-ACQUIRE Clinical Site Progress

Clinical Sites	CTA	CIRB	Site Ready	Enrolled
Ann Arbor	✓	✓	prep	
Baltimore	Pending	---	---	
Boston	✓	✓	✓	2
Chicago	✓	✓	prep	
Cincinnati	✓	✓	prep	
Columbus	✓	✓	✓	
Houston	✓	✓	prep	
La Jolla	✓	✓	prep	
New Haven	✓	✓	Prep	
Philadelphia	✓	✓	prep	
Roanoke	✓	✓	✓	3
Total	**10**	**10**	**3**	**5**

What impact has I-ACQUIRE had upon your site in working with your pediatric arm, and what implications does that have for the pediatric proposals coming through the pipeline?

Not applicable

Great to work with our pediatric site, hope that means greater enthusiasm for any future pediatric trials

Has helped bridge relationships and work through logistics to bring cutting edge research to our facility and neighboring sites

Unable to negotiate a partnership between RCC and childrens hospital due to the study requirements/budget. This was due to the number and expense of in-home PT visits required by I-ACQUIRE.

Of course you want to join the first ICH prevention study – ASPIRE – in recent NIH history!

- This is a great trial to contribute to an active clinical practice question and a wonderful way to build out your StrokeNet trial portfolio!

- Start thinking about your screening, consent and randomization workflow!

ASPIRE

Magdy Selim, MD, PhD
Pooja Khatri, MD
Sharon Yeatts, PhD
Jonathan Rosand, MD, MSc
Ashkan Shoamanesh, MD, FRCPC
Steven Greenberg, MD, PhD
Enrique Leira, MD, MS
David Tirschwell, MD, MSc
Daniel Woo, MD, MS

StATins Use in intracerebral hemorrhage patieNts

Beth Israel Deaconess Medical Center
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL
NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY
Funded by a Grant from the National Institutes of Health
CSC CNC
SATURN

Objectives and Overall Design

- To determine whether continuation vs. discontinuation of statin drugs after spontaneous lobar ICH is the best strategy
  - MACCE
  - Recurrent ICH
- To assess whether the decision to continue/discontinue statins should be influenced by an individual's APO-E genotype
- PROBE design
- 1456 subjects
- 140 sites

- Patients with spontaneous lobar ICH aged ≥50 years who are taking statins ICH onset
- Randomization 1:1 within 7 days of ICH onset
- Repeated structured assessments by phone for 24 months
  - MACCE
  - mRS
  - T-MoCA
  - EQ-5D

SATURN

Timeline

	May 2018	Dec 2018	April 2019	June 2019	Sep 2019	Oct 2019	Dec 2019	Jan 2020	Feb 2020
Study approved by NIH/NINDS Council	✓								
cIRB Approval		✓							
Clinicaltrials.gov Registration			✓						
Sites Selection			✓						
DSMB Review				✓					
NOA Receipt					✓				
CTA & cIRB packets to sites						P			
MOP finalized							P		
CRF finalized & programmed								P	
IM/Webinar								P	
Health Canada NOL								P	
Begin Enrollment									P

SATURN

Questions

- Magdy Selim (PI)

  mselim@bidmc.Harvard.edu

  Tel: 617-632-8913

- Kimberlee Bernstein (NCC SATURN Project Manager)

  gammk@ucmail.uc.edu

  Tel: 513-558-3970

SATURN

We are considering a series of webinars instead of an in-person investigator meeting. In your opinion:

This is more efficient and productive than an in-person meeting

This is likely to decrease enthusiasm for the study

An in-person meeting is certainly preferable

I have no preference. Either approach is fine

CREST-H The Holy Grail of Cognitive Impairment

If:

Chronic hypoperfusion causes cognitive impairment and that impairment is reversible…

Then:

We have an alternative reason to treat patients with "asymptomatic" carotid artery stenosis. (because they aren't actually symptomatic)

CREST-H FAQs

1. **Can we use CT perfusion instead of MRI?**

   -- Yes. CT perfusion is recommended as a backup to MRP. MRI is preferred as it gives us information for secondary aims about silent infarcts, WMH, and microbleeds.

2. **How much time does the patient spend in the scanner?**

   -- The total scanning time for MRI is 22 minutes. CT is even shorter.

3. **When should CREST-H consent take place?**

   -- Signing consent needs to take place after CREST-2 randomization. We recommend introducing CREST-H at the time of CREST-2 consent. (Mention cognitive outcomes and the extra $100.)

What is the biggest obstacle to enrollment into CREST-H at your site?

Patients are unwilling/unable to undergo additional MRI

Budgetary constraints

Enrollment in CREST 2

English speaking subjects only

No obstacles

STEP-STONE

StrokeNet Thrombectomy Platform – Starting with Optimization of Eligibility

StrokeNet Endovascular Platform

What is a Platform Trial?

An experimental infrastructure to evaluate multiple treatments, often for a group of diseases, and intended to function continually and be productive beyond the evaluation of any individual treatment

The NEW ENGLAND JOURNAL of MEDICINE

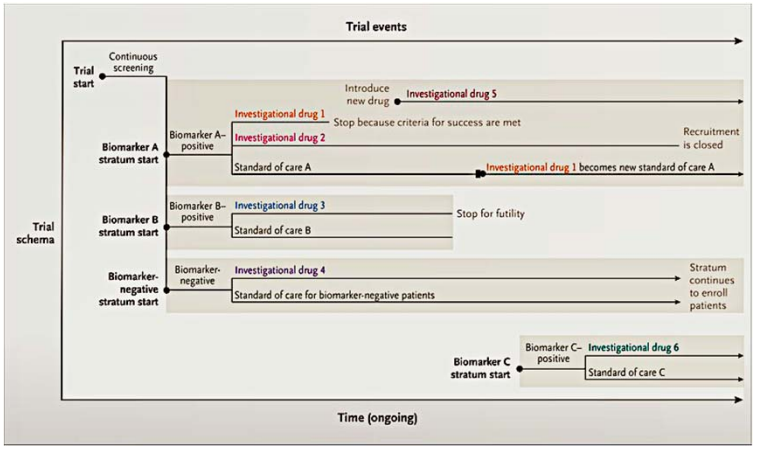
REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

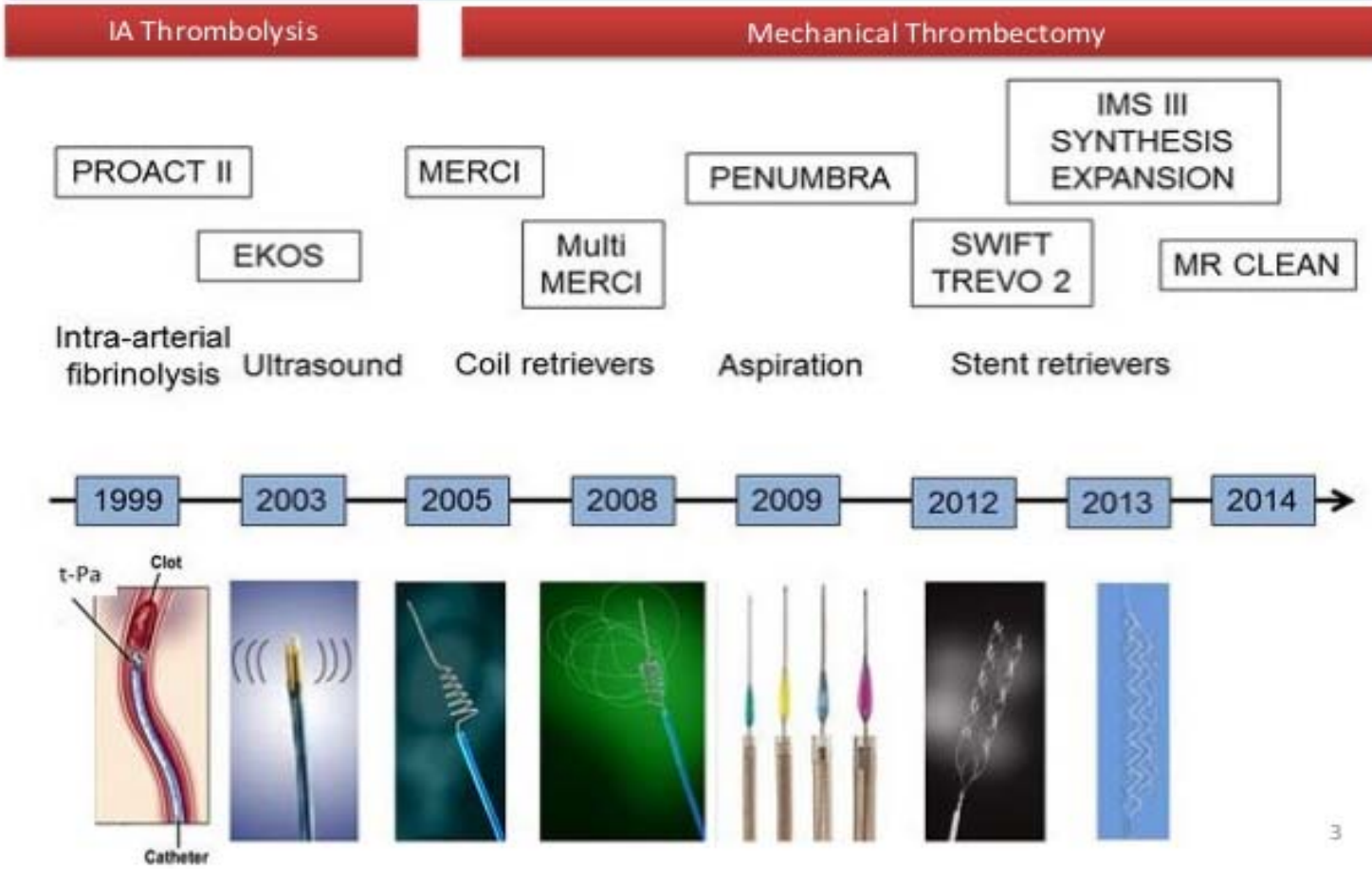
Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.



Woodcock J, NEJM, 2017.

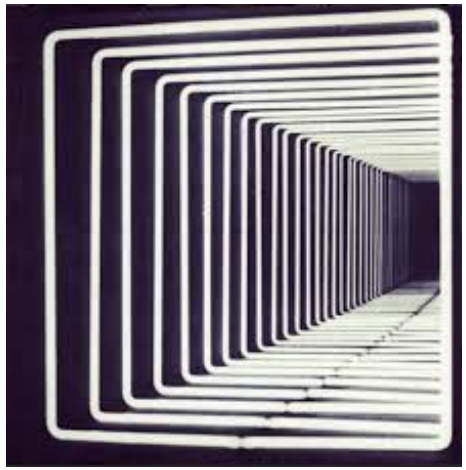
Evolution of endovascular techniques for acute ischemic stroke and clinical trials.

(Pierot et al., 2015)



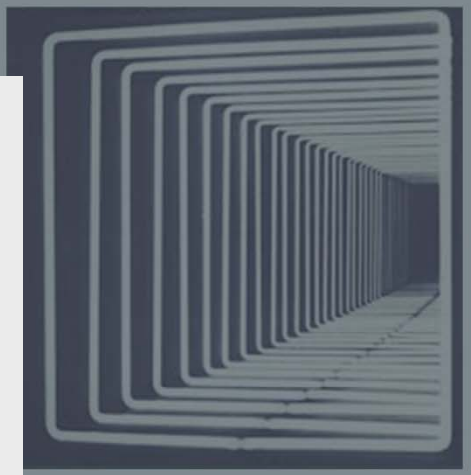
Current Approach to Clinical Trials

- **MR Clean**
  - Does it work in the ultra early population?
- **DAWN/ Defuse**
  - Does it still work when treating a little later?
- **Future Trial**
  - Another extension
- **Future Trial 2**
  - And another…



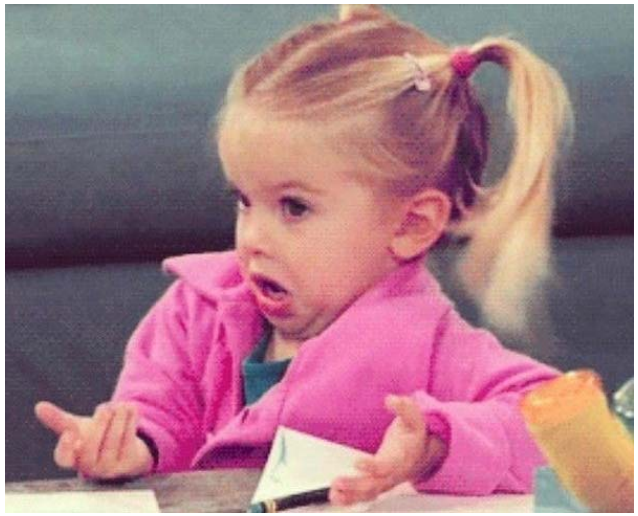
Current Approach to Clinical Trials

NINDS has put all scientific questions related to endovascular therapy (EVT) on hold for grant submission, and instead encouraged StrokeNet to develop a platform approach to address these and future questions more efficiently.



Instead…

Can we design a trial to efficiently answer the question, who ***shouldn't*** we treat?

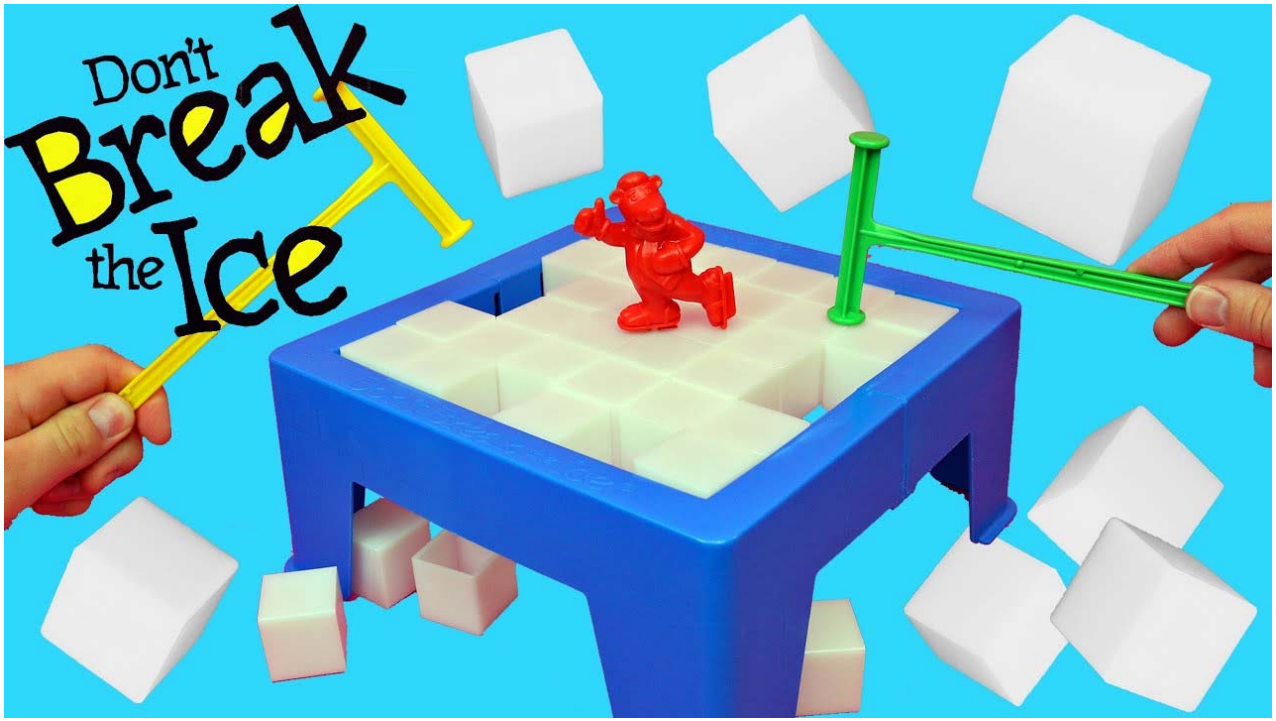


Two possible approaches

Option One:

Start by treating majority with EVT and turn-on randomization to medical management as evidence shows EVT doesn't work.

- Fewest (and rarest) patients are randomized so evidence of ineffective treatment is slow
- Risks exposing more people to futile/harmful treatment



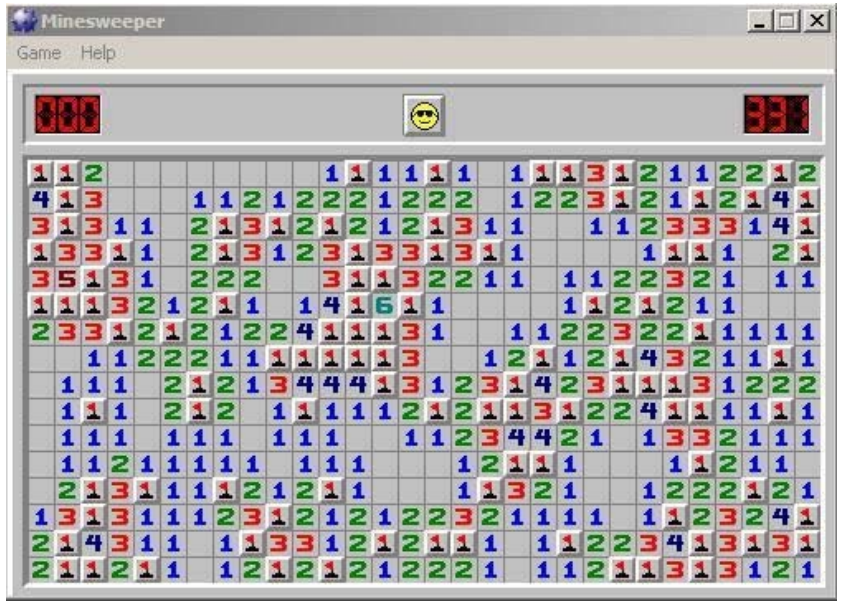
Two possible approaches

Option Two:

Start by treating only those with definitive evidence or absence of community equipoise and randomize the rest. Randomize increasing # to EVT as evidence accumulates

- Patients who are likely to benefit are slower to be assigned with 100% probability to treatment with EVT
- Potential to be overly cautious and difficulty defining "sufficient evidence"

Minesweeper Approach

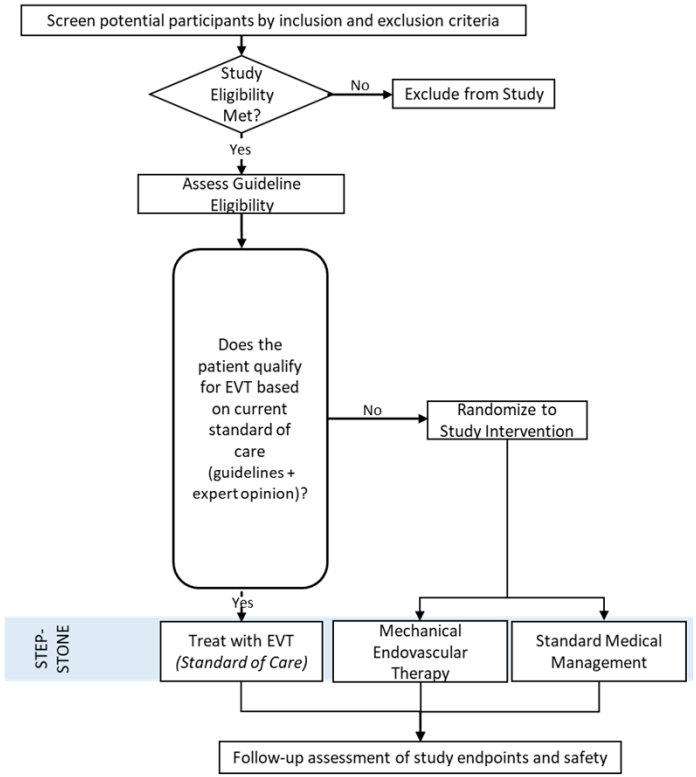


- Seven positive trials of Endovascular therapy within 6 hours to date
- Large populations of underexplored subjects who are not currently definitively eligible
- Individual trials would be costly
- Instead....Single trial that borrows information across groups and from previous trials

Step Stone Trial

- All patients with anterior circulation LVO at < 6 hours whether treated or not will be **enrolled** at participating centers
- Trial will start with a run-in phase (no randomization) to accumulate more observational data and 'tune' the model using expert feedback.
- After the run-in phase, prespecified subgroups will be **randomized** to either EVT or MM using this probabilistic model-based assignment.
- The randomization ratio (i.e., not necessarily 50/50) will be informed by the anticipated relative benefit of EVT using data from:
  - Previous trials
  - Currently enrolled subjects with observed outcome data
  - Interpretation by a multidisciplinary expert opinion

Trial Schema



Workflow at Sites

Subject with LVO arrives at trial hospital and groin-puncture within 6 hours possible.

All of these patients are enrolled if possible.

If non-randomized group, then treat with EVT per standard of care.

Non-randomized consent can be **prospective or retrospective**, but prospective consent is strongly recommended.

If randomized group, then consent followed by entering key covariates into WebDCU for randomization assignment.

Randomized consent must be **prospective.**

Subject's GWTG ID is entered into record and data is automatically transferred.

Study coordinator oversees data quality of key trial variables included in GWTG or WebDCU. Trial collects all GWTG data on EVT to ascertain any bias.

But how to decide who gets randomized?

- Primary outcome is **prognosis-adjusted sliding dichotomy** mRS at 90 days
- Probability of favorable outcome modeled using a **Bayesian hierarchical model with informative priors**
- Run-in phase of trial to tune the strength of the randomization

But how to decide who gets randomized?

- Prespecified variables, or combinations, closed once relative certainty is reached about benefit, or lack thereof.
  - An unblinded group of experts reviewing data in real time.
- At pre-specified points, *in-silico trials* will be used to seek guideline change for pre-specified subgroups

The following text is taken from the Senate Fiscal Year 2016 FDA Appropriations Bill (S. 1800) & Report (S. Rept. 114-82):

"In Silico Clinical Trials. – In silico clinical trials use computer models and simulations to develop and assess devices and drugs. …The Committee urges FDA to engage with device and drug sponsors to explore greater use, where appropriate, of *in silico* trials for advancing new devices and drug therapy applications."

Which covariates go in the model?

Guidelines: <6 Hrs

Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset.	I	A
Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the MCA segment 2 (M2) or MCA segment 3 (M3) portion of the MCAs.	IIb	B-R
Although its benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score >1, ASPECTS <6, or NIHSS score <6, and causative occlusion of the internal carotid artery (ICA) or proximal MCA (M1). Additional randomized trial data are needed.	IIb	B-R

Powers, 2018

Two possible approaches

Option One:

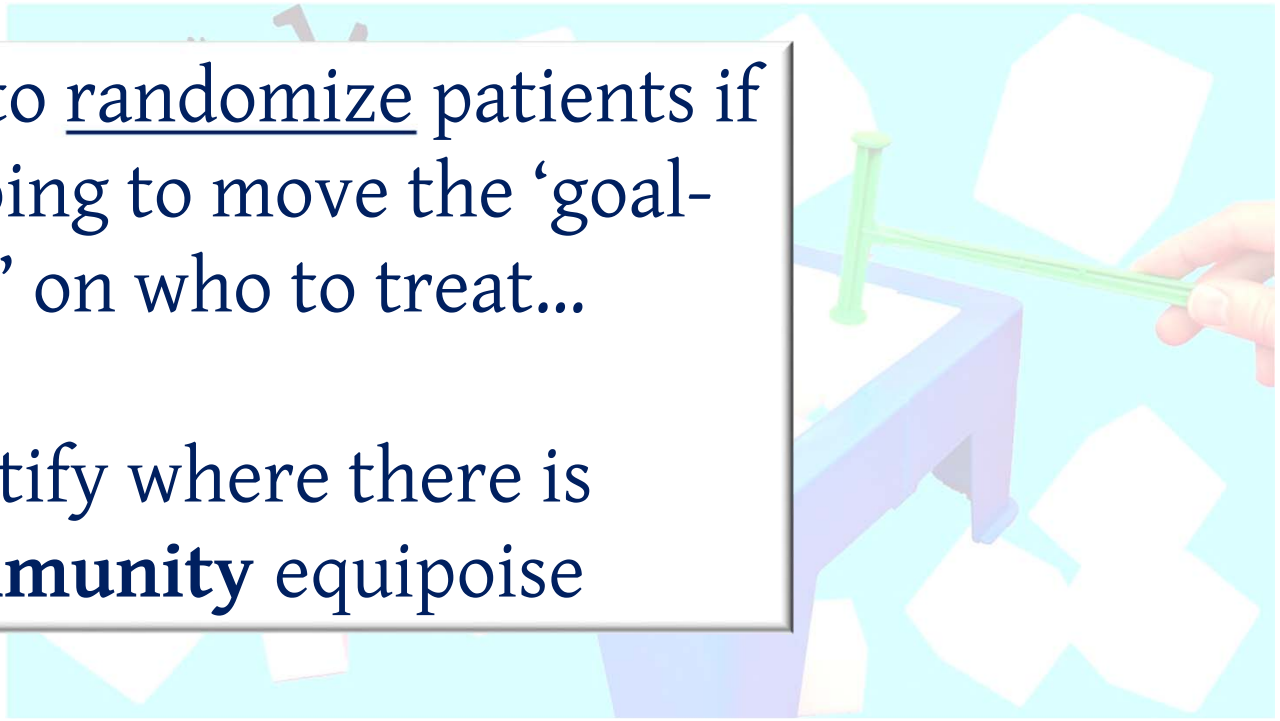
Start by treating e
turn-off randomiz
turn off as eviden
doesn't work.

- Fewest (and ra
randomized sc
ineffective tre

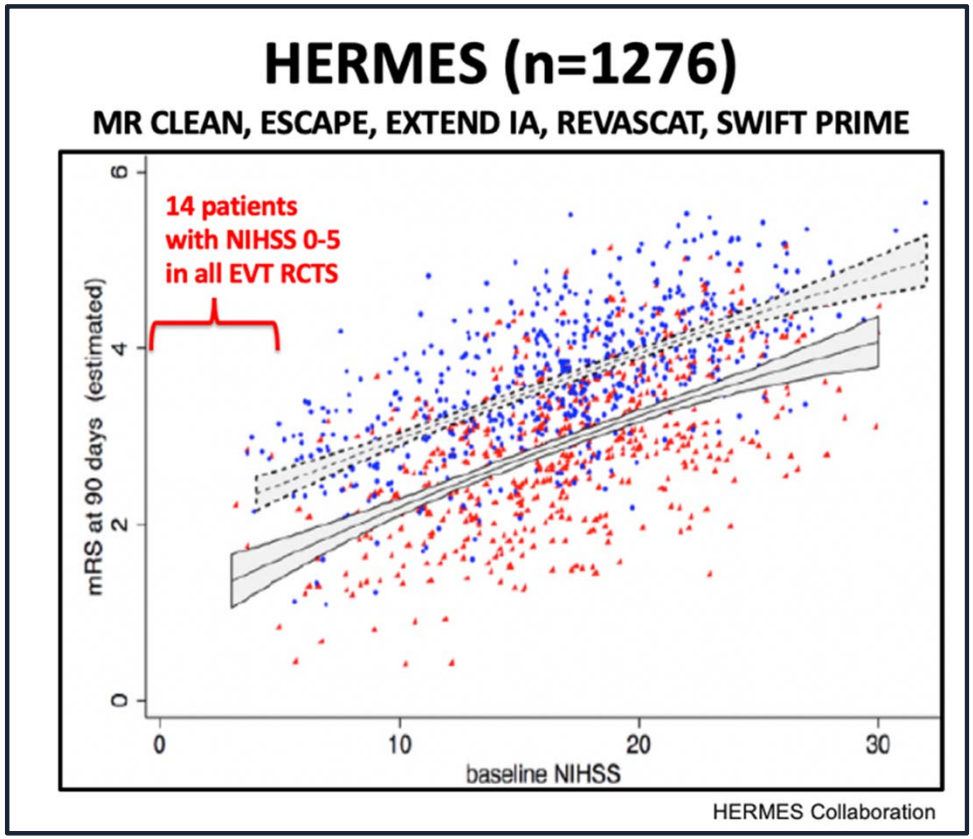
- Risks exposing
futile/harmful treatment

We need to <u>randomize</u> patients if we're going to move the 'goal-post' on who to treat...

Identify where there is **community** equipoise



Key Model Covariates: Baseline Low NIHSS



- Only 14 patients randomized in all EVT RCT trials to date (n=~1800 in final pooled data)
- Weight of nonrandomized evidence suggests treatment may be appropriate
- Ongoing industry-funded RCTs
  - ENDOLOW (US, Canada, Europe)
  - IN-EXTREMIS (Europe)

A5

Key Model Covariates: Baseline ASPECTS Score

- Only 126 ASPECTS 0-4 among ~1800 pts in the EVT RCTs
  - Direction of effect favored treatment
  - Central and local readings varied
- Good (7-10) vs moderate (5-6) vs bad (0-4) should be reasonably reliable.
  - Run-in phase to confirm
  - Run through all e-ASPECTS softwares provided by vendors
  - Revisit 0-4 category after 5-6?
- Ongoing industry-funded RCTs
  - TESLA
  - IN-EXTREMIS

ASPECTS <6 in HERMES

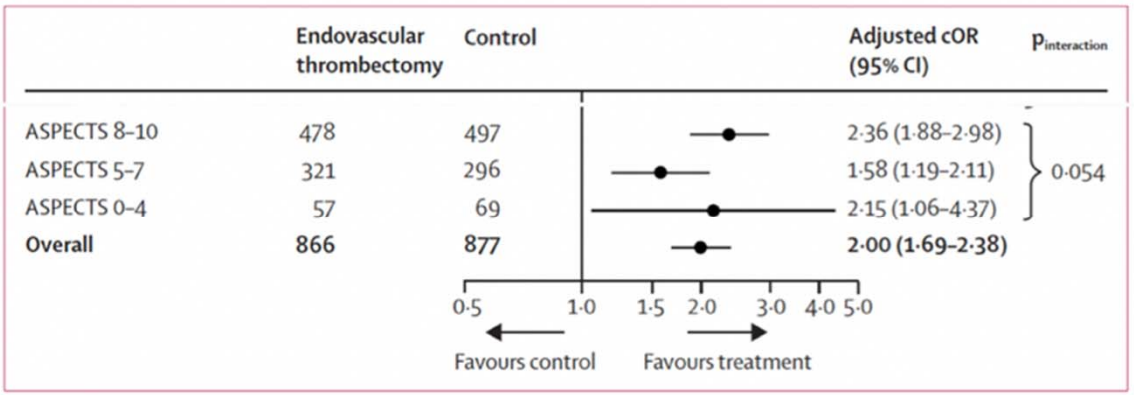


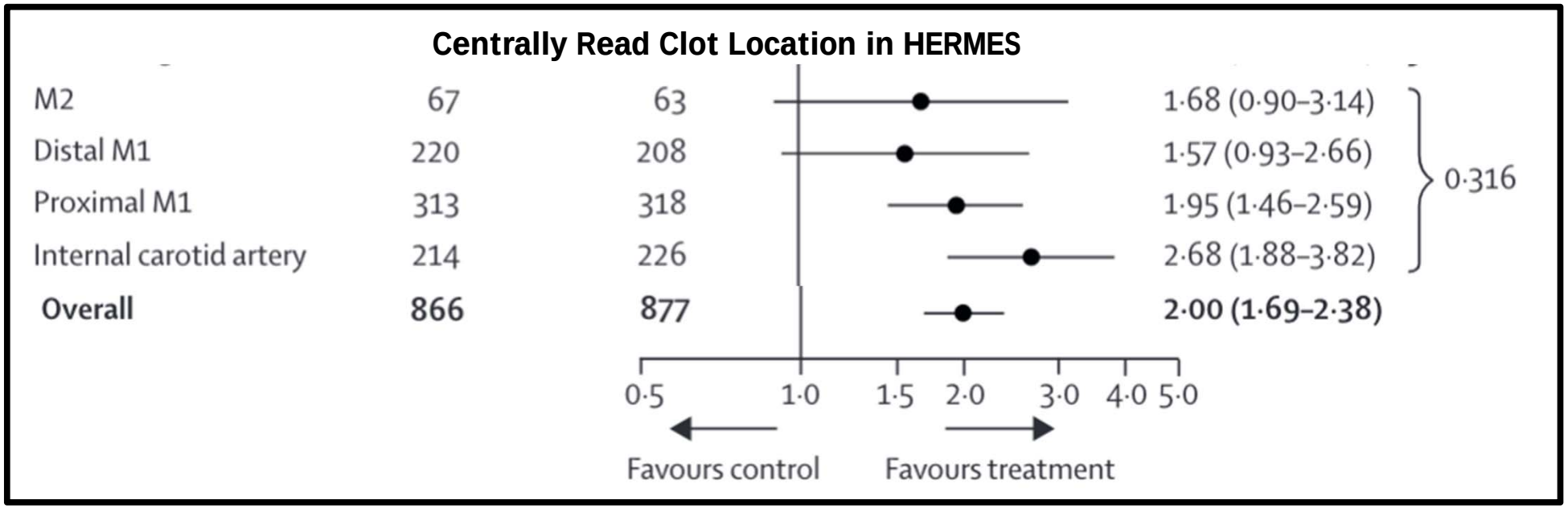
Figure 1: Forest plot of endovascular treatment effect on primary outcome (modified Rankin Scale shift at 90 days), by baseline imaging variable categories

Roman, Lancet Neurol, 2019

A5 We have been inconsistent in how we talked about this in the protocol. See proposal here for how to categorize initially.

Author, 10/27/2019

Key Model Covariates: Clot Location



- Only 130 M2s of total ~1800 in HERMES
- Will use data/consensus approach to decide which M2s to randomize first (ex: NIHSS <10?)

Back to the Big Picture…..

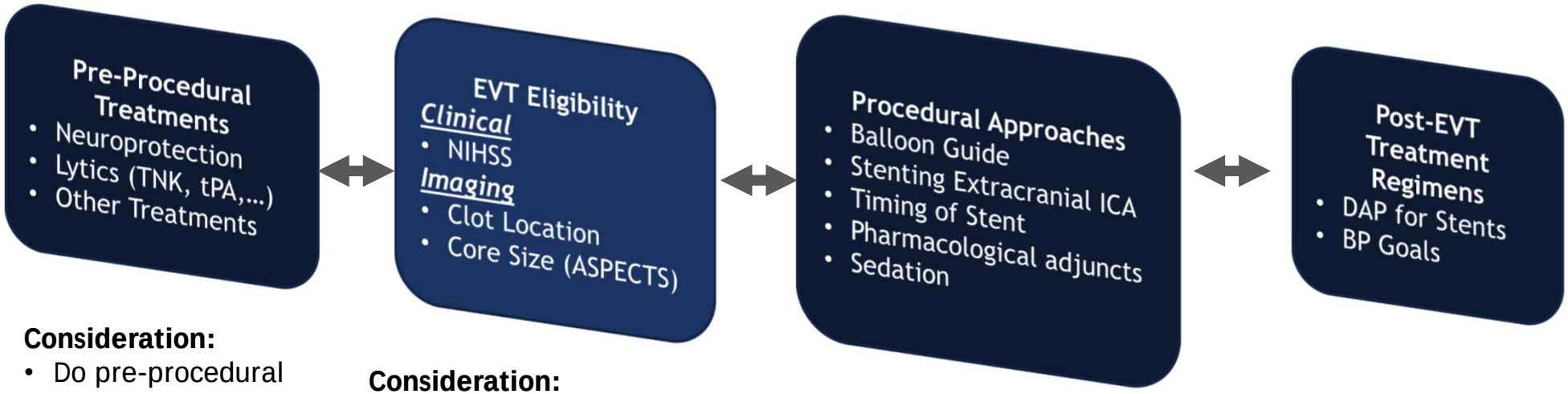
Scope of STEP-STONE

10,000+ Subjects

Scope of STEP-STONE

~25 Top EVT Sites

Long Term Plan



Consideration:

- Do pre-procedural treatments modify eligibility?
- Do they modify eligibility only under certain procedural constraints?

Consideration:

- Which criteria predict outcome?
- Which criteria predict adverse events?
- Can imaging replace clinical criteria?

Consideration:

- Are procedural differences constant across allowed eligibility?
- Do they interact with pre-procedural treatments?

Site Budget

- Option One: Traditional per-patient budget
- Option Two: Each RCC receives same percentage of PI and full coordinator. Can keep in house or sub-contract to sites in network as it works best
- Option Three: PIs select the 25-30 sites to participate, each gets a percent of PI and coordinator

Either effort model depends on meeting milestones. Possibility to increase coordinator if recruitment is above target.