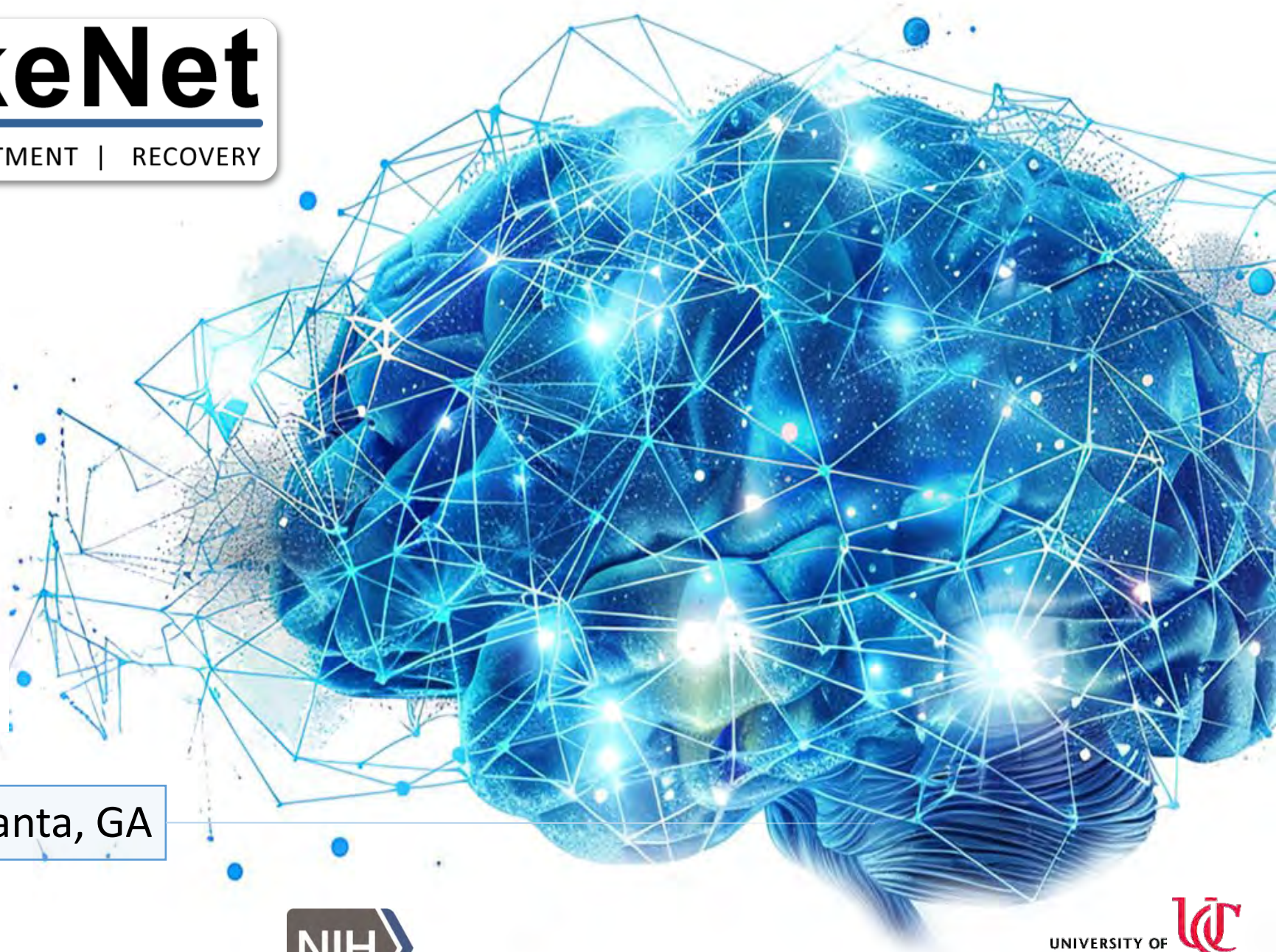
NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY



NETWORK MEETING

WELCOME

September 30, 2024 | Atlanta, GA

MUSC Medical University of South Carolina

NIH

UNIVERSITY OF Cincinnati


BREAKING NEWS
HURRICANE HELENE . . . NO MATCH FOR STROKENET RESOLVE
September 29-30, 2024 - Atlanta Georgia
LIVE


IOWA
LIVE





Welcome and Updates

Pooja Khatri, MD, MSc

NIH StrokeNET National Coordinating Center

University of Cincinnati

MUSC Medical University of South Carolina

NIH

University of Cincinnati

Agenda—Morning

8:45 am – 9:15 am	Welcome/Updates NDMC NINDS	Pooja Khatri Jordan Elm Scott Janis
9:15 am – 9:30 am	Training Core Update	Randy Marshall Devin Brown
9:30 am – 9:45 am	CRP Core Update	Heena Olalde Kinga Aitken
9:45 am – 10:45 am	ARCADIA-CSI Final Results & ARCADIA Secondary Results Discussion	David Tirschwell Maarten Lansberg Ron Lazar Hooman Kamel
10:45 am – 11:30 am	Themes for priority setting conferences	Pooja Khatri Steve Cramer Karen Johnston Hooman Kamel
11:30 am – 12:00 pm	Break and grab lunch to bring back to the room	

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Agenda—Afternoon

*****Reassemble in Salon at 12:00pm for working lunch*****

12:00 pm – 12:45 pm	Keynote Speaker "Embedding pragmatic trials within emergency and critical care" **Matthew Semler, MD** Associate Professor of Medicine, Anesthesiology, and Biomedical Informatics Associate Director of the Medical Intensive Care Unit Director, Center for Learning Healthcare Vanderbilt University

Please Note: The breakout sessions below will not be livestreamed. Remote attendees rejoin at 2:15pm

12:45 pm – 2:00 pm	Breakout session: Small group discussion on themes for priority setting conferences. There will be 3 groups:		
	• Recovery Group	Florida	Sean Savitz, Maarten Lansberg
	• Prevention Group	Alabama	Cheryl Bushnell, Randy Marshall
	• Acute Group	Salon C	Enrique Leira, Mark Alberts
2:00 pm – 2:15 pm	Break		
2:15 pm – 3:15 pm	Reassemble in Salon: Moderators to summarize small group discussions for larger group considerations. Each group will have 10 minutes for summary and 10 minutes for Q&A.		
3:15 pm – 3:30 pm	Questions/wrap-up		

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Housekeeping

- **Wifi** Marriott Conference
  - Access code: encore (don't need room #)
- **Online link**: https://tinyurl.com/4b3pw3n8
- **Restrooms** towards lobby (two rights after exiting room)
- **Charging stations** are on left and right of room
- Can leave **luggage** in Salon B (locked during mtg)
- **Parking passes** – see Rose or Kristine if not in your name badge holder
- **Airport buses** at 4pm
- Please ask your questions and bring your ideas today!

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Trial Portfolio as of Today

9 Studies Completed

- 6 Definitive (including 2 platform) and 2 Pilot Trials
- 1 Ancillary Study

1 Paused

15 Ongoing Studies

- 11 Trials, 3 Ancillary Studies, 1 Biomarker Validation Study

1 New Trial Funded

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Completed Studies

PREVENTION OF STROKE (2)

ARCADIA No evidence of benefit of apixaban for stroke with evidence of atrial cardiopathy

- **ARCADIA-CSI** Cognition and silent infarcts – final results pending

PRIMARY STROKE PREVENTION IN COVID (2)

ACTIV 4C Platform Antithrombotic approach for patients discharged from hospital with COVID-19

ACTIV 4A Platform Antithrombotic approach for inpatient COVID-19 pts

ACUTE STROKE TREATMENT (4)

MISTIE 3 No evidence of benefit of minimally invasive surgery for ICH evacuation

DEFUSE 3 Large treatment benefit of EVT for imaging selected patients at 4.5-16h from onset

I-DEF Futility of deferoxamine for three-month outcomes after ICH

MOST No evidence of benefit of adjunctive epfibatide or argatroban with intravenous thrombolysis

STROKE RECOVERY & REHABILITATION (1)

TELEREHAB Noninferiority of telehealth to in-person, dose-matched post-stroke rehabilitation

Completed Studies

PREVENTION OF STROKE (2)

ARCADIA No evidence of benefit of apixaban for stroke with evidence of atrial cardiopathy

- **ARCADIA-CSI** Cognition and silent infarcts – final results pending

PRIMARY STROKE PREVENTION IN COVID (2)

ACTIV 4C Platform Antithrombotic approach for patients discharged from hospital with COVID-19

ACTIV 4A Platform Antithrombotic approach for inpatient COVID-19 pts

ARCADIA primary paper (JAMA)
Secondary analyses today

ARCADIA CSI primary results today

Therapeutically anticoagulated noncritically ill pts but not critically ill pts (NEJM X 2)

No benefit of P2Y12 Inhibitors, SGLT2 inhibitors, or P-Selectin-Inhibitor Crizanlizumab
(JAMA, Lancet Diabetes Endocrin, Circulation)

Completed Studies

Paved for next ICH evac trials

Global impact on acute stroke care

Raised awareness of 6 month outcomes for ICH

Primary paper in NEJM this month

Precursor to newly funded Telerehab-2

ACUTE STROKE TREATMENT (4)

MISTIE 3 No evidence of benefit of minimally invasive surgery for ICH evacuation

DEFUSE 3 Large treatment benefit of EVT for imaging selected patients at 4.5-16h from onset

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STROKE RECOVERY & REHABILITATION (1)

TELEREHAB Noninferiority of telehealth to in-person, dose-matched post-stroke rehabilitation

15 Ongoing Trials/Studies

PREVENTION OF STROKE (9)

CREST-2 Endarterectomy/stenting of asymptomatic carotid stenosis (N=2486/2480)

- **CREST-H** Cognitive outcomes in hemodynamically impaired subset (N=392/385)

Sleep-SMART Treatment of obstructive sleep apnea (Ph 3, N=1601/3062)

SATURN Statin continuation in ICH survivors (N=600/1426)

- **SATURN-MRI** Silent stroke (N=229/894)

ASPIRE Apixiban for afib after ICH (N=340/700)

CAPTIVA Anticoagulation vs antiplatelets for intracranial stenosis (N=514/1683)

- **CAPTIVA MRI** Biomarkers of recurrent stroke in intracranial atherosclerotic stenosis (N=3/300)

FOCAS Corticosteroids for pediatric stroke due to focal cerebral arteriopathy (N=8/80)

ACUTE STROKE TREATMENT (3)

FASTEST FVIIa for acute ICH (N=543/860)

SISTER Novel clot-dissolving Ab, TS23, for ischemic stroke (N=9/300)

STEP Platform Registry-supported trial platform to optimize outcomes after LVO and MVO

STROKE RECOVERY & REHABILITATION (3)

TRANSPORT-2 Transcranial direct stimulation for UE recovery (N=129/129)

I-ACQUIRE Intensive infant rehabilitation for ischemic stroke (N=215/216)

VERIFY Acute prediction of UE motor recovery and function (N=252/657)

Telerehab-2 Telehealth in home vs usual care for UE motor function (N=0/202)

Prevention Updates

PREVENTION OF STROKE (9)

CREST-2 Endarterectomy/stenting of asymptomatic carotid stenosis (N=2486/2480)

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- **CAPTIVA MRI** Biomarkers of recurrent stroke in intracranial atherosclerotic stenosis (N=3/300)

FOCAS Corticosteroids for pediatric stroke due to focal cerebral arteriopathy (N=8/80)

Completed enrollment 10/JUL/2024!
CEA-MED follow up completed SEPT/2024 and CAS-MED follow up to be completed on 31/JUL/2025

CREST-H in follow up as well!

Prevention aim on hold as of 28/JUN/2024

Recovery aim ongoing (sample size reduction)

StrokeNet Thrombectomy Endovascular Platform

Acute and Recovery Updates

ACUTE STROKE TREATMENT (3)

FASTEST FVIIa for acute ICH (N=543/860)

SISTER Novel clot-dissolving Ab, TS23, for ischemic stroke (N=9/300)

STEP Platform Registry-supported trial platform to optimize outcomes after LVO and MVO

→ Key interim analysis in December

FDA approved amendment to incorporate an enrichment and promising zone design

→ New assets under active development

STROKE RECOVERY & REHABILITATION (4)

TRANSPORT-2 Transcranial direct stimulation for UE recovery (N=129/129)

I-ACQUIRE Intensive infant rehabilitation for ischemic stroke (N=215/216)

VERIFY Acute prediction of UE motor recovery and function (N=252/657)

Telerehab-2 Telehealth in home vs usual care for UE motor function (startup, N=202)

→ Completed enrollment 24/May/2024 and last follow up last week!

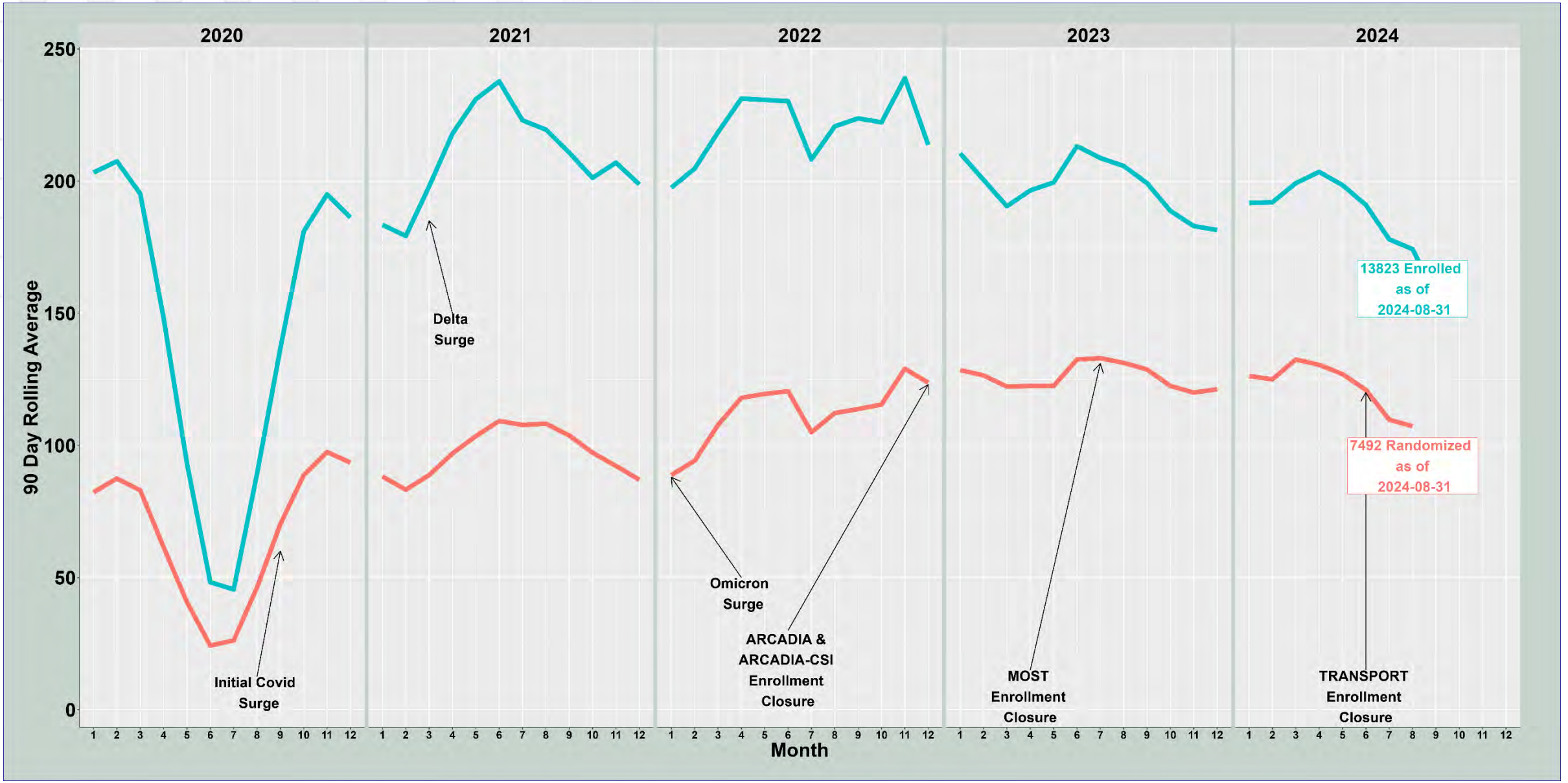
Anticipate results at ISC 2025

→ Almost completed enrollment!
12 months follow up remaining

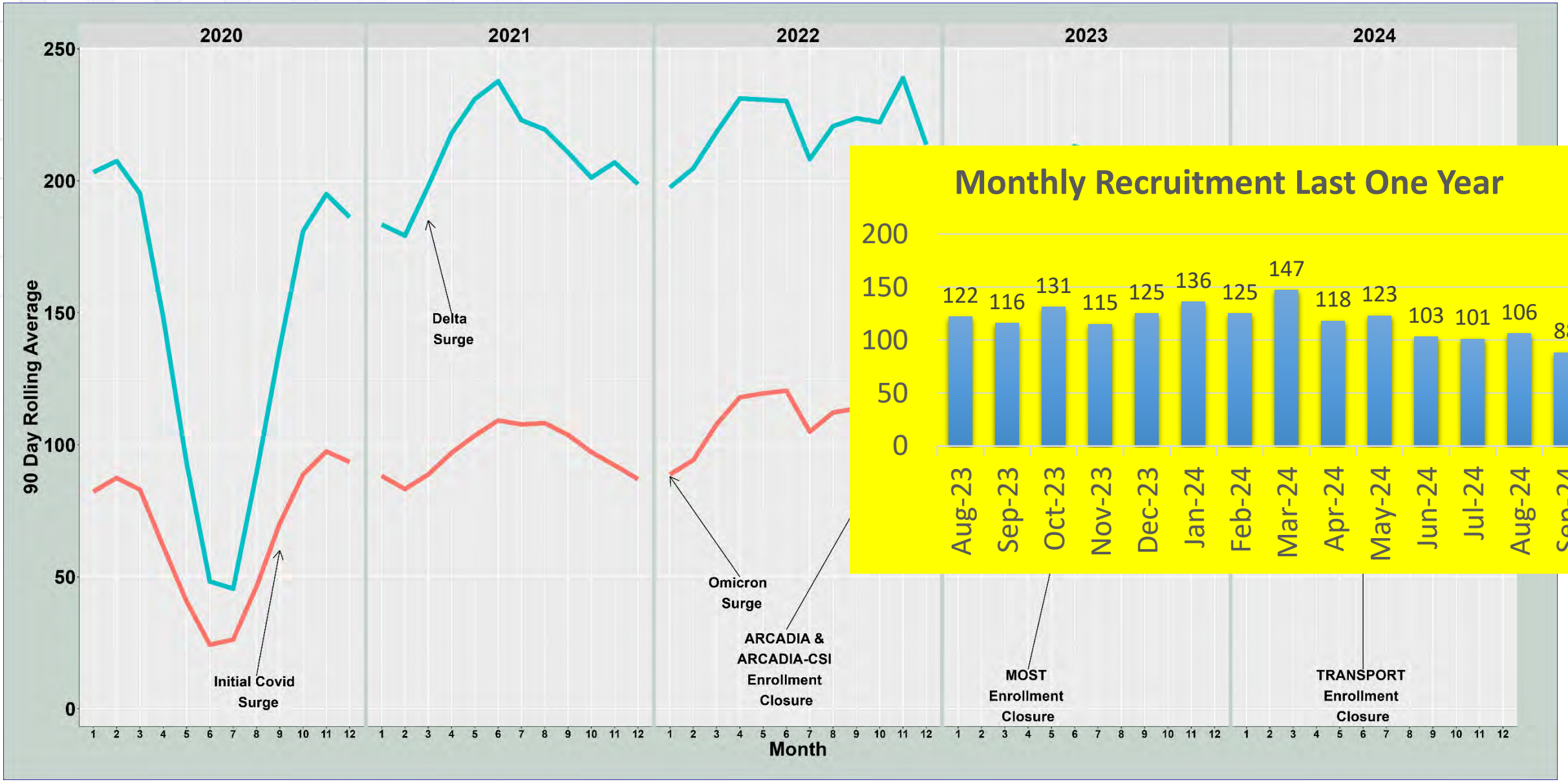
NEW

StrokeNet Thrombectomy Endovascular Platform

>13,000 Enrolled and >7000 Randomized



>13,000 Enrolled and >7000 Randomized



Examples of Innovative Design Features

- Adaptive enrichment – DEFUSE-3
- Multi-arm, multistage – MOST, CAPTIVA
- Patient-Reported Outcome -- Utility-weighted modified Rankin – MOST, FASTEST, STEP
- Covariate adjusted randomization – Telerehab, iACQUIRE, MOST, SATURN, TRANSPORT2
- Response adaptive randomization – Sleep SMART, MOST, SISTER, STEP
- Sample size re-estimation – ARCADIA, Sleep SMART, ASPIRE, SATURN
- Step forward randomization – FASTEST
- Emergency consent – FASTEST
- Infant population – iACQUIRE
- Utility function – SISTER
- Randomized, embedded, multifactorial, adaptive platform (REMAP) – STEP
- Registry-supported – STEP

International Trials

NIH StrokeNet Network
Standard Operating Procedure

SOP Number: ADM 27
SOP Name: Management of StrokeNet Trials with International Sites
Effective Date: 09/24/2024

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StrokeNet Trials Publications (Last One Year)

JAMA | Original Investigation

Apixaban to Prevent Recurrence After Cryptogenic Stroke in Patients With Atrial Cardiopathy
The ARCADIA Randomized Clinical Trial

JAMA Neurology | Original Investigation

Apixaban vs Aspirin in Patients With Cancer and Cryptogenic Stroke
A Post Hoc Analysis of the ARCADIA Randomized Clinical Trial

PEDIATRICS Content Authors/Reviewers

FAMILY PARTNERSHIPS | SEPTEMBER 04 2024

Parent Council for a Pediatric Stroke Rehabilitation Clinical Trial

Stroke: Vascular and Interventional Neurology

ORIGINAL RESEARCH

CREST-2 Commitment to Rigorous Assessment of Carotid Stenting for Primary Prevention of Stroke

Circulation
Volume 148, Issue 5, 1 August 2023; Pages 381-390
https://doi.org/10.1161/CIRCULATIONAHA.123.065190

American Heart Association.

ORIGINAL RESEARCH ARTICLE

Effect of the P-Selectin Inhibitor Crizanlizumab on Survival Free of Organ Support in Patients Hospitalized for COVID

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjunctive Intravenous Argatroban or Eptifibatide for Ischemic Stroke

Effect of sodium–glucose co-transporter-2 inhibitors on survival free of organ support in patients hospitalised for COVID-19 (ACTIV-4a): a pragmatic, multicentre, open-label, randomised, controlled, platform trial

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Committee Updates

		CHAIRS
Working Groups	**Acute**	Karen Johnston, MD & Jeff Saver, MD
	Prevention	Hooman Kamel, MD & Scott Kasner MD
	Recovery	Steve Cramer, MD & Steven Wolf, PT PhD
Cores	**Fellow Education/Training**	Randy Marshall, MD & Devin Brown, MD
	CRP Education/Training (new)	Heena Olalde, RN, MSN & Kinga Aitken, MPH, CCRP
	Diversity/Equity/Inclusion (new)	B. Boden-Albala, MPH, DrPH & L. Skolarus, MD
Advisory	**Patient Rep/Advocacy (new)**	Flannery O'Neil, MPH & Aqualyn Kennedy, MBA
	Pediatrics	Heather Fullerton, MD
	Preclinical (new)	Lauren Sansing, MD
	Telestroke	Chris Streib, MD & Abbey Staugaitis, RN, MSN, CCRC

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Committee Updates

Working Groups	**Acute**	Membership rotated; Trial development; Scientific themes for priority setting conferences
	Prevention	
	Recovery	
Cores	**Fellow Education/Training**	Stay tuned today
	CRP Education/Training (new)	
	Diversity/Equity/Inclusion (new)	Formed group–attending WGs–how to collect baseline demographics and analysing demographics of ongoing trials
Advisory	**Patient Rep/Advocacy (new)**	Expanded involvement, STEP ICF
	Pediatrics	Formed group –attdg WGs – STEP protocol
	Preclinical (new)	Formed group – attdg WGs
	Telestroke	Remote Consent Practices Survey, MOST eCONSENT pub (higher enrollment, fewer ICF PVs)

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NDMC Updates

Jordan J. Elm, PhD

StrokeNet National Data Management Center

Medical University of South Carolina

MUSC Medical University of South Carolina

NIH

University of Cincinnati

WebDCU™

Data → Information → Knowledge

375,000 CRFs!

50,000 queries!

1% error rate

Summary by Project

#	Project name	CRFs posted	CRFs data entered	CRFs submitted	% Site CRFs first submitted by due date	Site CRF data entry over due	DCRs	Average DCR response days	DCRs closed	Average DCR closing days	DCRs not responded	DCRs responded not closed	Open rule violation	Confirmed warning rule violation	Confirmed protocol violation	% Site data error	Updated on
	Total	*425020*	*376135*	*375692*		*405*	*50061*		*48306*		*621*	*1134*	*580*	*11773*	*743*		
1	TeleRehab	7598	6702	6702	80.2		298	9.5	298	24.6			0	10	136	0.27	17-Sep-2024
2	DEFUSE3	6659	5474	5469	85.1		1124	6.1	1114	16.6		10	5	266	21	0.91	17-Sep-2024
3	ARCADIA	121028	111037	110958	78.1	33	11984	27.1	11737	103.4	79	168	114	1656	31	0.5	17-Sep-2024
4	MOST	13188	10584	10583	81.6		4007	16.7	3992	57	8	7	0	236	146	0.92	17-Sep-2024
5	TRANSPORT2	14870	13161	13161	70.8		1060	18	1059	62.4	1		0	46	4	0.31	17-Sep-2024
6	SleepSMART	110927	100479	100415	81.9	104	12567	16.3	12302	69.4	165	100	44	1711	231	0.54	17-Sep-2024
7	ASPIRE	22386	18800	18742	80.3	52	2514	10.8	2468	24	32	14	53	537	7	0.55	17-Sep-2024
8	SATURN	49057	44997	44967	74.7	18	6430	14.8	6122	40.6	76	232	22	3066	41	1.52	17-Sep-2024
9	I-ACQUIRE	28286	23775	23759	58.4	74	1009	33.6	974	59.9	29	6	49	1024	3	0.11	17-Sep-2024
10	ARCADIA-CSI	3432	3323	3323	71.3	1	896	33.9	894	84.3	1	1	0	3	3	3.86	17-Sep-2024
11	FASTEST	15574	12889	12847	77.2	42	3540	12.1	3122	28.6	121	297	64	854	37	0.66	17-Sep-2024
12	VERIFY	7127	6205	6200	83.8	8	798	7.5	765	22.4	24	9	17	148	29	0.34	17-Sep-2024
13	CAPTIVA	24291	18237	18099	80.8	66	3781	9.4	3424	35.4	73	284	178	2129	54	0.57	17-Sep-2024
14	FOCAS	374	283	280	80.6	7	28	4.1	15	7.8	10	3	30	8	0	0.1	17-Sep-2024
15	SISTER	223	189	187	83.2		25	4.1	20	6.5	2	3	4	79	0	0.13	17-Sep-2024

Note: Data in this report are updated daily. Subjects enrolled within 24 hours may not be included.
CRFs posted: all required CRFs plus data entered optional CRFs, inludes CRFs with data provided by sites and other parties.
% Site CRFs first submitted by due date: includes CRFs with data provided by sites only.
Site CRF data entry over due: includes CRFs with data provided by sites only.
% Site data error: includes CRFs with data provided by sites only.

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Completed

CRF Data Entry Summary by Project

Project name	CRFs posted	CRFs submitted	% Site CRFs first submitted by due date	DCRs	Average DCR response days	DCRs closed	Average DCR closing days	Confirmed protocol violation	% Site data error
TeleRehab	7598	6702	80.2	298	9.5	298	24.6	136	0.27
DEFUSE3	6659	5469	85.1	1124	6.1	1114	16.6	21	0.91
ARCADIA	121028	110958	78.1	11984	27.1	11737	103.4	31	0.5
MOST	13188	10583	81.6	4007	16.7	3992	57	146	0.92
ARCADIA-CSI	3432	3323	71.3	896	33.9	894	84.3	3	3.86

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Jordan ELM Sign Out

Help

List: Subject Demographics Summary by Project

Page 1 of 1 Show 15 of 15

Page Actions

#	Project name	Sample size	Enrolling sites	Subjects enrolled	Last enrollment date	% Female	% Male	% Hispanic	% Not-Hispanic	% American Indian / Alaska Native	% Asian	% Black / African American	% Native Hawaiian or Pacific Islander	% White	% More than one race	Updated on
	Total	***12367***	***807***	***5987***	***9/17/2024***	***45.6***	***54.4***	***9.7***	***89.8***	***0.5***	***8***	***22.6***	***0.4***	***66.2***	***0.6***	
1	CAPTIVA-MRI	300	2	3	04-Sep-2024	66.7	33.3		100		33.3			66.7		17-Sep-2024
2	SISTER	300	6	7	05-Sep-2024	28.6	71.4		100	14.3				85.7		17-Sep-2024
3	DEFUSE3	476	38	182	23-May-2017	50.5	49.5	13.2	86.3	0.5	3.3	8.2		86.8		17-Sep-2024
4	FASTEST	860	71	532	17-Sep-2024	35	65	8.6	91	0.2	55.1	8.3	0.4	33.8		17-Sep-2024
5	I-ACQUIRE	240	16	213	16-Sep-2024	48.4	51.6	17.8	80.3		3.8	8.5	0.5	78.9	2.8	17-Sep-2024
6	SATURN	1456	103	594	13-Sep-2024	55.6	44.4	10.4	89.4	0.5	4.5	9.6	0.2	84.8	0.2	17-Sep-2024
7	ASPIRE	700	106	334	10-Sep-2024	44.9	55.1	6.6	91.9	0.3	5.4	14.1	0.9	75.7	0.9	17-Sep-2024
8	ARCADIA	1100	141	1015	14-Dec-2022	54.3	45.7	8.1	91.4	0.4	1.7	21.1	0.3	74.9	0.3	17-Sep-2024
9	FOCAS	80	7	8	10-Sep-2024	12.5	87.5	25	75		25	25		37.5		17-Sep-2024
10	MOST	1200	57	514	01-Jul-2023	49.8	50.2	7.8	91.8		2.7	25.1	0.2	71.4	0.2	17-Sep-2024
11	TeleRehab	124	11	124	03-Jan-2018	27.4	72.6	2.4	96		8.1	26.6		64.5		17-Sep-2024
12	SleepSMART	3062	117	1593	13-Sep-2024	42.1	57.9	10.2	89.4	0.8	3.3	28.6	0.4	64.3	0.5	17-Sep-2024
13	VERIFY	657	23	241	08-Sep-2024	38.2	61.8	7.5	91.3		1.2	38.2	0.4	58.1	0.8	17-Sep-2024
14	CAPTIVA	1683	95	498	16-Sep-2024	42	58	14.1	85.7	1.2	4	38.8	1	49.6	1.6	17-Sep-2024
15	TRANSPORT2	129	14	129	14-Jun-2024	41.9	58.1	8.5	91.5		3.1	41.1		53.5	0.8	17-Sep-2024

Note 1. Only subjects counting towards the sample size are included.
2. Subjects enrolled in ancillary studies are not counted separately, because they have been counted in their parent projects.
3. Percentages in the Total row are obtained by the total subject counts in the demographic category divided by total subjects enrolled across all projects.
4. Data in this report are updated daily. Subjects enrolled within 24 hours may be not included.

6,000 patients

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List: Subject Demographics Summary by Project

Page 1 of 1 Show 15 of 15

#	Project name	Sample size	Enrolling sites	Subjects enrolled	Last enrollment date	% Female	% Male	% Hispanic	% Not-Hispanic	% American Indian / Alaska Native	% Asian	% Black / African American	% Native Hawaiian or Pacific Islander	% White
	Total	***12367***	***810***	***6006***	***9/22/2024***	***45.6***	***54.4***	***9.7***	***89.7***	***0.5***	***8***	***22.6***	***0.4***	***66.1***
1	FASTEST	860	72	536	22-Sep-2024	35.1	64.9	8.8	90.9	0.2	55	8.4	0.4	33.6
2	FOCAS	80	7	8	10-Sep-2024	12.5	87.5	25	75		25	25		37.5
3	CAPTIVA	1683	96	502	18-Sep-2024	41.8	58.2	14.3	85.5	1.2	4	38.8	1	49.6
4	TRANSPORT2	129	14	129	14-Jun-2024	41.9	58.1	8.5	91.5		3.1	41.1		53.5
5	VERIFY	657	23	243	08-Sep-2024	38.7	61.3	7.4	91.4		1.2	37.9	0.4	58.4
6	SleepSMART	3062	117	1595	18-Sep-2024	42	58	10.2	89.4	0.8	3.3	28.7	0.4	64.3
7	TeleRehab	124	11	124	03-Jan-2018	27.4	72.6	2.4	96		8.1	26.6		64.5
8	CAPTIVA-MRI	300	2	3	04-Sep-2024	66.7	33.3		100		33.3			66.7
9	MOST	1200	57	514	01-Jul-2023	49.8	50.2	7.8	91.8		2.7	25.1	0.2	71.4
10	ARCADIA	1100	141	1015	14-Dec-2022	54.3	45.7	8.1	91.4	0.4	1.7	21.1	0.3	74.9
11	ASPIRE	700	107	336	19-Sep-2024	44.9	55.1	6.5	92	0.3	5.7	14	0.9	75.6
12	I-ACQUIRE	240	16	214	20-Sep-2024	48.1	51.9	18.2	79.9		3.7	8.4	0.5	78.5
13	SATURN	1456	103	598	20-Sep-2024	55.7	44.3	10.4	89.5	0.5	4.5	9.5	0.2	84.9
14	SISTER	300	6	7	05-Sep-2024	28.6	71.4		100	14.3				85.7
15	DEFUSE3	476	38	182	23-May-2017	50.5	49.5	13.2	86.3	0.5	3.3	8.2		86.8

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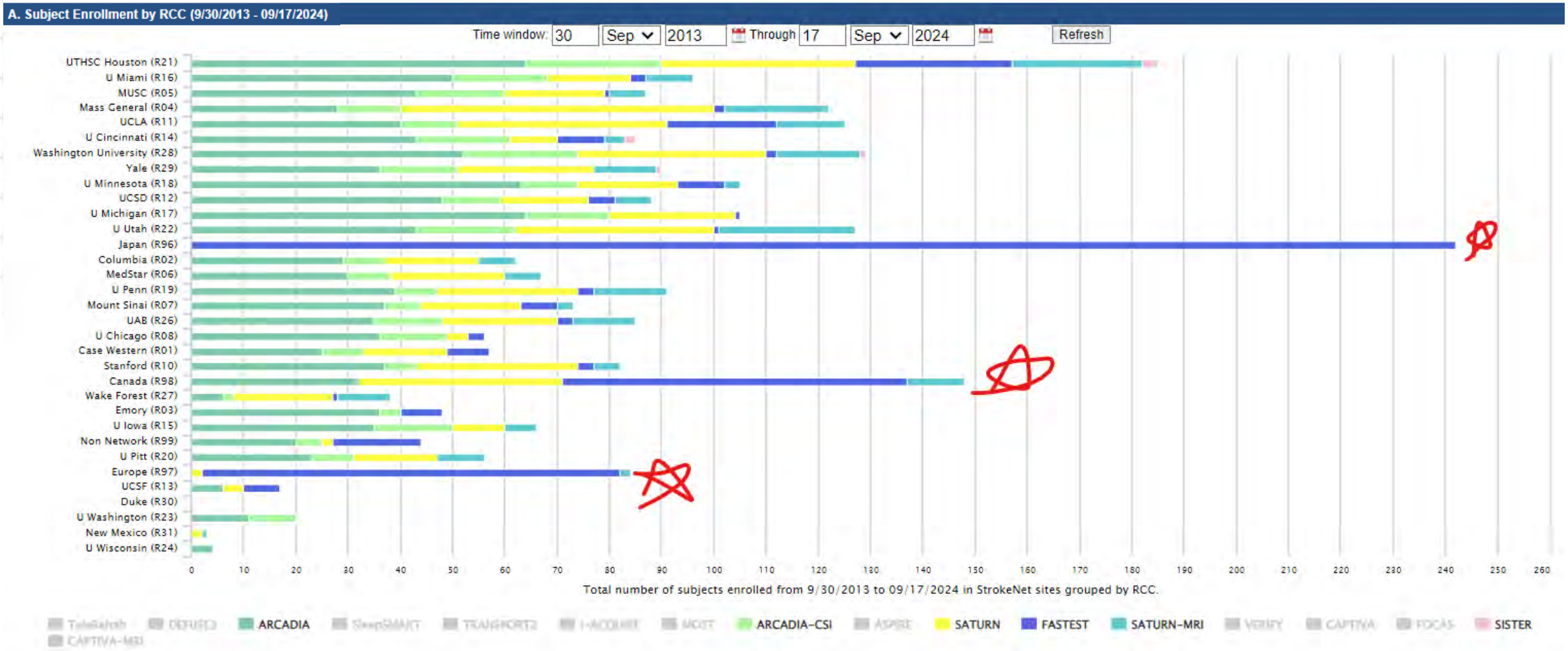
4. Data in this report are updated daily. Subjects enrolled within 24 hours may be not included.

Increased International Trials: Subject Enrollment



WebDCU upgrade to .NET platform

- 2-factor user authentication
- Increased data security protection
- More robust tools for data validation logic rules and skip pattern set up
- Future StrokeNet studies -- new platform upon development
- Ongoing StrokeNet studies - upgraded platform over the coming year(s)

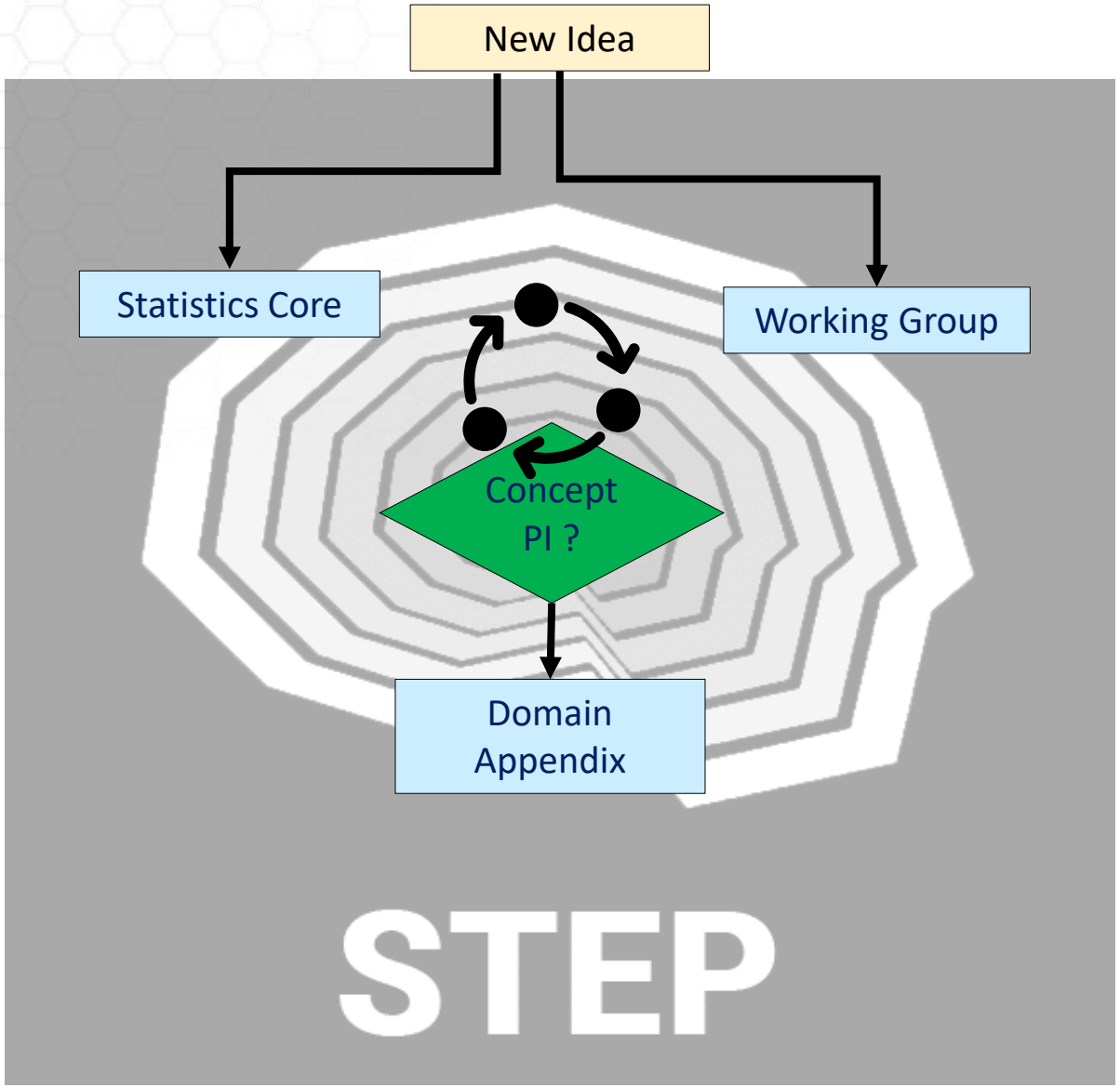
Standardization to increase efficiency

- CRFs -- library form structure, includes data field definitions, code, data validation rules, skip patterns, and associated emails
- Enhance the system stability, increase new project development efficiency and facilitate cross-project summary report generation.
- Integration of procedures at clinical sites, central pharmacy, central lab, and safety and efficacy outcome adjudication team members

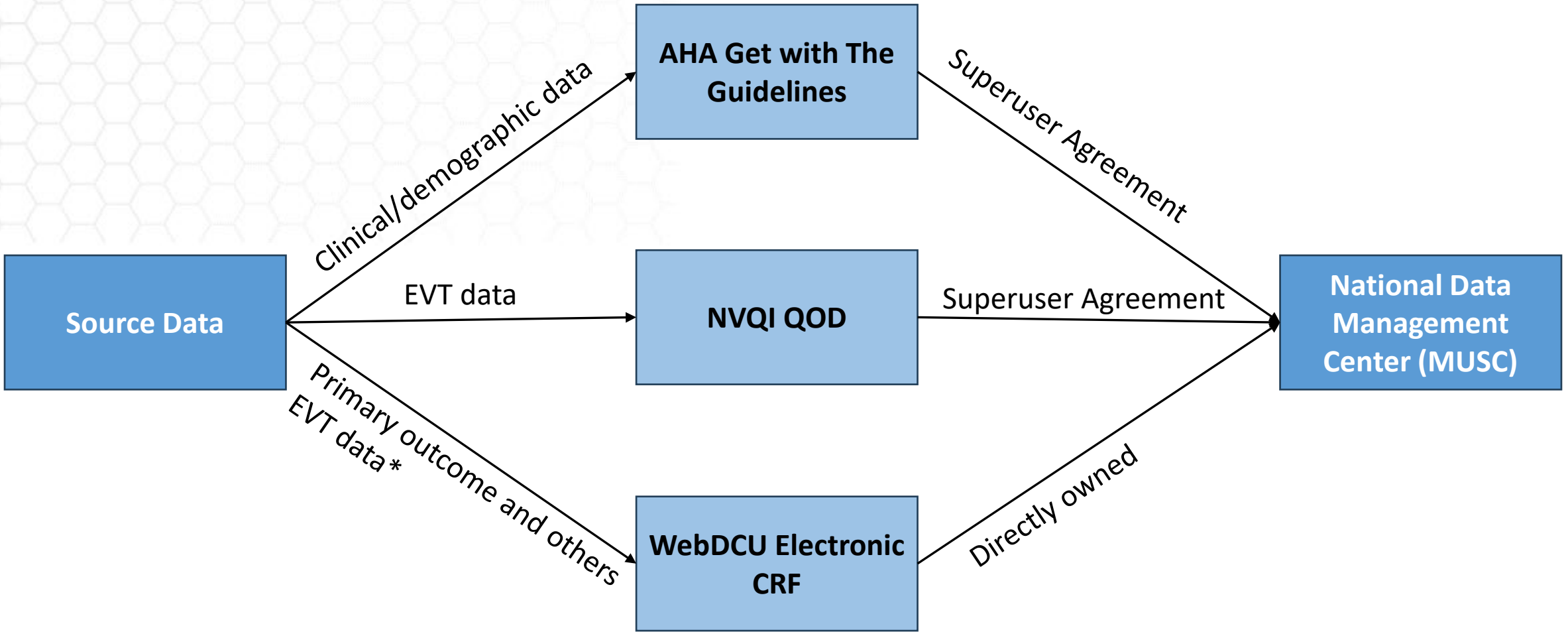
STEP

FDA approval	cIRB approval	CTA and cIRB packets sent	Site onboarding	DSMB meeting	Protocol training	First site released
June 2023	May 2024	June 2024	August 2024	Sept 2024	October 2024	Nov 2024

New Concept Development Work-Flow



STEP Data Transfer Procedures



Since original funding date 2013

167 — Study proposals

132 — Working Group

63 — ECS approved

110 — Grant submissions/resubmissions

BIOSTATISTICS

Data from September 2013- September 2022

Since original funding date 2013

78 — Feasibility surveys developed

2506 — Project-sites registered
(ranging from 12 sites to >200 sites/project)

34,628 — User accounts set up (not individual users)

17 — Studies developed (incl. ancillary studies)

PROJECT MANAGEMENT

Data from September 2013- September 2022

Since original funding date 2013

8,386 — Informed consents centrally monitored

344 — On-site monitoring visits conducted

141 — Remote monitoring visits conducted

8 — Trials sending quarterly site report cards

SITE MONITORING

Data from September 2013- September 2022

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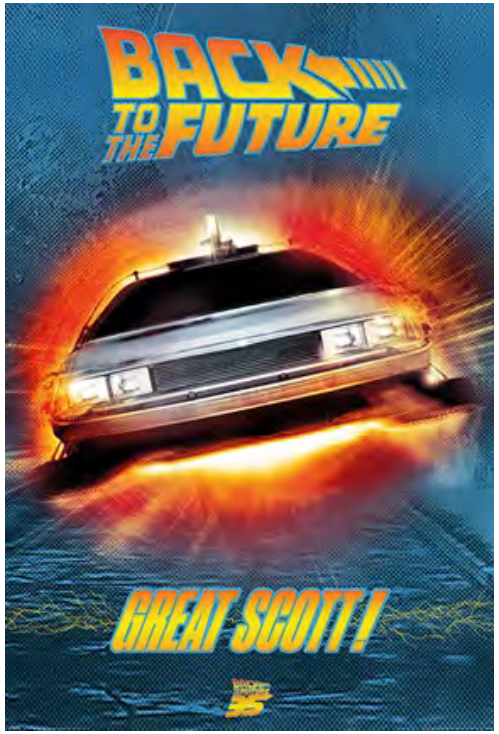
PREVENTION | TREATMENT | RECOVERY

NINDS UPDATE

Scott Janis, PhD, MA

NINDS Perspective: What we have learned from the past to help us guide our future



MUSC Medical University of South Carolina

NIH

UNIVERSITY OF Cincinnati

NINDS StrokeNet TEAM

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And Health Disparities
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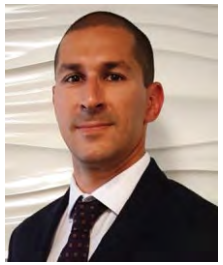
Program Scientist DEI CORE



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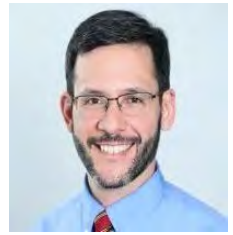
Program Scientist CAPTIVA MRI/ Telerehab 2



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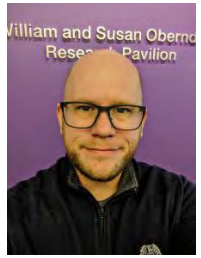
Program Scientist FOCAS

StrokeNet DSMB

Lina Garcia, M.D.
Clinical Coordinator
Division of Clinical Research
StrokeNet DSMB I Liaison



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Health Program Specialist
Division of Clinical Research
StrokeNet STEP DSMB Liaison

Alva Recinos, M.D.
Health Program Specialist
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StrokeNet Fogarty Expert

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SPAN Program

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Program Director
Division of Neuroscience

Sandra Hewett, PhD
Program Director
Division of Neuroscience

Jim Koenig, PhD
Program Director
Division of Neuroscience

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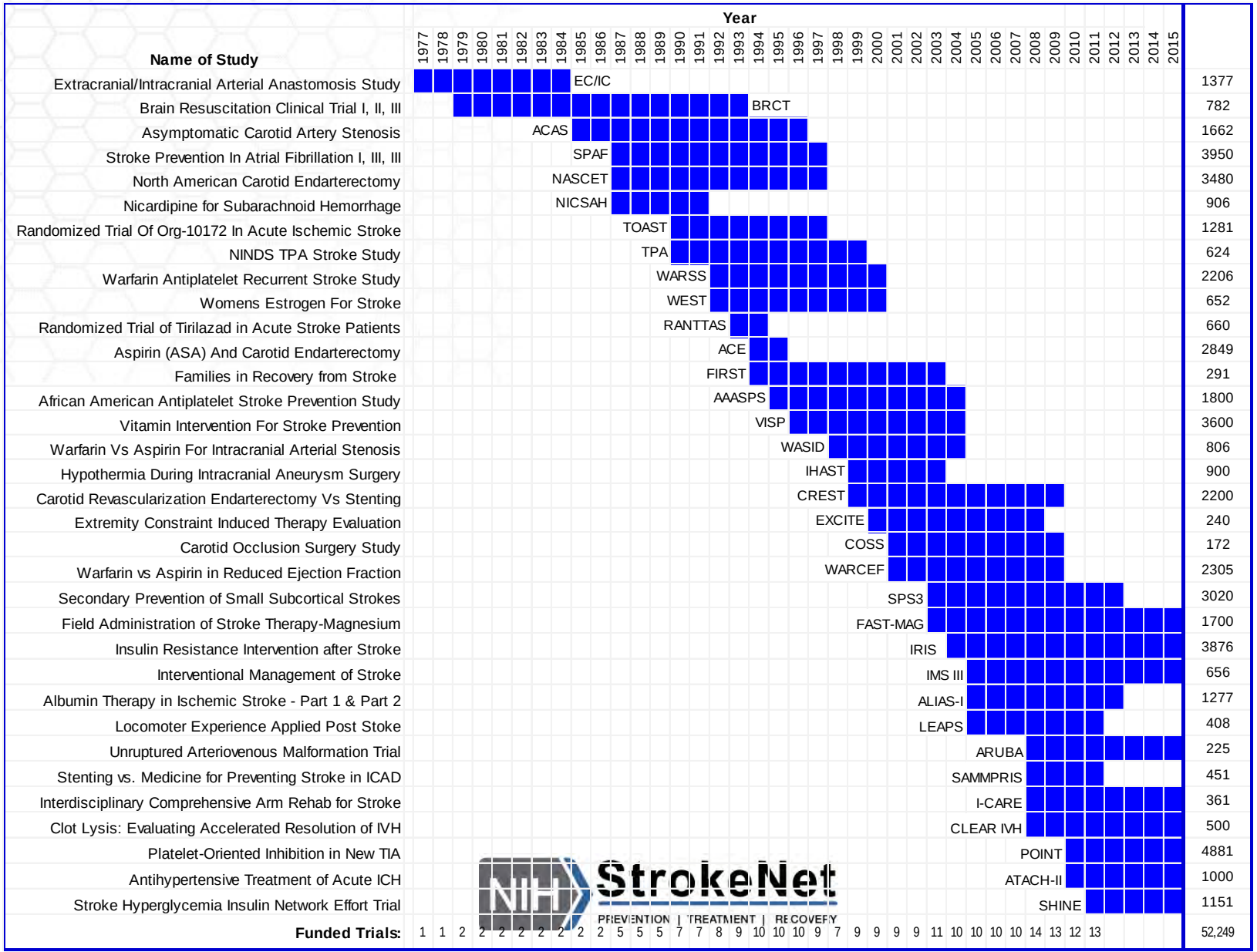
Major Clinical Trials in Stroke 1977-2011

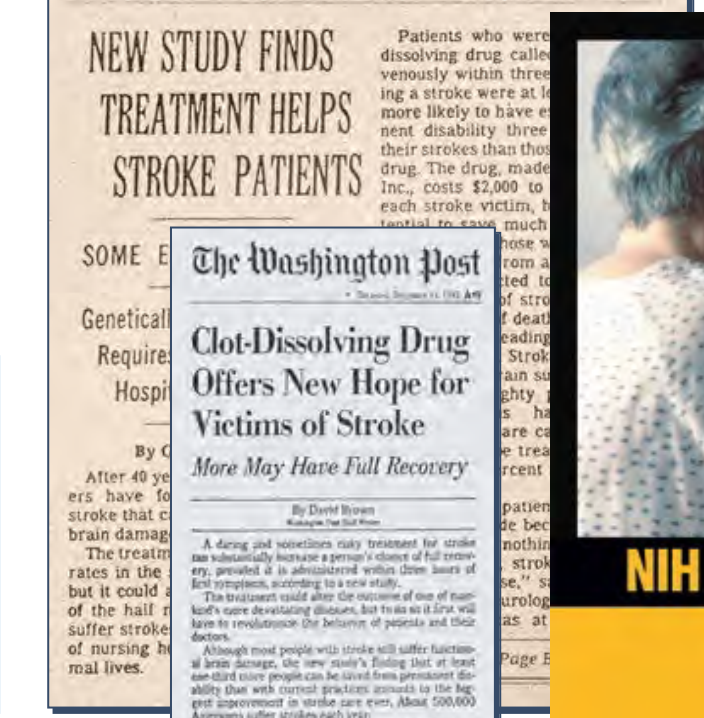


Getting NINDS Trials Started

- The Extracranial - Intracranial Bypass Trial
  - Started 1977
  - Ended 1984
  - Pivotal event in history of stroke clinical trials
  - Established that the stroke community could tackle very difficult questions and get answers that would be accepted and applied in practice
  - Set high standards of performance
- Brain Resuscitation Clinical Trial
  - Emergency consent

The Stroke Master Agreement

- Pilot studies
- Led to three trials
  - TOAST
  - NICSAH
  - NINDS TPA Study
- NIH Stroke Scale
- 50 center network



The New York Times

Copyright © 1995 The New York Times THURSDAY, DECEMBER 14, 1995

NEW STUDY FINDS TREATMENT HELPS STROKE PATIENTS

Patients who were dissolving drug called venously within three ing a stroke were at l more likely to have e nent disability three their strokes than thos drug. The drug, made Inc., costs $2,000 to each stroke victim, b tential to save much

SOME E

Geneticall Require Hospi

By C

After 40 ye ers have fo stroke that c brain damag The treatm rates in the but it could of the half suffer stroke of nursing h mal lives.

The Washington Post

Clot-Dissolving Drug Offers New Hope for Victims of Stroke

More May Have Full Recovery

By David Brown

A daring and sometimes risky treatment for stroke can substantially increase a person's chance of full recovery, provided it is administered within three hours of first symptoms, according to a new study.

The treatment could alter the outcome of one of mankind's more devastating diseases, but to do so it first will have to revolutionize the behavior of patients and their doctors.

Although most people with stroke still suffer functional brain damage, the new study's finding that at least one-third more people can be saved from permanent disability than with current practices amounts to the biggest improvement in stroke care ever. About 500,000 Americans suffer strokes each year.

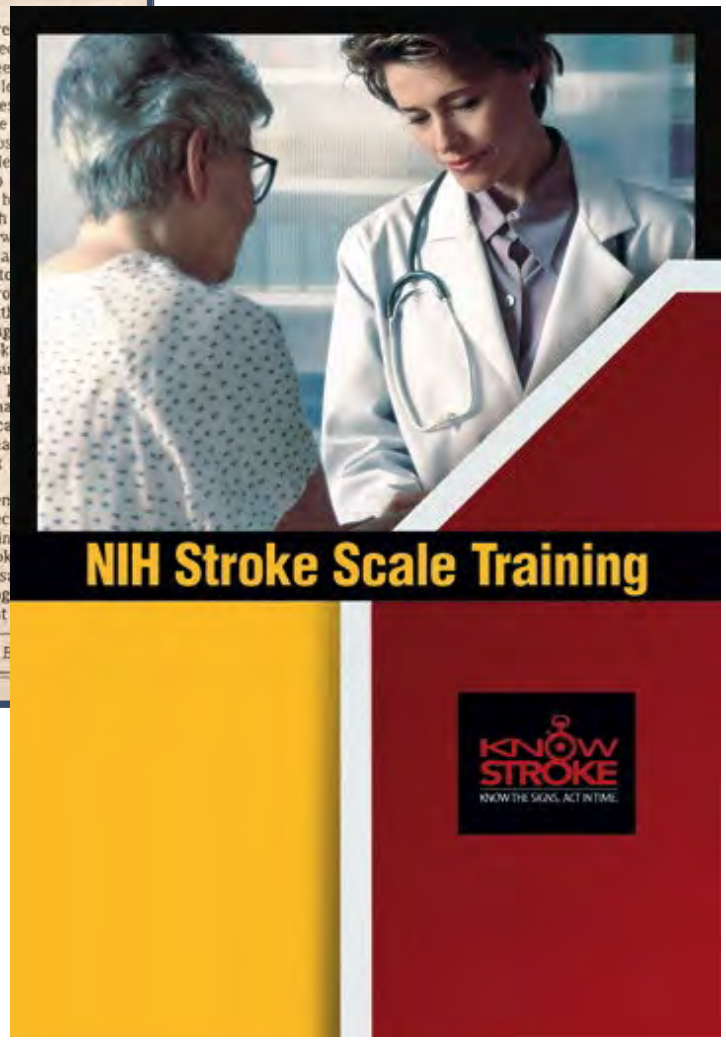
The study involved 624 patients and tested the safety and usefulness of tissue plasminogen activator (t-PA), a clot-dissolving drug now used in the treatment of heart attacks. About 80 percent of strokes are caused by blood clots, which either form in a blood vessel in the brain or travel there from elsewhere in the body.

Twenty percent of patients who did not get t-PA had a full recovery from their stroke when evaluated by neurological examination three months later. Of those who got t-PA, 31 percent recovered. Three other measurements of daily functioning were also used and they showed a 30 to 50 percent greater likelihood of recovery in t-PA patients.

"T-PA treatment can make a real difference to [patients'] neurological outcome, and to their overall daily functioning," said Thomas Brott, a physician at the University of Cincinnati and one of the leaders of the study, speaking at a news conference yesterday.

About 400,000 of the strokes suffered by Americans each year are caused by blood clots, and theoretically

See STROKE, A10, Col. 1



NIH StrokeN

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Report of the Stroke Progress Review Group - April 2002

Stroke Priorities for the 21st Century

National Institute of Neurological Disorders and Stroke

During the Presidentially designated Decade of the Brain—1990 to 2000—scie progress in improving our unde also called "brain attack." Str cause of death in the United St long-term disability, and a sign health worldwide.

scientists are improving our understanding of differences various popula- earn how ffect these

Research on stroke is among National Institute of Neurological component of the Federal govern

- Develop regional stroke center networks that will improve information-sharing and collaboration among health care providers, both regionally and nationally.

SPOTRIAS. **In May 2001, NINDS initiated the SPOTRIAS, to facilitate translation of basic research findings into clinical practice in settings where patients with acute ischemic and hemorrhagic stroke are evaluated and treated very rapidly after onset of their symptoms. Broader goals of this program include career development opportunities for new investigators, sharing of human tissue resources, and encouragement of collaborations among investigators across institutions.**

SPOTRIAS

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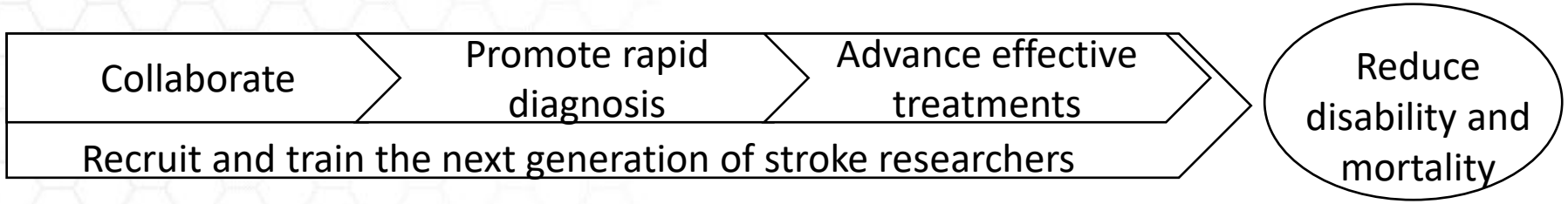
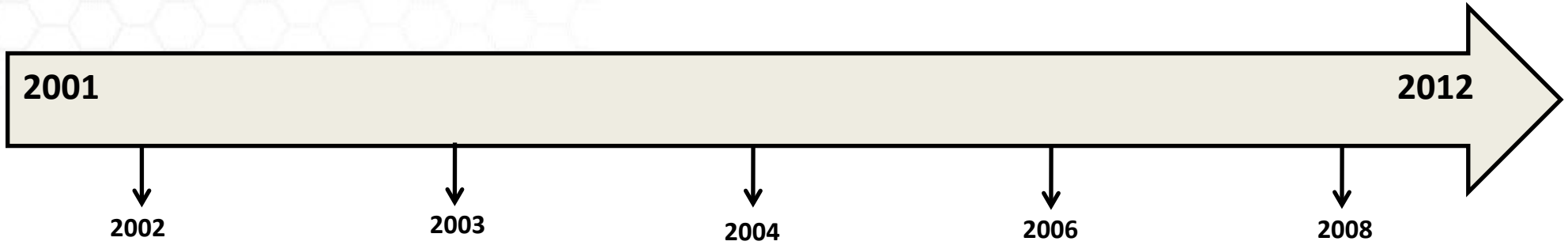
SPOTRIAS aimed to promote new therapeutic approaches for acute stroke

Conceptual model for SPOTRIAS





Centers:

UC Health

UCLA Health System

Columbia University Medical Center

Partners HealthCare

Washington University in St. Louis

UTHealth

UC San Diego Health System

National Institute of Neurological Disorders and Stroke

SPOTRIAS

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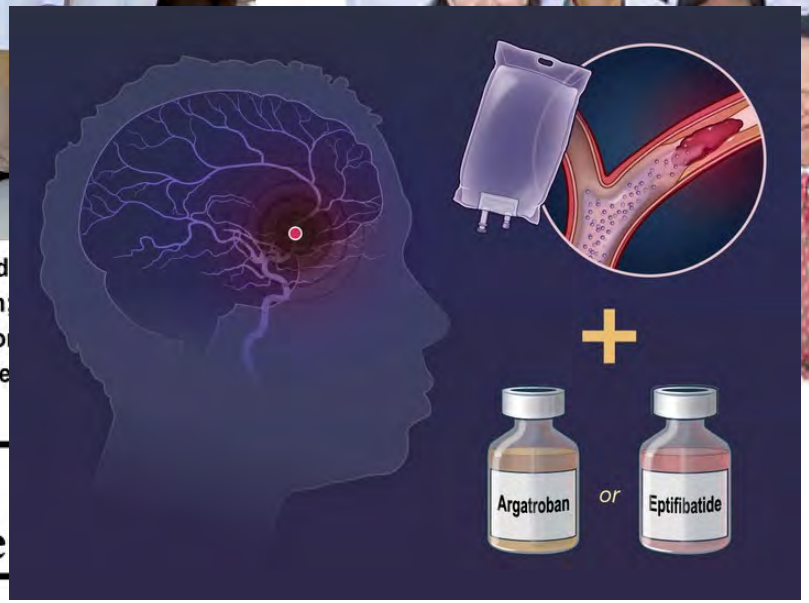
Building a team

2008 Greater Cincinnati/Northern Kentucky Stroke Team

Front Row: Aigang Lu; Pooja Khatri; Jeanne Sester; Jenny Osborne; Dan Woo; Dawn Kleind
Joe Broderick; Matt Flaherty; Joe Clark; Brett Kissela; Ed Jauch; Kathy Franklin
Back Row: Diana Oberschmidt; Alisha Hodge; Mary Haverbusch; Kathy Alwell; Charlie Moo
Janice Carrozzella; Angela Merritt; Irene Ewing; Pam Schmit; Liz Venn; Jane Eile
Julie Brock; Bonnie Combs; Elaine Miller; Judy Spilker

UNIVERSITY OF Cincinnati College

University of Texas-Houston Stroke Center



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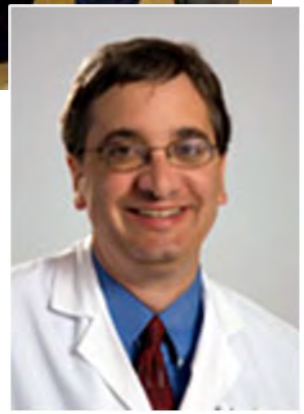
Building a team

UCSD Stroke Center

UCLA Stroke Center



NIH S

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MR Rescue

Building a team

NINDS Intramural

Columbia University Medical Center

Partners Stroke Team

Washington University stroke center

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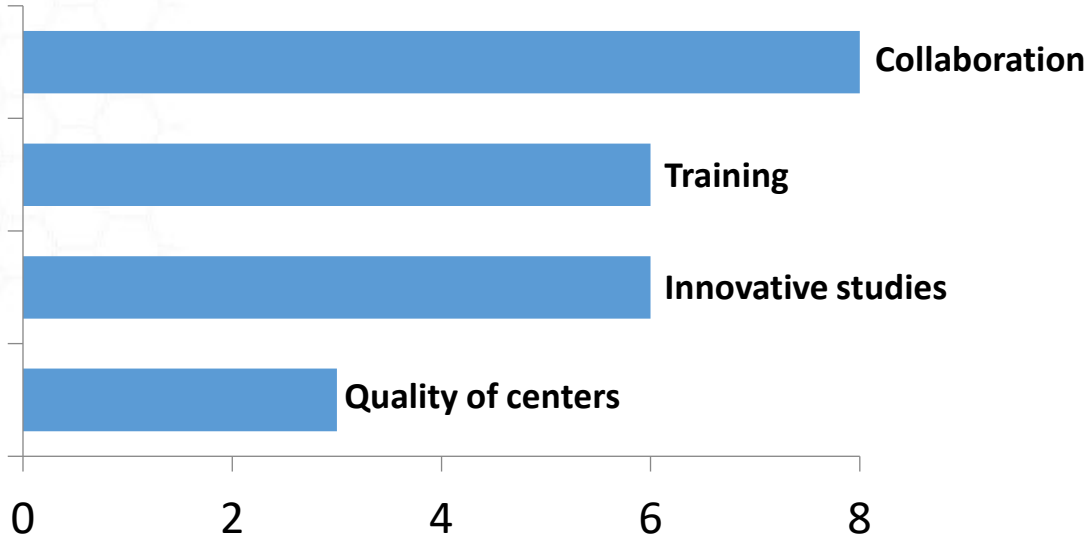
Collaboration was a clear strength of the SPOTRIAS program

Top listed strengths of SPOTRIAS

Methodology

- Asked interviewees to list the top three strengths of SPOTRIAS
- Answers that were stated two or more times were included in analysis

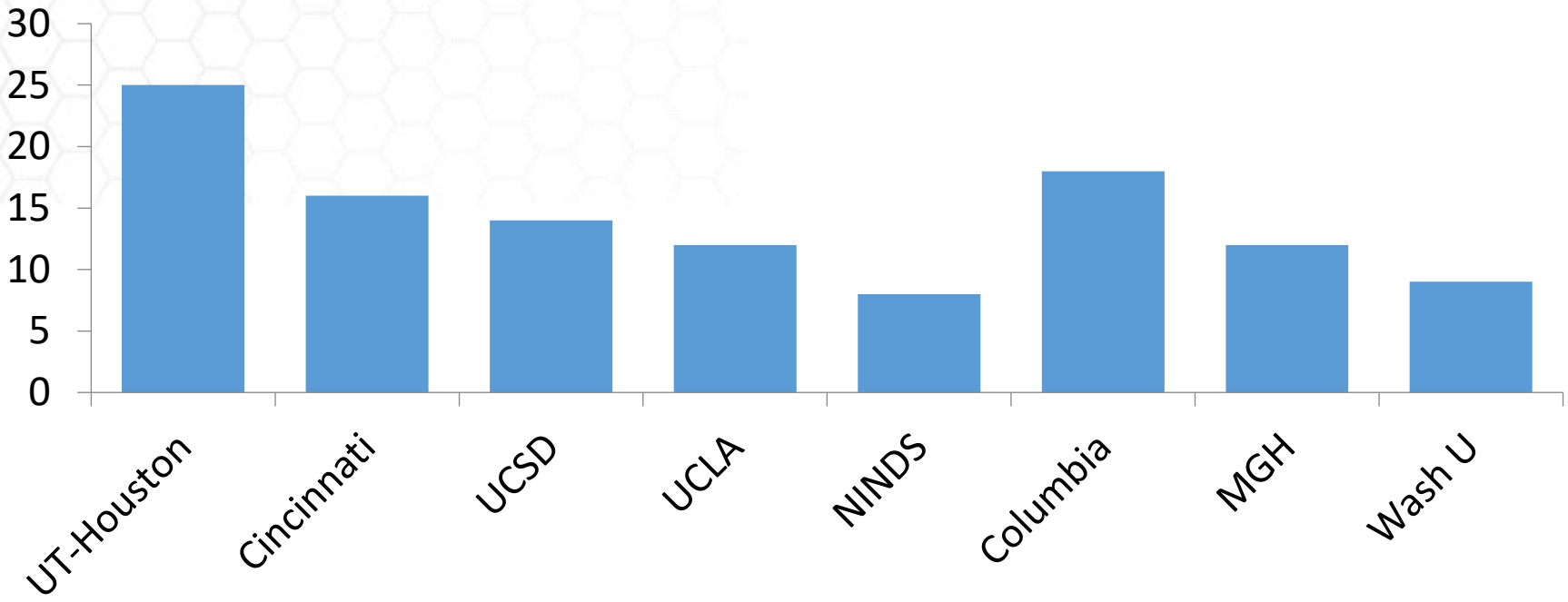


The SPOTRIAS collaboration requirement "changed the culture" of research across departments and institutions

Source: Interviews

SPOTRIAS centers have trained the next generation of stroke researchers

Number of total fellowship trained researchers from each SPOTRIAS center*



*Centers listed by date of entry into the SPOTRIAS program

Source: http://www.spotrias.org/training/,accessed July 17, 2012

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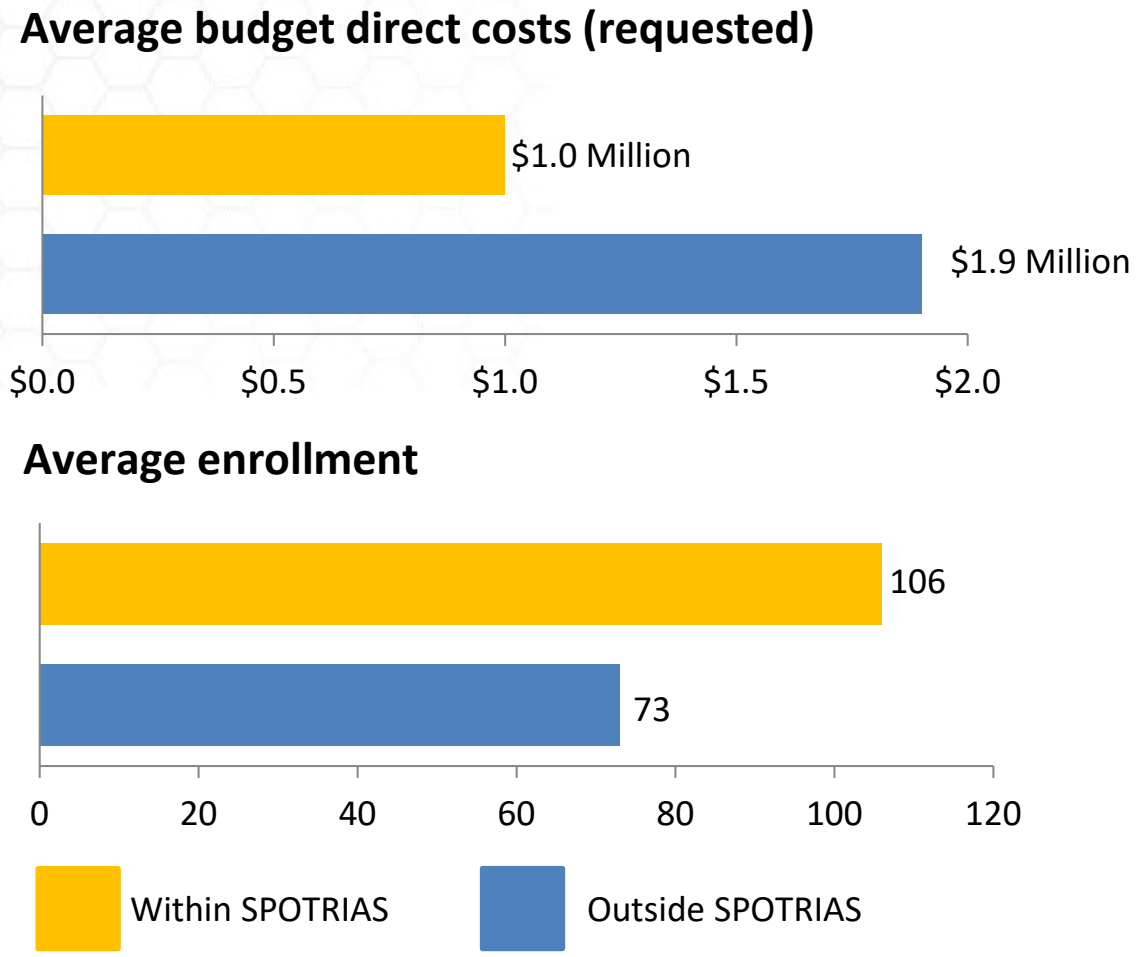
Funded SPOTRIAS clinical trials tended to have smaller requested budgets than NINDS trials outside SPOTRIAS



Source: www.clinicaltrials.gov; SPOTRIAS grants; NINDS

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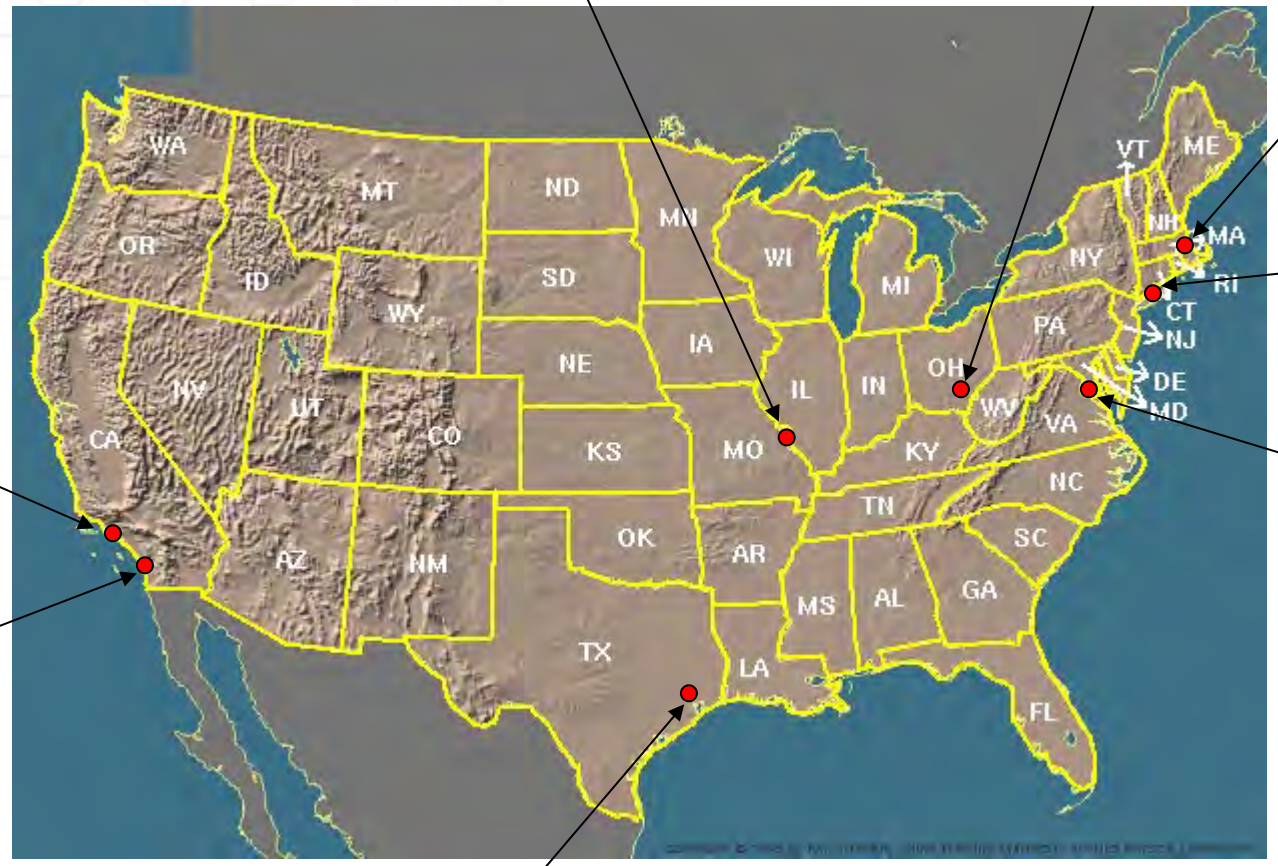
Beginning of a Stroke Network



Washington University in St. Louis

UC Health

Partners HealthCare

Columbia University Medical Center

National Institute of Neurological Disorders and Stroke

UCLA Health System

UC San Diego Health System

UTHealth

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Stroke Research Priorities Meeting 2012

Research Priority Setting

A Summary of the 2012 NINDS Stroke Planning Meeting Report

Barbara G. Vickrey, MD, MPH; Thomas G. Brott, MD; on behalf of the Stroke Research Priorities Meeting Steering Committee and the National Advisory Neurological Disorders and Stroke Council; Walter J. Koroshetz, MD; on behalf of the National Institute of Neurological Disorders and Stroke

Prevention

1) Prevention of Vascular Cognitive Impairment (VCI)
2) Imaging Biomarkers in Stroke Prevention: From Bench to Bedside
3) Expediting High Priority Comparative Effectiveness Research (CER) Trials in Stroke Prevention

Treatment

1) Preclinical and Clinical Studies to Improve Early Reperfusion Therapy and Establish Limitations of Late Reperfusion Therapy
2) Preclinical and Clinical Studies to Achieve Robust Brain Protection
3) Expand and Integrate Existing Stroke Trial Networks to Accelerate Translation

Recovery

1) Translational Research Using Neural Interface Devices for Stroke and Other Neurologic Disorders
2) Program for Translational Research Targeting Early Recovery after Stroke in Humans

Cross-cutting

Accelerate the Translation of Stroke Research in Preclinical Animal Models into Clinical Studies of Highly Promising Treatments

The NINDS Stroke Clinical Trial Network (NIH StrokeNet)

Infrastructure established in 2013; renewed in 2018 and 2023

Goals:

- Maximize efficiencies to develop and conduct a balanced portfolio of high-quality, multi-site phase 1, 2 and 3 clinical trials in stroke prevention, treatment, and recovery
  - Includes biomarker validation and ancillary studies to StrokeNet trials
- Educate future stroke researchers

Infrastructure:

- National Coordinating Center (NCC)
- National Data Management and Statistical Center (NDMC)
- 27 Regional Coordinating Centers (RCCs) with clinical performance and satellite sites representing over 700 stroke hospitals (including Canada, Europe, and Japan)
- Central Institutional Review Board; central research pharmacy, imaging core, and a training and education core
- Each RCC has annual support for portion of a trainee's effort

Clinical trials and studies funded separately from the infrastructure, through peer-reviewed funding mechanisms open to investigators from academia, foundations, or industry

NIH StrokeNet
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Funded by a Grant from the National Institutes of Health

NIH StrokeNet
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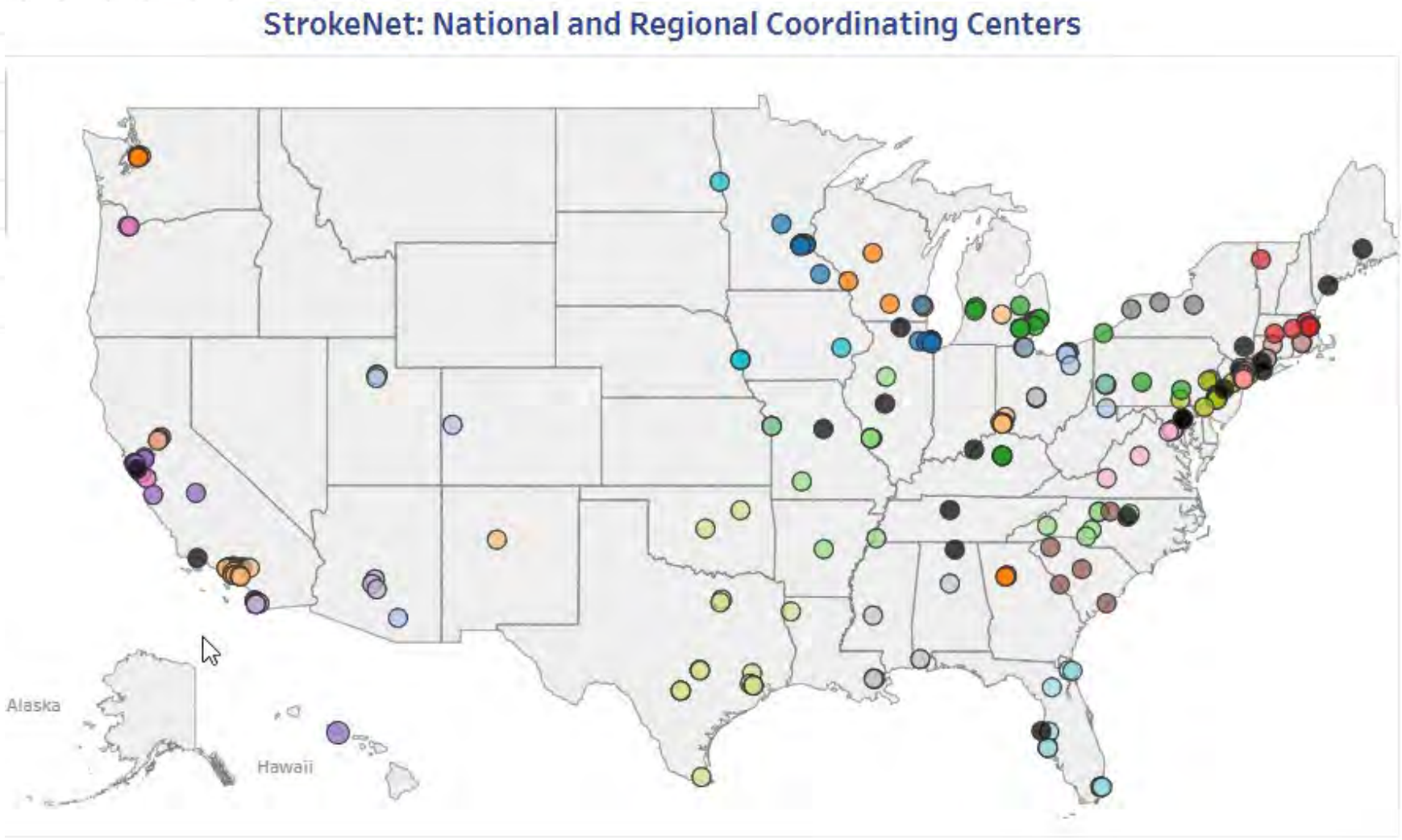
http://nihstrokenet.org/

NIH StrokeNet Sites



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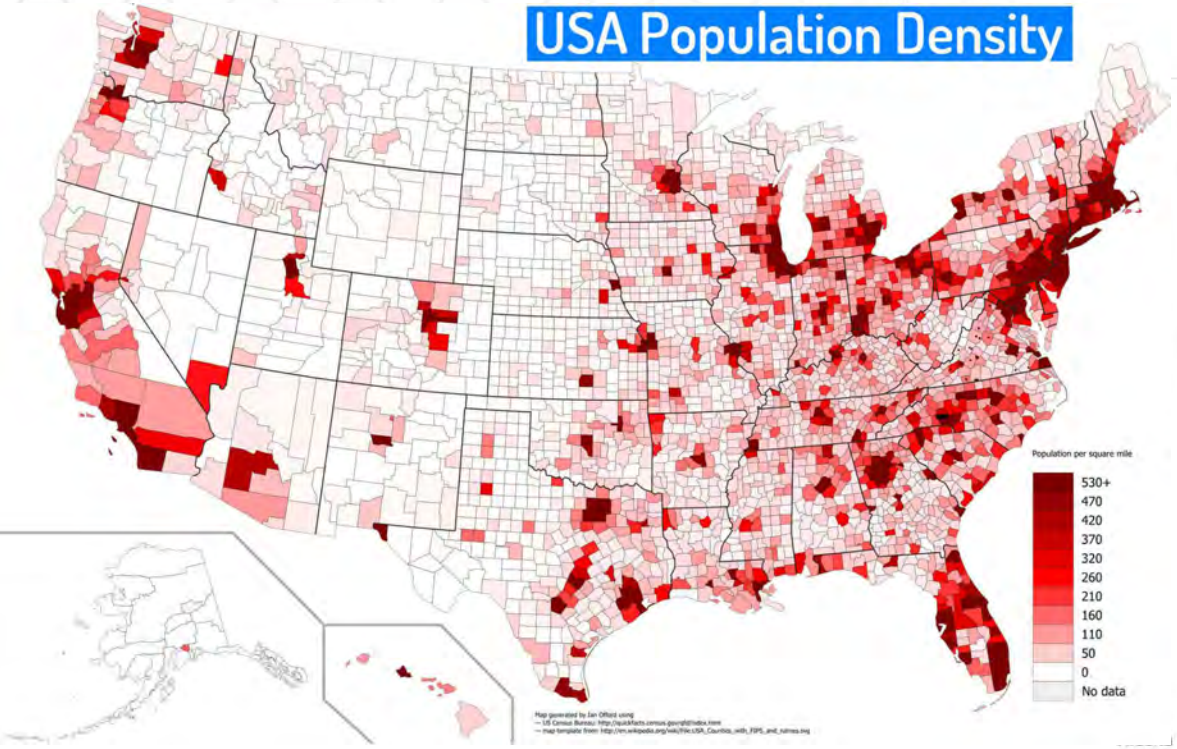
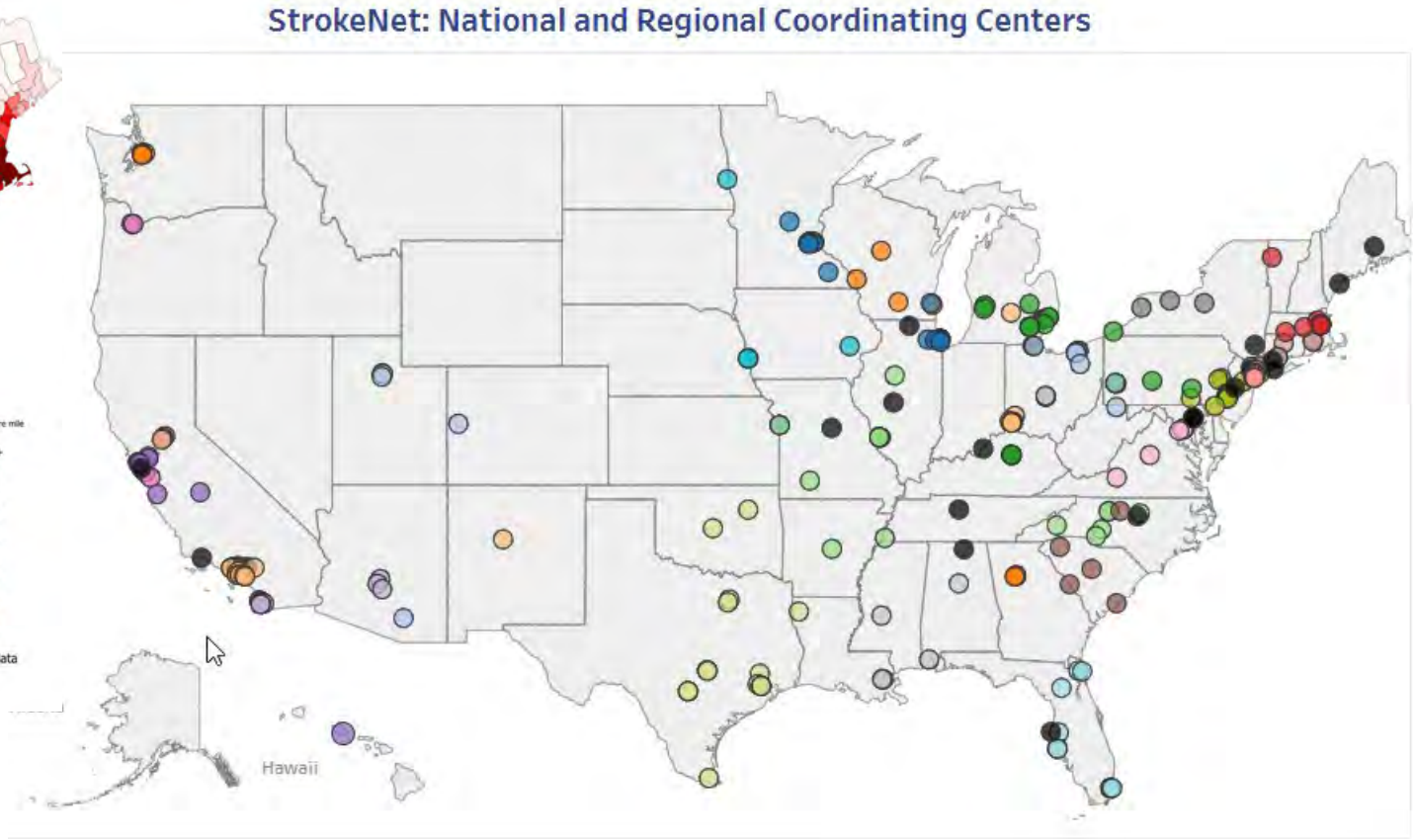
Coverage of U.S. Population





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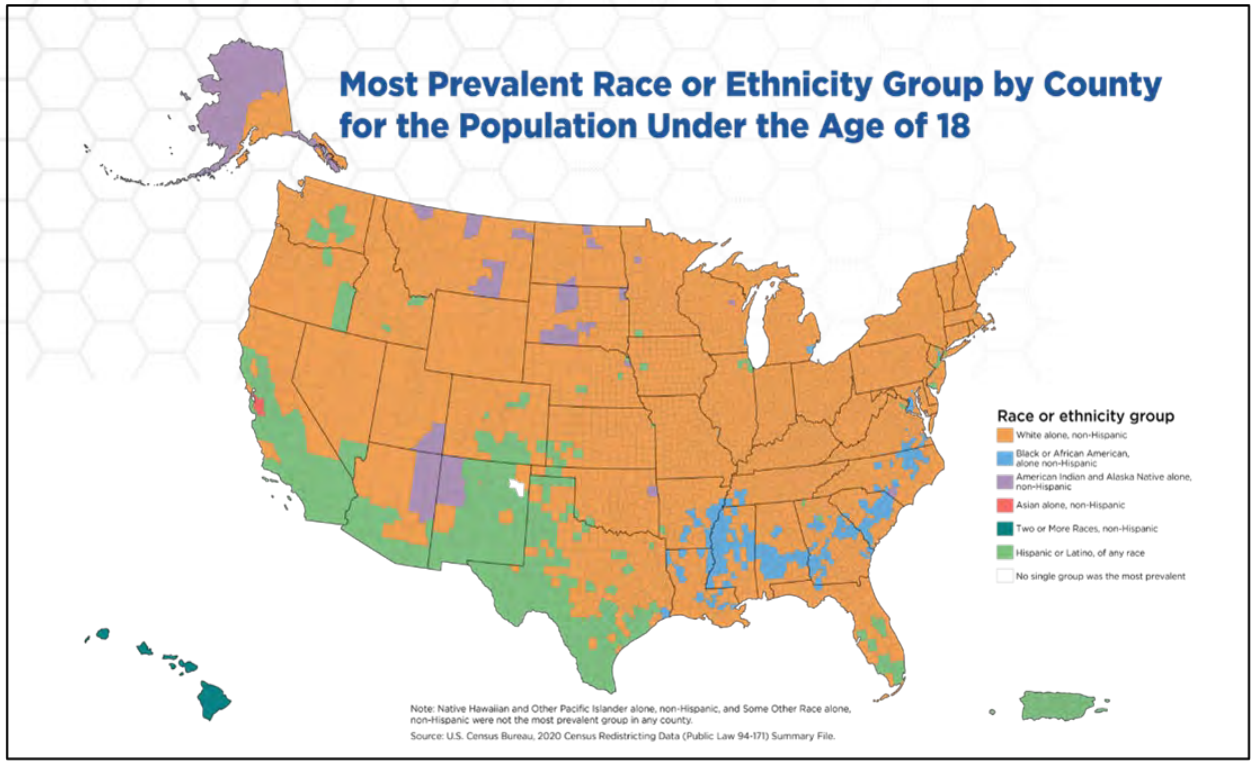
U.S. Race and Ethnic Population



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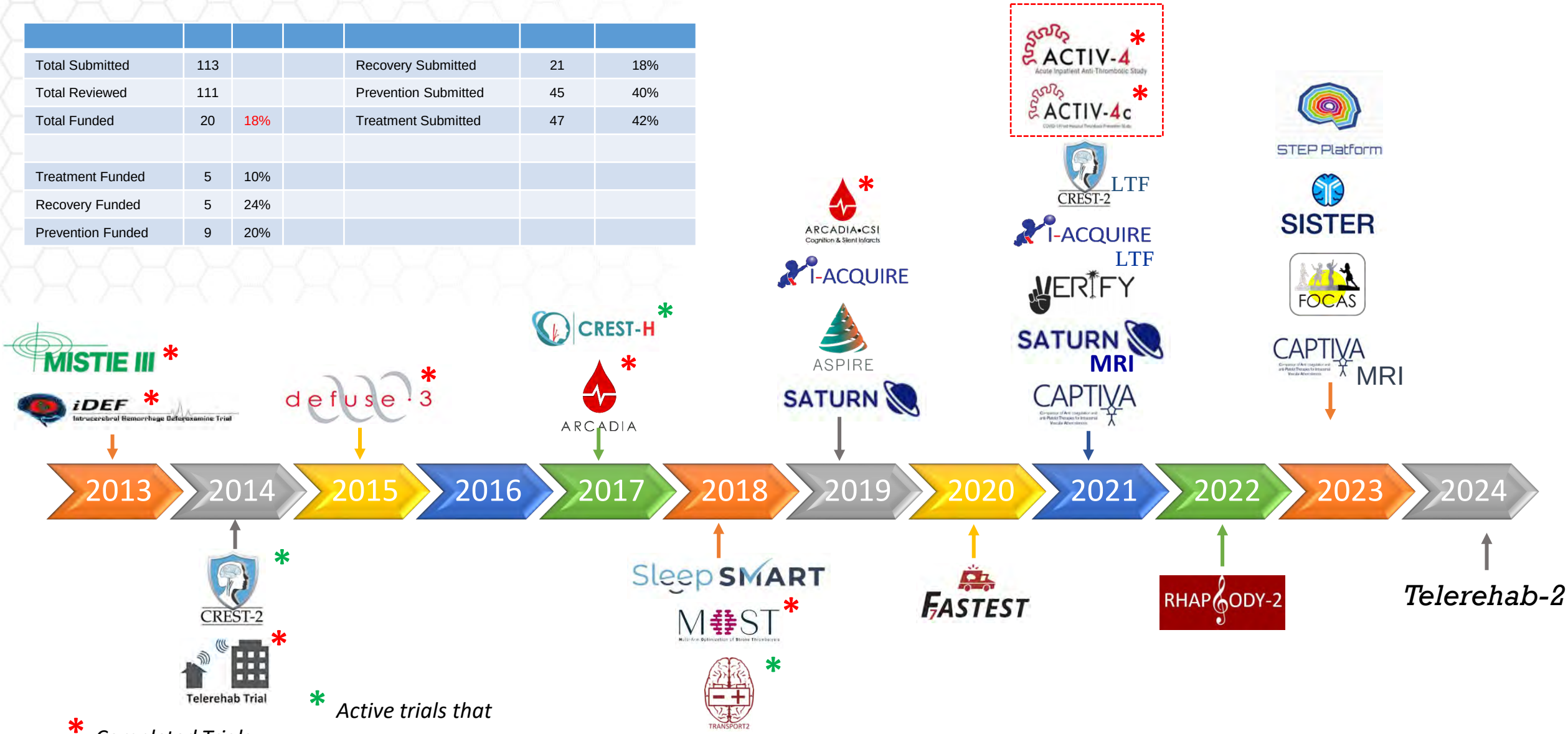
NIH StrokeNet by the Years

*As of 8/31/24, the network has consented and enrolled **13,823** and randomized **7492** participants in a StrokeNet study*

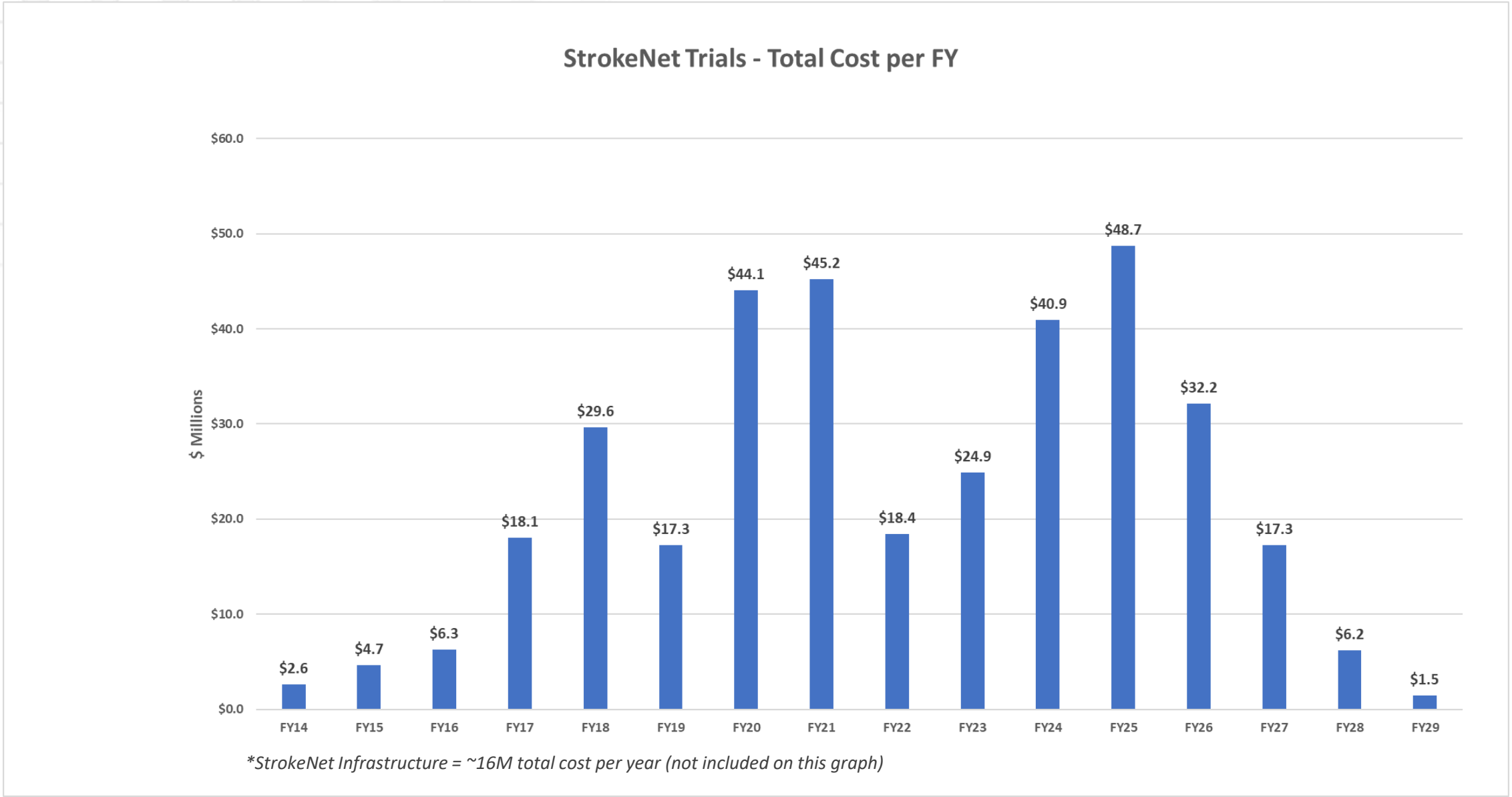
Total Submitted	113			Recovery Submitted	21	18%
Total Reviewed	111			Prevention Submitted	45	40%
Total Funded	20	18%		Treatment Submitted	47	42%
Treatment Funded	5	10%				
Recovery Funded	5	24%				
Prevention Funded	9	20%				



* *Completed Trials*

* *Active trials that completed enrollment*

StrokeNet Projects (funded cooperative agreements)



StrokeNet Infrastructure = ~16M total cost per year (not included on this graph)

Time from Submission to First patient enrolled

Application to Funding Approval (Days)	Application to Award Start (Days)	Funding Approval to Award Start (Days)	Application to First Patient Enrolled (days)	Award Start to Study Start (Days)	Award Start to First Patient Enrolled (Days)	
523	758	233	1093	295	319	Mean Days
260	297	106	372	113	122	Std Dev
486	712	223	1084.5	270	304.5	Median Days
16.2	23.7	7.4	36.2	9.0	10.2	Months
198	392	19	528	127	100	Min Days
1223	1427	465	1838	570	642	Max Days

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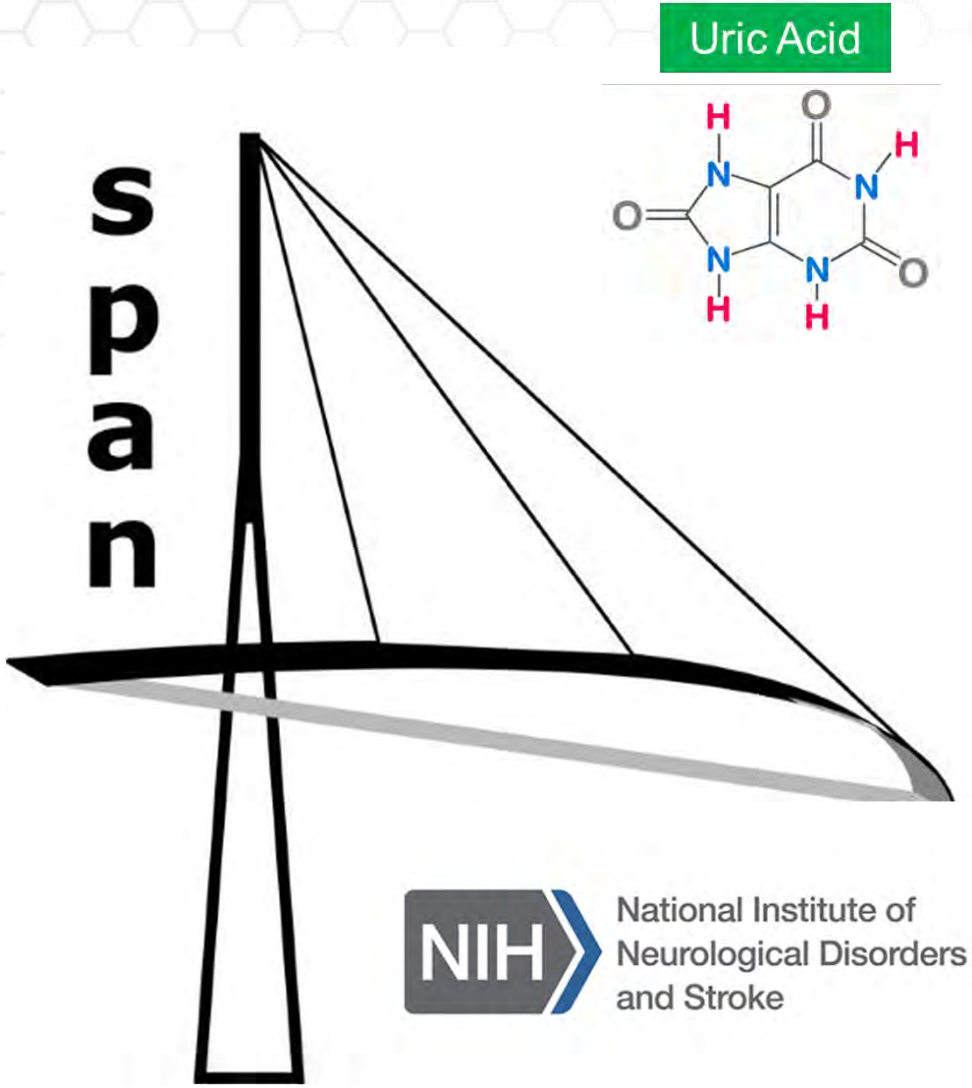
Stroke Preclinical Assessment Network (SPAN)



The Stroke Pre-Clinical Assessment Network (SPAN) seeks to conduct late-stage preclinical studies of putative neuroprotectants combined with reperfusion.

NIH National Institute of Neurological Disorders and Stroke

JOHNS HOPKINS MEDICINE

UNIVERSITY OF CALIFORNIA SAN DIEGO

UNIVERSITY OF IOWA HEALTH CARE

MCG REMOTE ISCHEMIC CONDITIONING

NIH Stroke PREVENTION | TREATMENT | RECOVERY

MGH 1811

Clinical Networks Evaluation Working Group

of the National Advisory Neurological Disorders and Stroke (NANDS) Council

- Presentation to the NANDS Council
- February 2, 2022

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Top-line Recommendations

Top 2 Recommendations

Proactively identify priorities

Monumentally improve pre-award/review efficiency

Strengthen internal and external community engagement

Set explicit goals to address equity, diversity, and inclusion and resource achieving them

Enhance clinical workforce development, readiness, and retention

Strengthen regular network evaluation and timely improvement

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Workable solutions based on the NINDS Clinical Networks Evaluation Working Group

Proactively identify priorities

- Work with community (through workshops/conferences, strategic planning) to identify areas of high unmet need and scientific priority
- Strengthen generation of research ideas through existing network structures, (e.g. disease area interest groups)
- Require appropriate representation of diverse populations

Monumentally improve pre-award/review efficiency

- Innovate and accelerate Network award and review processes
- Streamline NINDS extramural pre-review processes
- Consider Administrative Core for non-academic coordination functions

Strengthen regular network evaluation and timely improvement

- Develop 5-year network evaluation plan
- Conduct Listening Sessions with investigators and community partners 2x/year for input on performance

Strengthen internal and external community engagement

Set explicit goals to address equity, diversity, and inclusion and resources for achieving them

Enhance clinical workforce development, readiness, and retention

StrokeNet Thrombectomy Platform (STEP)

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

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

1995 - 2018

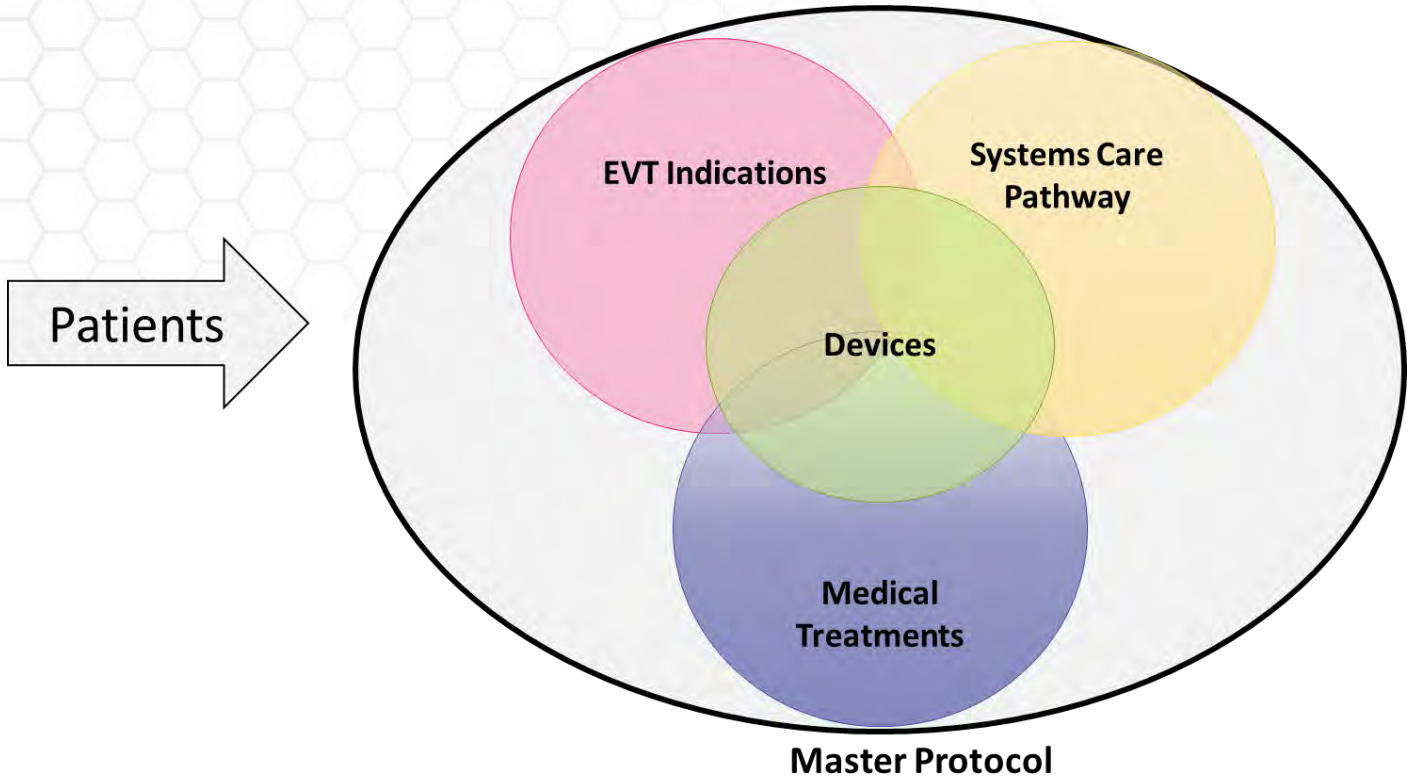
- 1999 - EMS Bridging Trial
- 2004 - IMS I
- 2007 - IMS II
- 2012 - DEFUSE 2
- 2012 - IMS III
- 2012 - MR RESCUE
- 2018 - DEFUSE 3

2018 - 2023

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

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

What types of questions for STEP



Clinical trials that will address:

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

How to Apply – Research Opportunity Announcement

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

13 Proposals already submitted

- Biospecimen Core funded for baseline blood collection
  - 24hr blood draw
  - Isolation of DNA that can be used for genetics and epigenetics and RNA for transcriptomics
  - Isolation of plasma for proteomic analyses
  - ***Future opportunities*** for R01 applications

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

Workable solutions based on the NINDS Clinical Networks Evaluation Working Group

Proactively identify priorities

- Work with community (through workshops/conferences, strategic planning) to identify areas of high unmet need and scientific priority
- Strengthen generation of research ideas through existing network structures, (e.g. disease area interest groups)
- Require appropriate representation of diverse populations

Monumentally improve pre-award/review efficiency

- Innovate and accelerate Network award and review processes
- Streamline NINDS extramural pre-review processes
- Consider Administrative Core for non-academic coordination functions

Strengthen regular network evaluation and timely improvement

- Develop 5-year network evaluation plan
- Conduct Listening Sessions with investigators and community partners 2x/year for input on performance

Strengthen internal and external community engagement

Set explicit goals to address equity, diversity, and inclusion and resources for achieving them

Enhance clinical workforce development, readiness, and retention

Setting our priorities

- Again, NINDS is engaged in a planning our next set of stroke priorities. But this time we are looking to leverage the scientific powerhouse we have in the network to work with our broader stroke community.
- Goal is not to use our time to pitch the trials we are working on.
- Identify scientific gaps and the opportunities that we can use our stroke network to advance.
- Starting with the network as a think tank. Then will move to include the boarder stroke community.
- The format will be a Princeton like conference that we will support through a conference grant.
- Objective is to help us (NINDS) prioritize funding and look for opportunities to streamline our research mechanisms (i.e., STEP and SPAN).
- ALL voices are important! We are here and we are listening…

Education and Training Core Update

Randolph Marshall, MD, MS
Devin Brown, MD
September 30, 2024
Atlanta, GA

Education and Training Core

- Mission: To develop stroke-related knowledge and skills for RCC trainees through interactive content and mentorship

- Vision: To become the preeminent platform for education and training of future leaders in stroke research

Education and Training core

- Randolph Marshall (Chair)
- Devin Brown (Co-Chair)
- Scott Janis (NINDS)
- Tatjana Rundek
- Cemal Sozener
- Farhaan Vahidy
- Anthony Kim
- PLUS 2 new members…

- Andrea Escobar (RCC PM/coordinator)
- Stephanie Wilbrand (RCC PM/coordinator)
- ***Kelsey Eklund, MD, U Colorado (Trainee)***
- ***Dylan Ryan, MD, Duke (Trainee)***

- *Jeanne Sester (ETC Core coordinator)*

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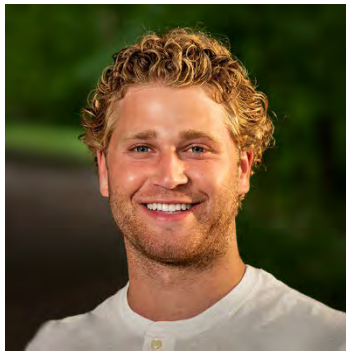
Diego Arias, PhD
MUSC

Paragol Balali, MD
UPENN *

Kriti Bhayana, MD
Texas



Ryan Bowen, PhD
Washington U.

Elizabeth Byrd, PhD, RN
UAB *

Julián Carrión-Penagos, MD
UCSD

Nitin Ramanujam Chakravarthula, MBBS
Minnesota

Kelsey Eklund, MD
New Mexico

Mert Erdenizmenli, MD
UCLA

Nathanial Fleming, MD
UCSF

Julie Gudenkauf, MD
Iowa *

Ashkan Javadzadeh, MD
USC

Lorelei Johnson, PhD
Wake Forest *

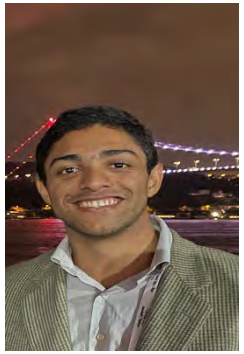
Sean Kelly, MD, PhD
Mount Sinai

Lovisa Ljungberg, MD
Cincinnati

Michael McCartin, MD
Chicago

Luis Carlos De Carvalho Paixao, BMBCh *
Miami

Srinath Ramaswamy, MD *
Columbia

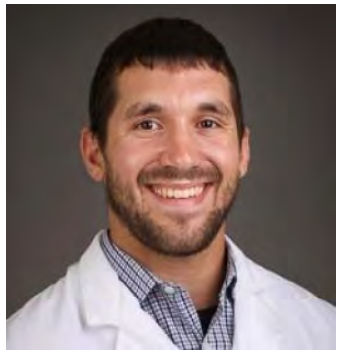


Savio Batista dos Reis, MD *
Emory

Lucas Rios Rocha, MD
Pittsburgh

Kazandra Rodriguez, PhD *
Michigan

Johanna Rotta, MD *
MGH



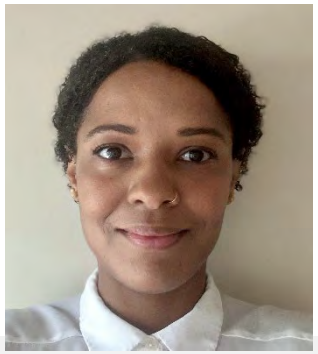
Dylan Ryan, MD
Duke

Sepideh Kiani Shabestari, PhD
Stanford

Aaron Shoskes, DO *
Utah

Liqui Shu, MD *
Yale

Gregory States, PhD
Case Western



Cesarina Tholian, MD
MedStar

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2024-2025 Trainees (n=28)

Career stage	
Clinical Fellow	13
Junior Faculty	9
Post-Doctoral Research Fellow	5
Non-MD trainee	1

Demographics	
Male	17
Female	11
Latino/Hispanic	5
African American	1

Degrees	
MD	16
DO	1
MBBCh/MBBS	2
MD, MSc	1
MD, PhD	1
Non MD Trainee	0
PharmD, BCPS	0
PhD/expected	6
PhD, RN	1
PhD, PT, DPT	0

Disciplines	
Biomedical Engineering	2
Emergency Medicine	1
Emergency Medicine Pharmacist	0
Medicine	2
Neurologist/ Vascular Neurologist	18
Nursing	1
Neuroscientist	1
Pediatric Neurologist	1
Physical Therapy	1
Speech Pathology	1
Data Science	0

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Education Training Core

Core Programming –

- Grand Rounds Webinar Series
- *Professional Development Webinar Series*
- *Basic Science Webinars*
- *Learning Communities*
- Mentored Trainee Research with presentations

NIH StrokeNet Grand Rounds Schedule 2024-2025

Date	Topic	Speaker	Institution
July 25	Treating No-Reflow in the Microcirculation after EVT	Ope Adeoye, MD	Washington Univ., St. Louis
Aug 29	Coma & Recovery of Consciousness: Prognosis and Biomarkers	Jan Claasen, MD, FNCS	Columbia University
Sept 26	Opportunities to Work with Community Health Workers to Enhance Inclusion and Optimize Recruitment and Retention in Trials	Bernadette Boden-Albala, MPH, DrPH	University of California Irvine
Oct 24	Dosing in Rehab Interventions	Steven Wolf, PhD	Emory
Nov 21	Thrombolysis in Patients with Recent DOAC use	Magdy Selim, MD	BIDMC Harvard
Jan 30,	Don't Neglect Neglect! Identification, Subtypes, and Interventions	Lorie Richards, PhD	University of Utah
Feb 27	Cerebral Arteriopathies	Aneesh B. Singhal, MD	MGH Harvard
Mar 27	Gloves Off for Acute Stroke Management: Fellow Case Presentations to 2 Stroke Experts	Negar Asdaghi, MD Brett Meyers, MD	U Miami UCSD
April 24	Determinants of Sex Differences in Stroke Risk and Cognitive Impairment	Eliza Miller, MD	Columbia University
May 29	AI: Risk or Benefit to the Future of Stroke Care?	Guido Falcone, MD	Yale

Professional Development Webinar series 2024-5

Date	Topic	Speaker	Time	Institution
Aug 19	Grant Writing	Dan Woo, MD	12 Noon	University of Cincinnati
Sept 4	Tips for a Successful Scientific Presentation	Enrique Leira, MD	1 PM	University of Iowa
Oct 24	Mentoring	Devin Brown, MD	4 PM	University of Michigan
Nov 4	Statistical Analysis – Collaborating with Data Mgt & Statistical Teams – Experts in Research	Jordan Elm, PhD	12 Noon	MUSC

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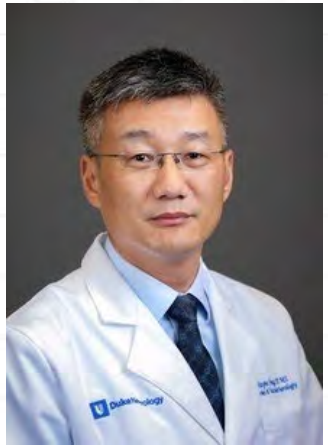
Basic/Translational Science Schedule 2024-2025

Date	Topic	Speaker	Institution
Oct 8 **12:00 pm ET**	Pharmacogenomics in Stroke Precision Medicine.	Dr. Guillaume Paré	McMaster University
Mar 20 **2:00 pm ET**	Novel Hemostatic Interventions for Spontaneous Intracerebral Hemorrhage	Kunjan Dave, PhD Sebastian Koch, MD	University of Miami University of Miami

2024-2025 Learning Community Group Leaders



Wayne Feng, MD

Brett Cucchiara, MD

Anthony Kim, MD

Cemal Sozener, MD

Brad Worrall, MD

Learning Communities 2024-2025

ANTHONY		
31 University of New Mexico	Kelsey Eklund, MD	Non-traditional stroke risk factors
26 University of Alabama Birmingham	Elizabeth M. Byrd, PhD, RN	Stroke transitions of care
13 UCSF	Nathanial Fleming, MD	primary and secondary prevention
14 UC	Lovisa Ljungberg, MD	Post-stroke transitions of care
06 Medstar	Cesarina S Thohan, MD	Health disparities
BRAD		
04 Massachusetts General	Johanna Rotta, MD	Vascular neurology and dementia
15 Iowa	Julie C. Gudenkauf, MD	Infectious and inflammatory conditions
18 Minnesota	Nitin Chakravarthula, MBBS	Cardiac CT Angiography
19 UPENN	Pargol Balali, MD, MSc	Biomarkers for ICH
21 Texas	Kriti Bhayana, MD	Pediatric Stroke
BRETT		
02 Columbia Health Sciences	Srinath Ramaswamy, MD	RCVS, ESUS
07 Mount Sinai	Sean M. Kelly, MD, PhD	Risk factors
11 USC	Ashkan Javadzadeh, MD	ICH, SVD, Moyamoya
12 UCSD	Julián Carrión-Penagos, MD	Venous thrombosis, Telestroke
22 Utah	Aaron Shoskes, DO	Cancer-associated stroke
30 Duke Univesity	Dylan Ryan, MD	Stroke in patients cancer

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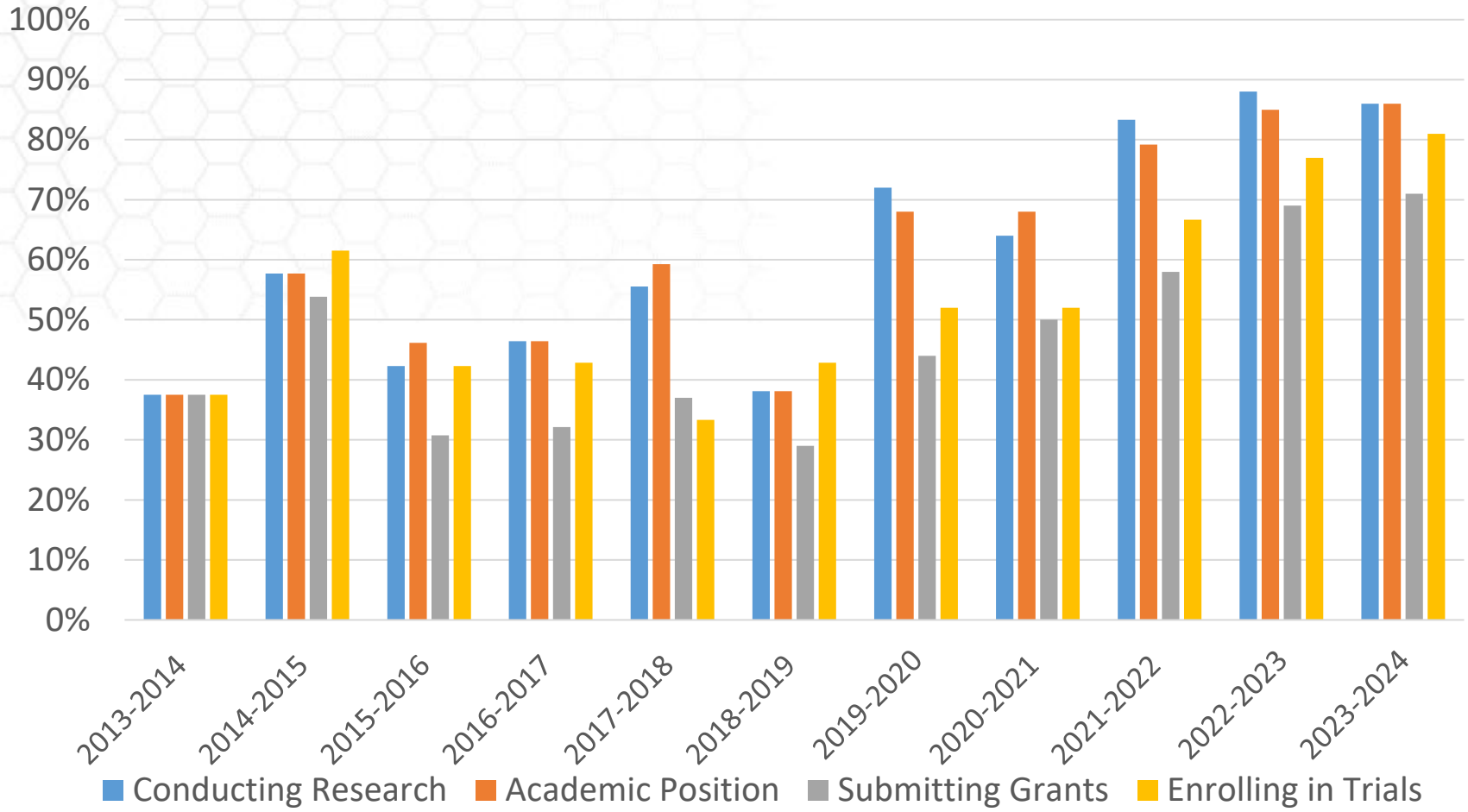
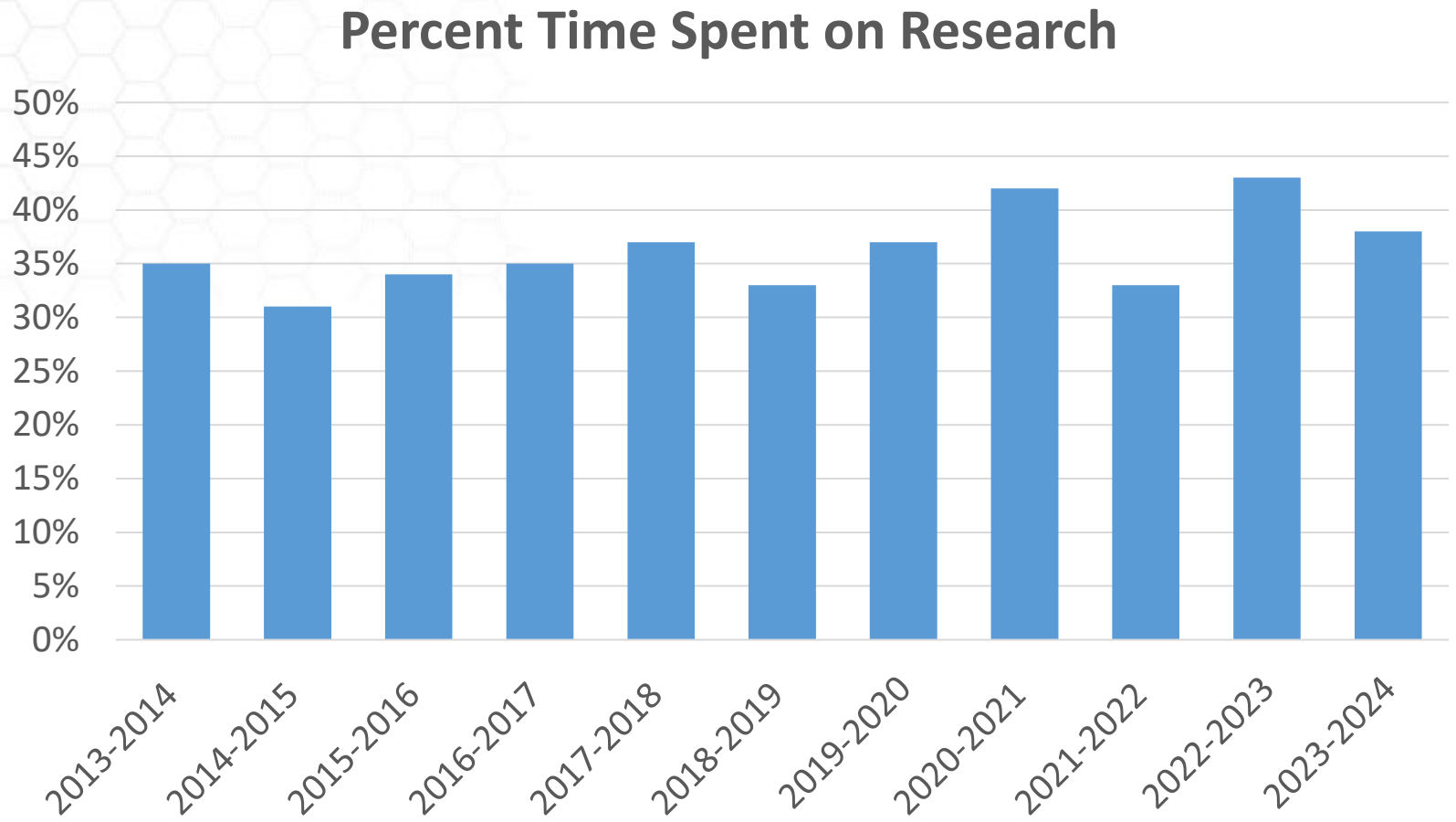
Learning Communities 2024-2025

CEMAL		
03 Emory University	Savio Batista dos Reis, MD	INR, Acute Stroke, Neuroimaging
08 Chicago	Michael P. McCartin, MD	Prehospital Management
11 UCLA	Mert Erdenizmenli, MD	Tenecteplase, large vessel occlusions
16 Miami	Luis Carlos Paixao, BMBCh, MSc	“No-Reflow” Phenomenon, Machine Learning
20 U. Pittsburgh	Lucas Rios Rocha, MD	LVO, cerebral hemodynamics
WAYNE		
01 Case Western Reserve	Gregory States, PhD	Biomechanics and control systems
05 MUSC	Diego E. Arias, PhD	Neuromodulation, electric field modeling
10 Stanford	Sepideh Kiani Shabestari, PhD	Stroke recovery, Immune response
17 Michigan	Kazandra ("Kay") M. Rodriguez, PhD	motor learning and recovery
27 Wake Forest (Western NC)	Lorelei Johnson, PhD	Post-stroke aphasia recovery
28 MARCC (Washington University)	Ryan Bowen, PhD (PhD expected)	Brain Network Repair
29 Yale University (Southern NE)	Liqi Shu, MD	Machine learning and rehabilitation

Post-training Survey Results on Research



Post-training Survey Results on Research



Grants Submitted as PI

2023—2024: 1 K23, 1 CTSI pilot award, 1 AHA Early faculty independence award

2022-2023: 3 K23's, 1 CTSI pilot award

2021-2022: 1 AHA grant

2020-2021: 1 K08, 2 R03's, 1 DoD, 1 F32

2019-2020: 2 K23's, 1 R21, 2 R03's, 1 R00

2017-2018: 2 K23's, 3 R01's, 2 R21's, 1 R03, 1 UG3/UH3, 2 R34's, 2 R44's

2016-2017: 1 K23, 3 R01's, 2 R21's, 1 R03, 1 L30, 2 VA grants, 1 CTSA Pilot grant

2015-2016: 2 K23's, 1 R01, 1 R21, 1 R03

2014-2015: 1 K23, 2 R01's, 1 AHA CDA

Metrics

- Mandatory attendance on Grand Rounds Webinars, Professional Development webinars, participation in Learning Communities
- Mandatory trainee presentations
  - In-person at national meeting (3)
  - Remote during a special, mentored 3-hour session (9)
  - Time slots during the Professional Development Webinar series (16)
- Other service activity to the StrokeNet Community (e.g. trainee volunteer on the Education and Training Core.)
- End of year survey: publications, grant submissions, professional appointments post-StrokeNet training
- Database kept by Jeanne Sester

Optional opportunities (available to all)

- Single observation of a Working Group meeting
- Attend StrokeNet Steering Committee Meetings (monthly)
- Track enrollment in StrokeNet trials/studies

Brand new and recently implemented programming

- Trainee attendance at Clinical Trial/Study Executive Committee Meetings
  - CAPTIVA (2)
  - VERIFY (1)
  - I-ACQUIRE (1)
- Trainee members of Working Groups
  - Acute (2)
  - Prevention (2)
  - Rehab/Recovery (2)

Engagement of current trainees

Training Core Members	Ryan (Duke), Eklund (U Colorado)
Acute stroke Working Group	McCartin (U Chicago), Paixao (U Miami)
Prevention Working Group	Chakravarthula (U Minnesota), Ramaswamy (Columbia)
Rehab/recovery Working Group	Rodriguez (U Michigan), Shu (Yale)
CAPTIVA Exec Committee	Eklund (U Colorado), Rotta (MGH)
VERIFY Exec Committee	Shu (Yale)
I-ACQUIRE Exec Committee	Bhayana (UT Houston)

Reminder: Deadlines

- Request for new Trainees' training plans – May
- Solicit Grand Rounds Webinar topics and speakers – May
- Survey to Trainees – June
- Final Trainee Progress report – June
- Trainee Contact form – June
- Update from prior trainees – June

Self-directed learning opportunities (trainees, coordinators, mentors)

- https://www.nihstrokenet.org/education
  - Introduction to the Principles and Practice of Clinical Research (IPPCR) https://ocr.od.nih.gov/courses/ippcr.html
  - Ethical and Regulatory Aspects of Clinical Research https://bioethics.nih.gov/courses/ethical-regulatory-aspects.shtml | https://videocast.nih.gov/PastEvents?c=22
  - Principals of Clinical Pharmacology https://ocr.od.nih.gov/courses/principles-clinical-pharmacology.html

CRP Training and Education Core Updates

Heena Olalde, RN, MSN
University of Iowa

Kinga Aitken, MD, MPH, CCRP
University of Utah

MUSC Medical University of South Carolina

NIH

University of Cincinnati

Committee Members

Co-Chairs
Heena Olalde, RN MSN
Kinga Aitken, MD MPH CCRP

Tammy Davis, RN

Jason Weimer, MA

Krystal Schmidt

Abbey Staugaitis, RN MSN

David Haney

Karen Rapp, RN, BSN

Laura Benken, MBA

Amy Sulken, CCRP

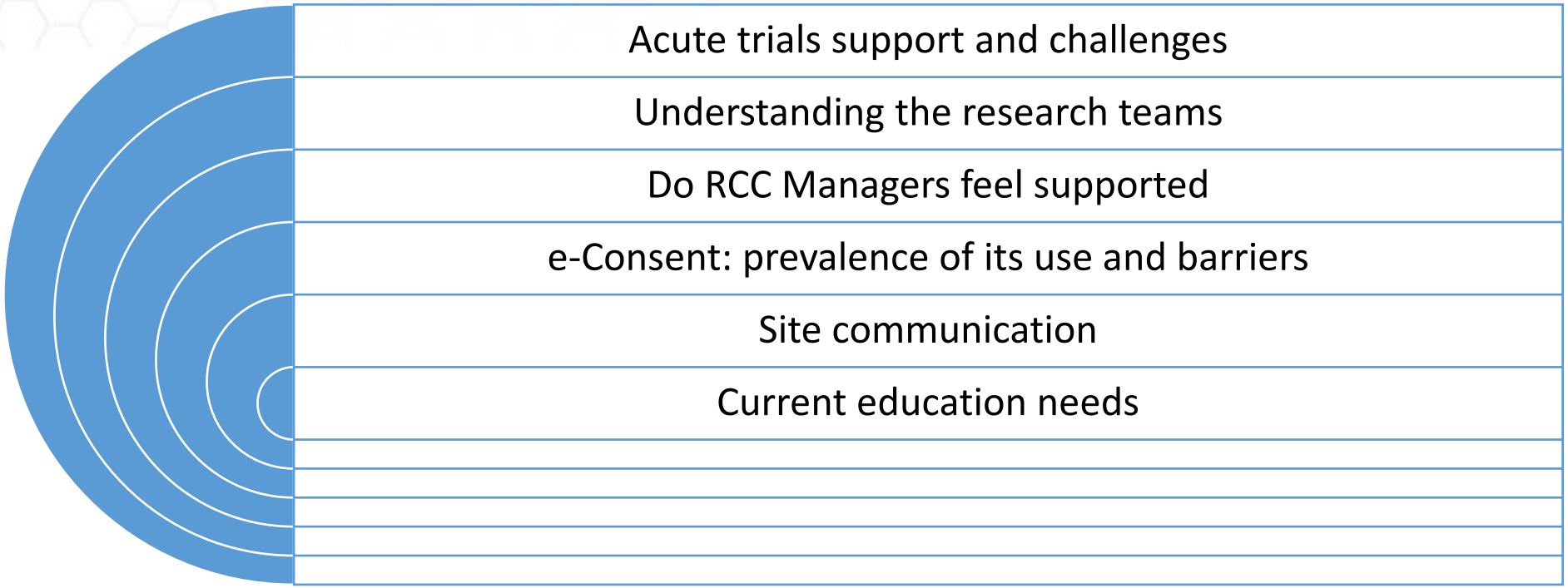
Jennifer Golan, MS

Kalli Beasley, MPH

Kristine Konsulis

Summary of activities

- Nov 2023- Jan 2024: baseline assessments, RCC one-on-one meetings
  - Data collected from 25 RCC (1 RCC didn't have a manager, 1 new RCC that wasn't set up)
- Continued new RCC manager mentoring



Acute trials support and challenges

9 RCC without 24/7 after hours coverage

- Not a dedicated 24/7 coordinator
- Not expected to come in over nights/weekend.
- No additional pay. Comp time is offered if the coordinator happens to stay after hours
- IDS Pharmacy is expensive after business hours
- Limited pharmacy hours
- Small team, no back-up coordinators

16 RCCs with 24/7 or limited after hours coverage (7am-11pm or similar)

- Few sites have an actual call schedule for coordinators
- Higher salaries to compensate for on call
- Acute stroke recruitment is done remotely (clinicians are boots on the ground)
- Hard work/life balance for the 24/7 coordinators, lots of turn over
- Research pharmacy is 24/7
- The coordinator is on call 24/7 by their choice. No back up coordinator coverage

Understanding the research teams

- Have mix of RNs, CCRPs, non-licensed or certified research assistants, International medical graduates, post bac interns, etc.
- Clear career path- 3 levels of coordinators: 1. Entry level (e.g. RA1), 2. Experienced coordinators(e.g. RA2), 3.Research nurse coordinators
- Some of the research coordinators do not have reliable clinical knowledge
- Most RCCs have CTSAs
- Optional training opportunities exist at most sites

Do RCC Managers feel supported?

Yes

- Engaged PIs who have great working relationships with Manager and team
- Supportive department that recognizes the hard work and prestige
- Weekly meetings with stroke attendings
- Ability to work in a hybrid model has been helpful for work life balance

No

- Feels lost, did not get much education when transitioning to manager role
- Concepts are a bit abstract
- Past year has been hard
- StrokeNet coordinator for a long time, regulatory duties are new and challenging
- Being understaffed

eConsent: usage and barriers

Positives:

- Most RCCs and satellites have some version of eConsent currently approved for use
- Most sites are comfortable with remote consent and eConsent in the acute setting
- A few sites have dedicated tablets and are trying to use mostly eConsent
- Only 4 RCCs are paper only

Negatives:

- Challenging to use, especially in person, for older patients
- Some institutions strongly prefer paper for in person interactions
- Lack of dedicated tablet for research purposes

e-Consent needs

- Clear top to bottom expectation coming from StrokeNet
- Possibly providing a tablet to use for consent with future trials
- Educational session to increase comfort

Site communication

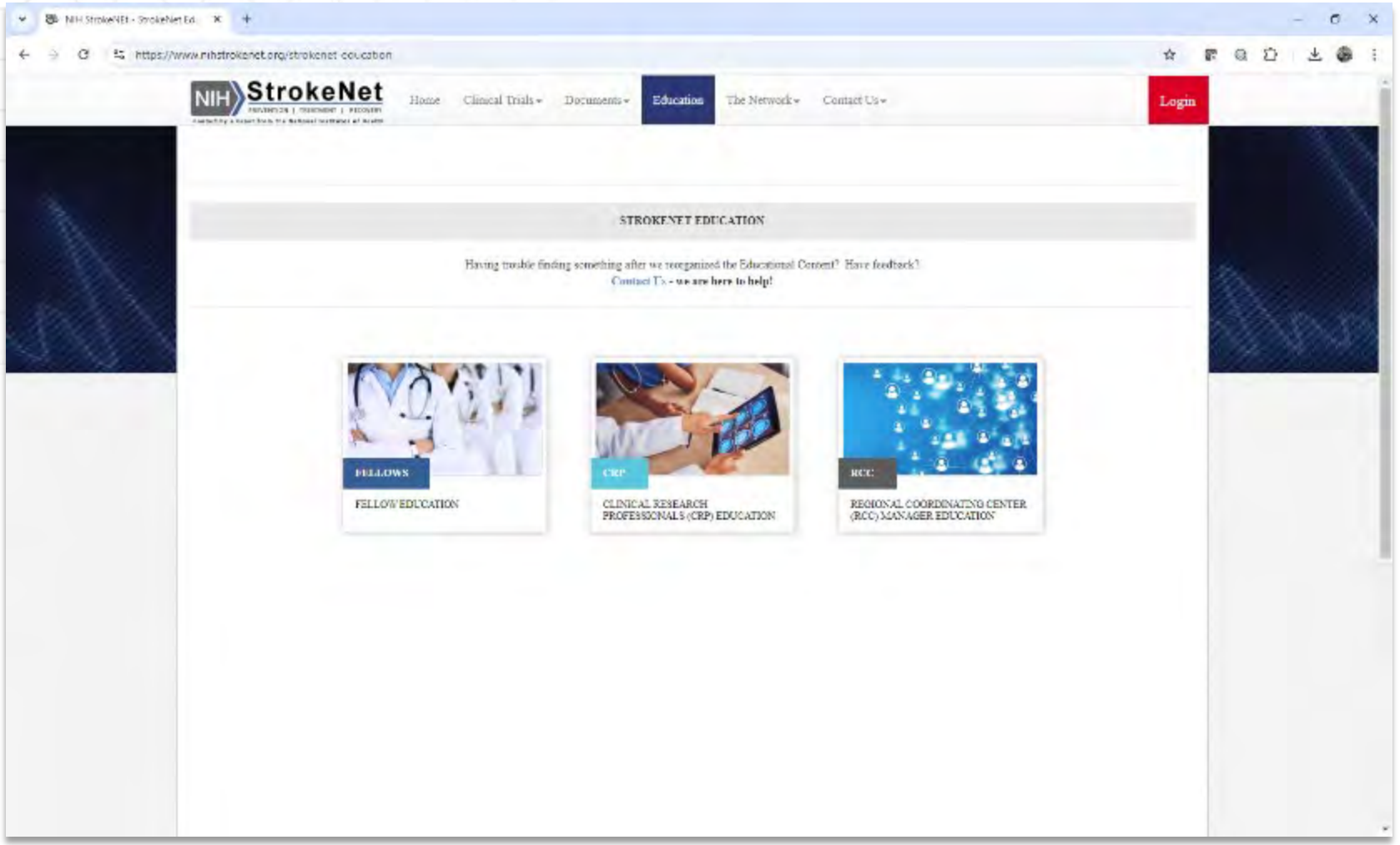
Mostly direct communication: in person, email, phone, text

Current education needs

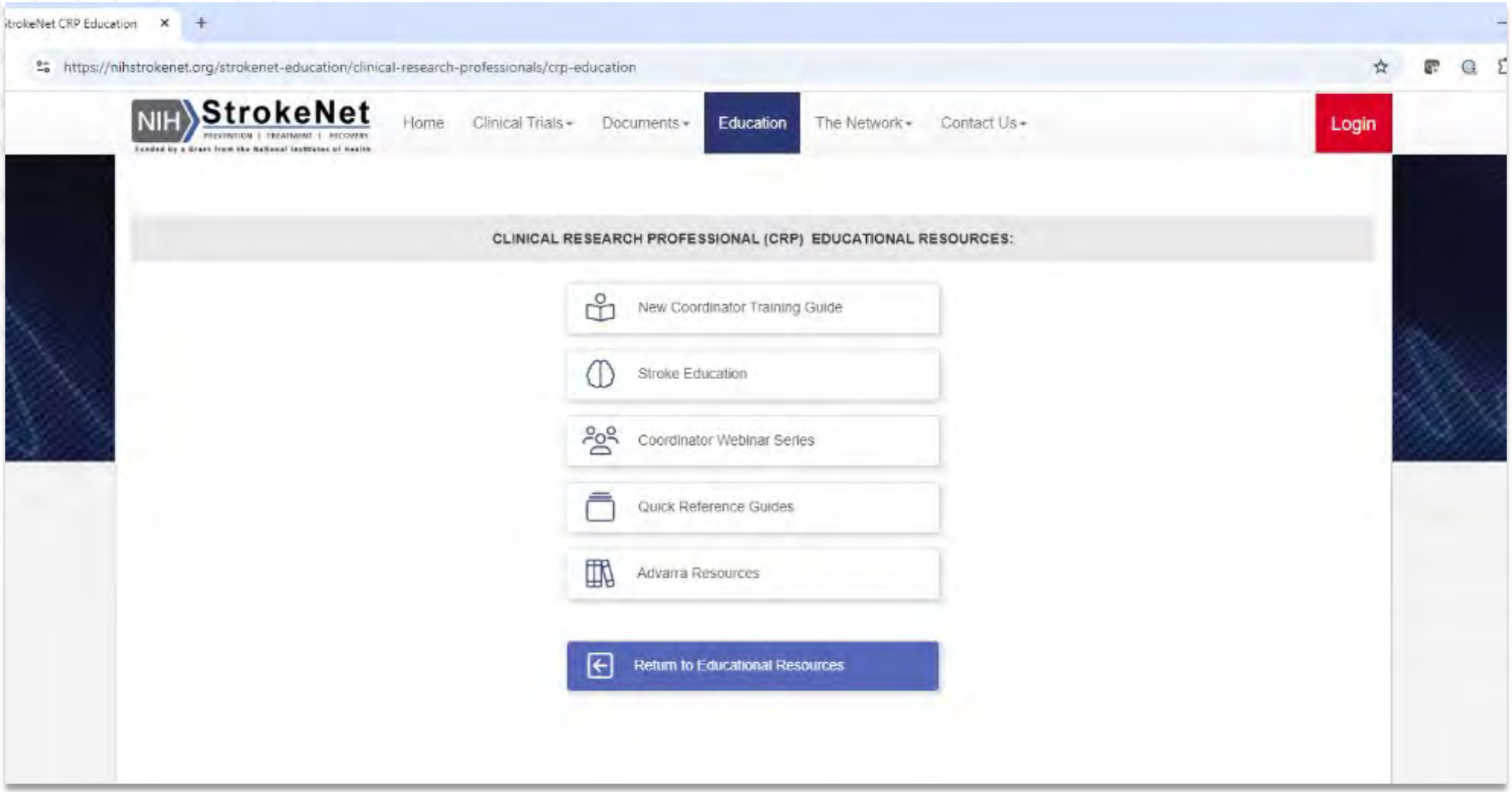
- Short, pragmatic how-to videos and slides on basics (source documentation, how to make a correction, AE/SAE reporting, checklists)
- Reorganization of the existing resources and WebDCU Toolbox
- Re-naming of webinars, abstracting the education to a separate slide deck, # system to make it searchable by keywords
- One on one mentorship is helpful, should be consistent for all new RCC managers
- Strengthening stroke knowledge, SOC vs research, imaging, etc.
- Lunch and Learns, in person boot camps for coordinators/ managers where cases are discussed on a peer-to-peer basis
- Clear definition of roles and responsibilities between study team members (PI/Sub-I/fellow/manager/coordinators/trial specific central PM)


we hear you

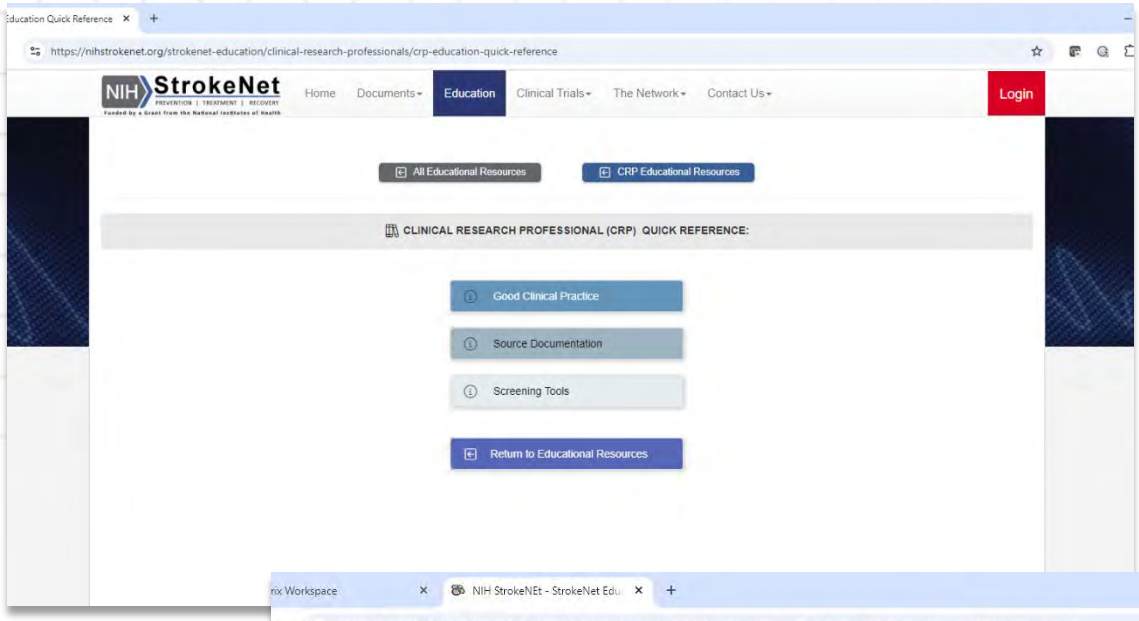
Updated website: https://nihstrokenet.org/strokenet-education

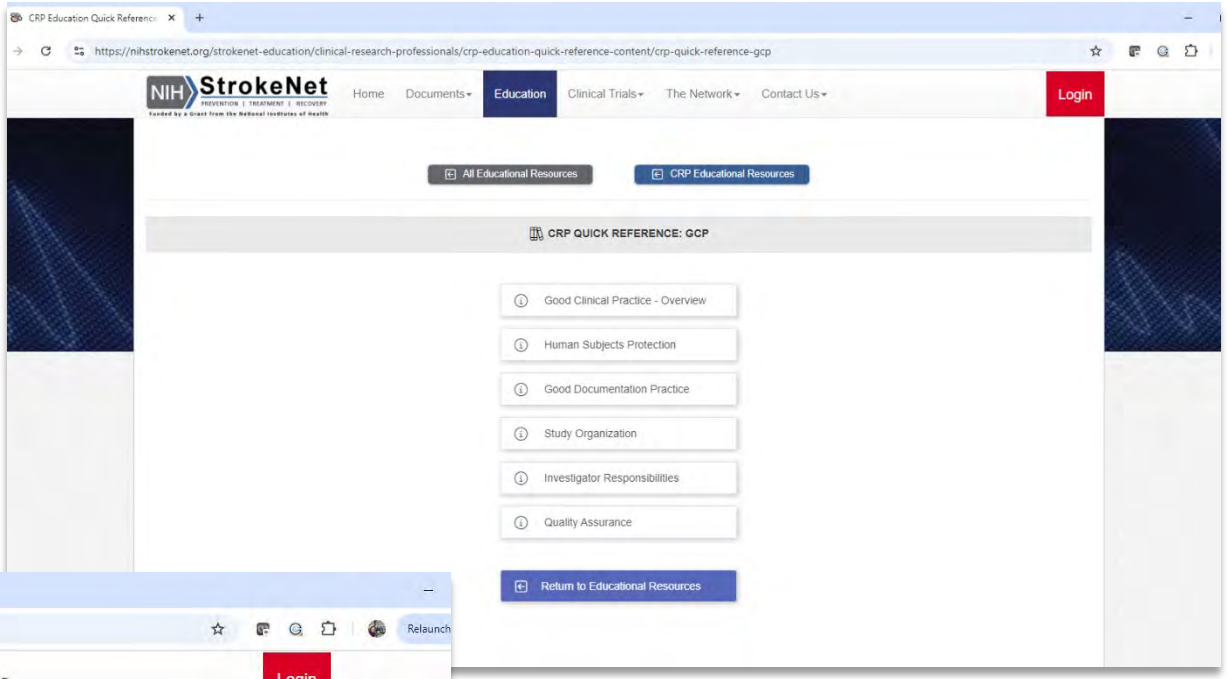


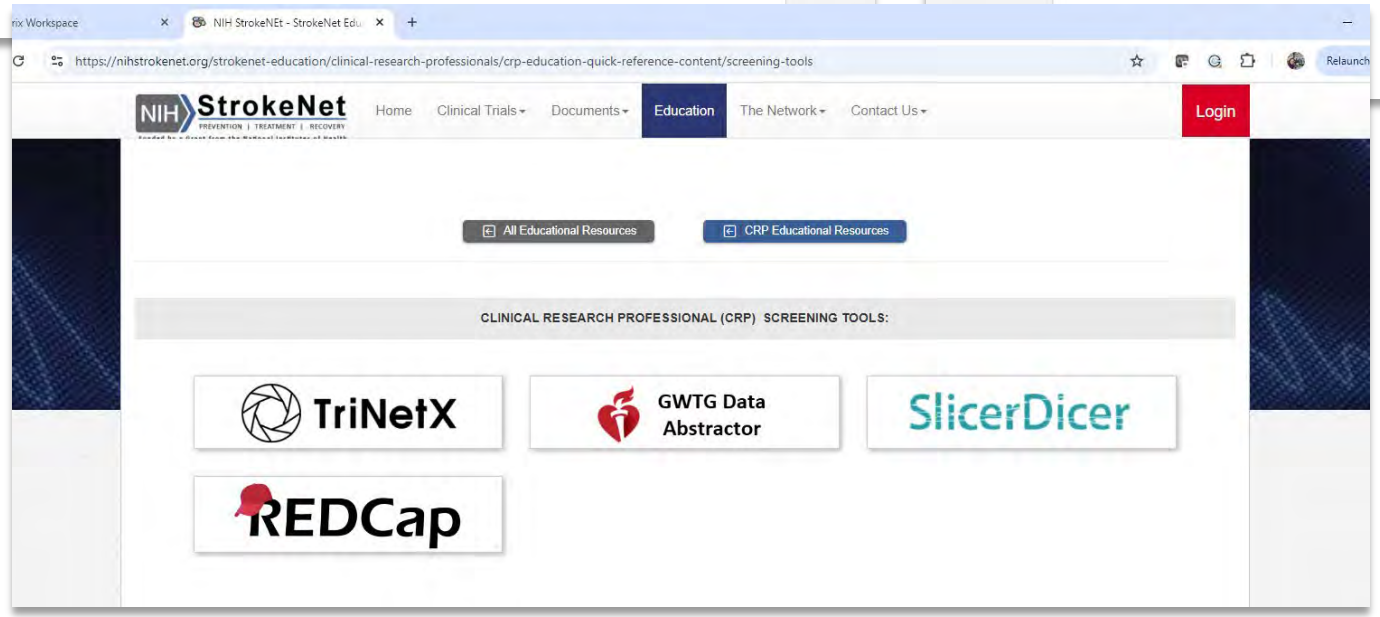
Updated website



Updated website







Updated website: https://dcu.musc.edu/campus/

WebDCU™ CTMS Training

- Logging In and Changing Password MP4
- WebDCU™ Setup MP4
- Regulatory Management MP4
- Lab Kit Tracking MP4
- Editing Your DOA MP4
- Adding Study Team Members MP4
- Adding Screen Failures MP4
- Study Design and CRF Collection Schedule MP4
- Subject CRF Binder MP4
- Data Entry MP4
- F104 Adverse Event MP4
- Rule Violations MP4
- Data Clarification Requests MP4
- Helpful Tools MP4
- Finding Help MP4

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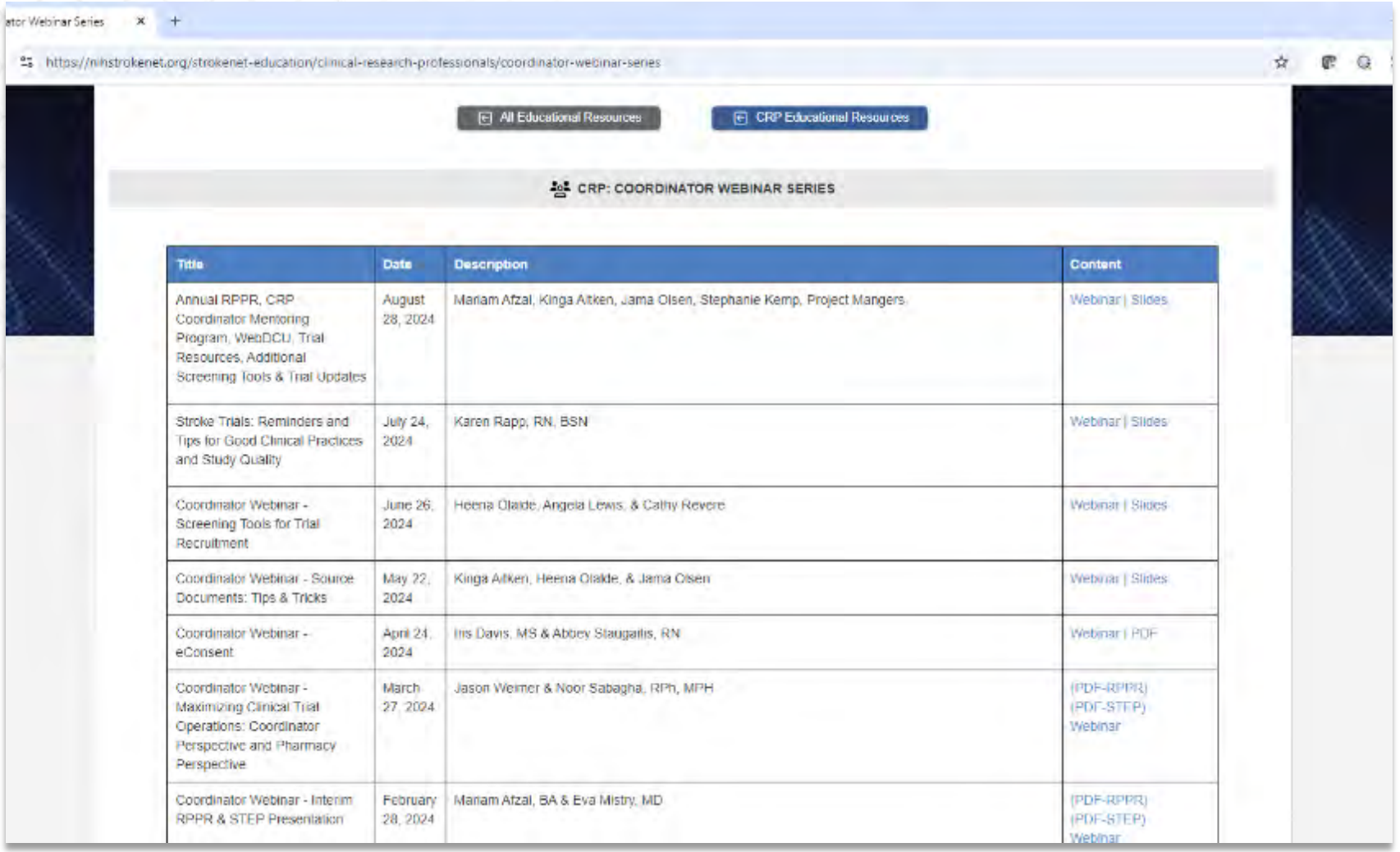
Coordinator Webinars



Title	Date	Description	Content
Annual RPPR, CRP Coordinator Mentoring Program, WebDCU, Trial Resources, Additional Screening Tools & Trial Updates	August 28, 2024	Mariam Afzal, Kinga Aitken, Jama Olsen, Stephanie Kemp, Project Mangers	Webinar | Slides
Stroke Trials: Reminders and Tips for Good Clinical Practices and Study Quality	July 24, 2024	Karen Rapp, RN, BSN	Webinar | Slides
Coordinator Webinar - Screening Tools for Trial Recruitment	June 26, 2024	Heena Olalde, Angela Lewis, & Cathy Revere	Webinar | Slides
Coordinator Webinar - Source Documents: Tips & Tricks	May 22, 2024	Kinga Aitken, Heena Olalde, & Jama Olsen	Webinar | Slides
Coordinator Webinar - eConsent	April 24, 2024	Iris Davis, MS & Abbey Staugaitis, RN	Webinar | PDF
Coordinator Webinar - Maximizing Clinical Trial Operations: Coordinator Perspective and Pharmacy Perspective	March 27, 2024	Jason Weimer & Noor Sabagha, RPh, MPH	(PDF-RPPR) (PDF-STEP) Webinar
Coordinator Webinar - Interim RPPR & STEP Presentation	February 28, 2024	Mariam Afzal, BA & Eva Mistry, MD	(PDF-RPPR) (PDF-STEP) Webinar

Future webinars

- October 2024 - Career advancement: Abby Staugaitis, Dave Haney and Mariam Afzal
- Integration of clinical care & research: PI and coordinator perspective
- Grant management 101, everything an RCC manage must know (Mariam Afzal)
- WebDCU navigation
- Roles and responsibilities for PI, Sub-I, RCC Manager, Trial Coordinators
- Collaboration with DEI Core

NEW CRP Mentoring Program

- Open to any CRC participating in at least 1 SN trial
- Small group, interactive learning sessions w/ mentor
  - Max 5 mentees/ mentor
- Certificate of completion offered
  - can be used towards professional clinical research certification/re-certification
- Mentors: subject matter experts vetted by the CRP Core
- Go live: January 1, 2025

Topics

Topics from 4 sections:

- StrokeNet policy
- Consenting (e.g. role play, eConsent, tech back method)
- Regulatory and Data Management (GCP, documentation best practices, start-ups, cIRB reliance Cincinnati vs Advarra, Monitoring)
- Communication and professionalism
  (e.g. how to communicate with clinicians/pts/families)

Additional Education Topics?

What other educational topics would you like to see the StrokeNet CRP core address in the coming months?

Please contact co-chairs:

- Heena Olalde at heena-olalde@uiowa.edu
- Kinga Aitken at kinga.aitken@hsc.utah.edu

Questions?

On Treatment Analysis

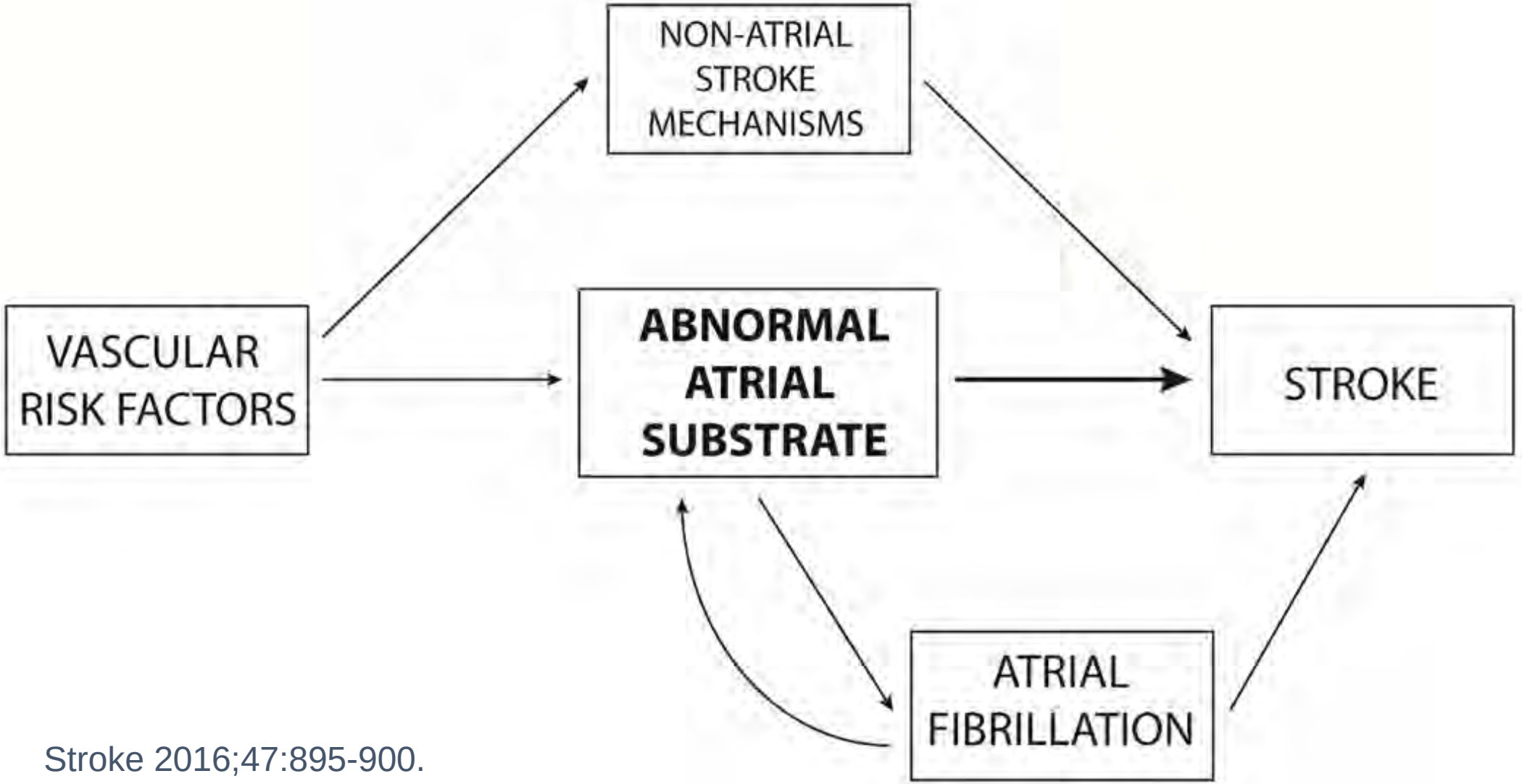
…a work in progress!

David Tirschwell, WT Longstreth Jr., Mitchell Elkind, Richard Kronmal, Hooman Kamel for the ARCADIA Investigators

Table I Definition of atrial cardiomyopathy

'Any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations'.

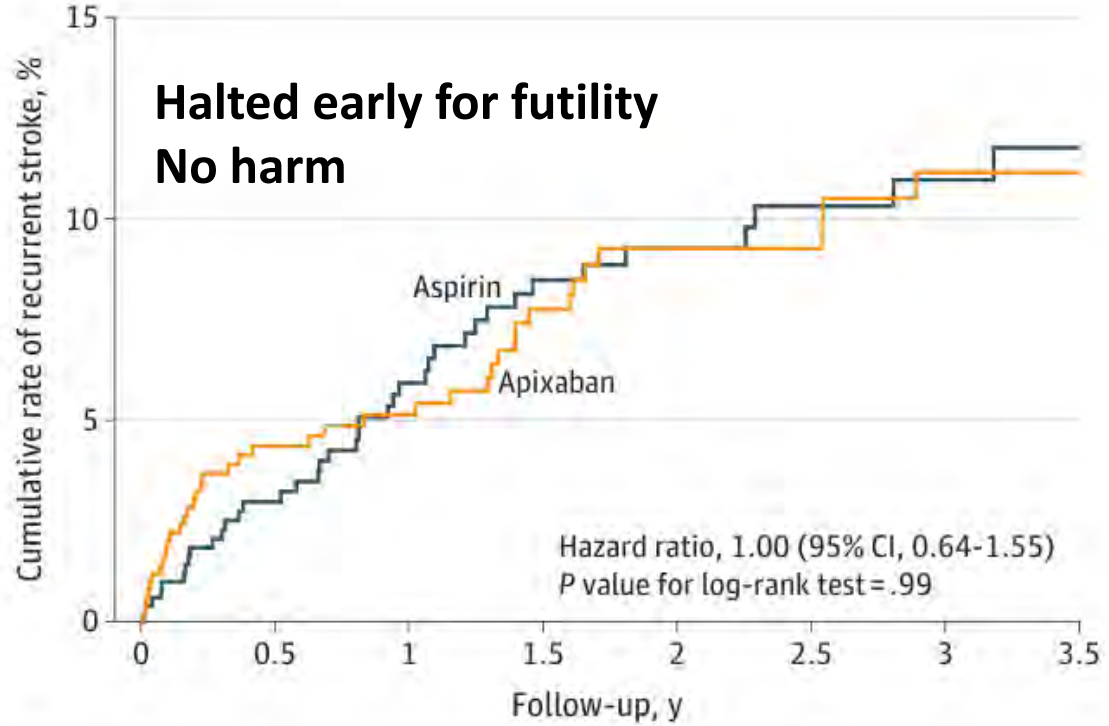
J Arrhythm. 2016 Aug;32(4):247-78



Stroke 2016;47:895-900.

ARCADIA Trial – Overview, ITT results

- Double blind RCT
- Recent cryptogenic stroke
- Atrial Cardiopathy
  - Serum marker (NT-proBNP)
  - ECG marker (PWTFV1)
  - ECHO marker (LADI)
- Aspirin vs. Apixaban
- 1° Outcome: time to recurrent stroke of any type
- ITT survival analysis



No. at risk								
Apixaban	507	400	327	256	188	146	121	74
Aspirin	508	395	317	262	195	145	119	74

Recurrent stroke included stroke of ischemic, hemorrhagic, or unknown type. The mean (SD) follow-up period in both groups was 1.8 (1.3) years.

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JAMA.2024;331(7):573-581

Intention to Treat (ITT) vs. On Treatment

- On Treatment ~= “per protocol” (PP)
- In a perfect trial, these are the same; the hypothesis is the effect of the treatment on outcomes, presumes patients take the treatment
- Begin to diverge when adherence to intervention decreases
  - Likely more relevant in trials with prolonged interventions
- ITT may give a smaller estimate of true effect, but better generalizability
  - On treatment effect may be more relevant to individual patient decision
  - Positive trial result may effect/increase adherence in clinical practice, thus making the ITT effect inaccurate
- On treatment estimates vulnerable to post randomization selection bias and confounding; may require adjustment

NEJM 2017. 377;14: 1391-1398

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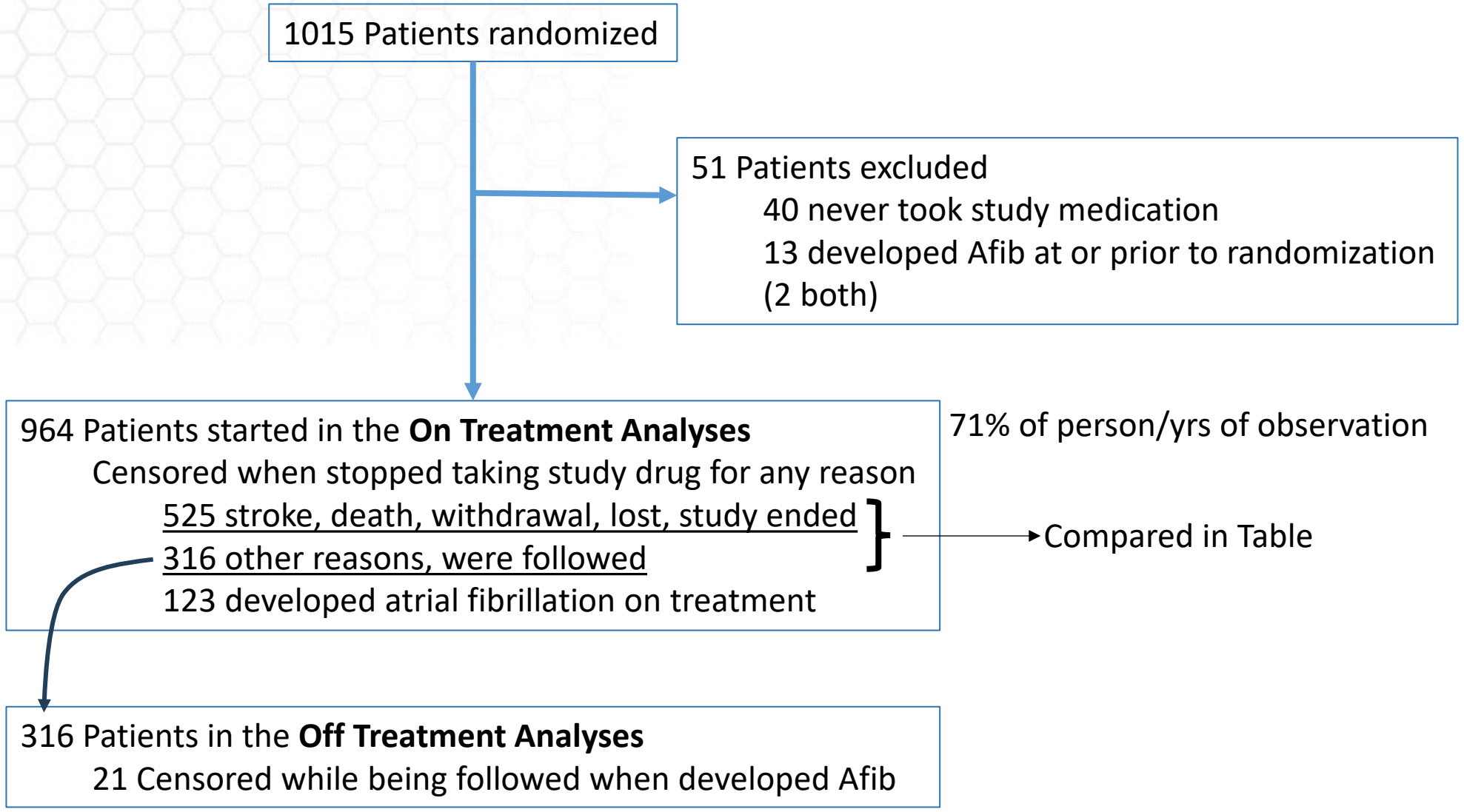
On Treatment Population



Analyses

- On treatment group
  - censored at time of Afib or when stopped study medication for any reason
- Off treatment group
  - Enter when study treatment stopped, censored at time of Afib, reached end point or study ended
- Additional analyses
  - Adherence
  - Subgroup analyses
- Cox models for HRs, interaction testing

Table 1. Demographics, patients **Never Followed Off Study Drug** vs. **Followed Off Study Drug**

Patient Characteristic	Never Followed Off Study Drug (N = 525)	Off Study Drug Followed (N = 316)	P value
Aspirin/Apixaban	269/256	160/156	.86
Age (yrs), mean (SD)	67 (11)	67 (11)	.95
Gender, N (% Female)	278 (53%)	176 (56%)	.41
Race, N (%)			
Asian	9 (1.7%)	7 (2.3%)	
Black	98 (19%)	81 (26%)	.08
White	401 (78%)	221 (71%)	
Other	7 (1.4%)	2 (.64%)	
Medical History N (%)			
TIA/Stroke	99 (19%)	67 (21%)	.4
Heart Failure	**24 (4.6%)**	**34 (11%)**	**<.001**
Ischemic Heart Disease	52 (10%)	31 (9.9%)	.98
Hypertension	399 (76%)	251 (80%)	.25
Diabetes	**142 (27%)**	**118 (37%)**	**.0019**
Smoker	219 (42%)	142 (45%)	.34
Weight (kg), mean (SD)	85 (20)	84 (21)	.54
SBP (mm Hg), mean (SD)	134 (18)	137 (19)	.082
Baseline NIHSS, median (IQR)	1 (0-3)	1 (0-3)	.75
Baseline mRS, median (IQR)	1 (0-2)	1 (0-2)	.42
Atrial Cardiopathy Biomarkers			
NT-proBNP, median (IQR)	**488 (864)**	**689 (1512)**	**.015**
PWTFV1, median (IQR)	4915 (2593)	4803 (2872)	.56
LADI, median (IQR)	1.9 (.34)	1.9 (.38)	.4

Main On Treatment Survival Analysis (1289 pyrs)

Table. Efficacy outcomes while patients were on study drug with censoring when atrial fibrillation first detected

Outcome	*number (rate per person years)* Aspirin Group (N = 488)	Apixaban Group (N = 476)	Hazard Ratio (95% CI)
On Study Drug			
Primary Outcome: Recurrent stroke of any type	32 (0.050)	23 (0.036)	0.73 (0.43, 1.25)
Components of primary efficacy outcome			
Ischemic stroke	30 (0.046)	22 (0.034)	0.74 (0.43, 1.29)
Hemorrhagic stroke	2 (0.003)	0 (0.000)	
Stroke of undetermined type	0	1 (0.001)	
Secondary efficacy outcomes			
Recurrent ischemic stroke or systemic embolism	30 (0.046)	22 (0.034)	0.74 (0.43, 1.29)
Recurrent stroke of any type or death from any cause	35 (0.054)	28 (0.044)	0.81 (0.49,1.34)

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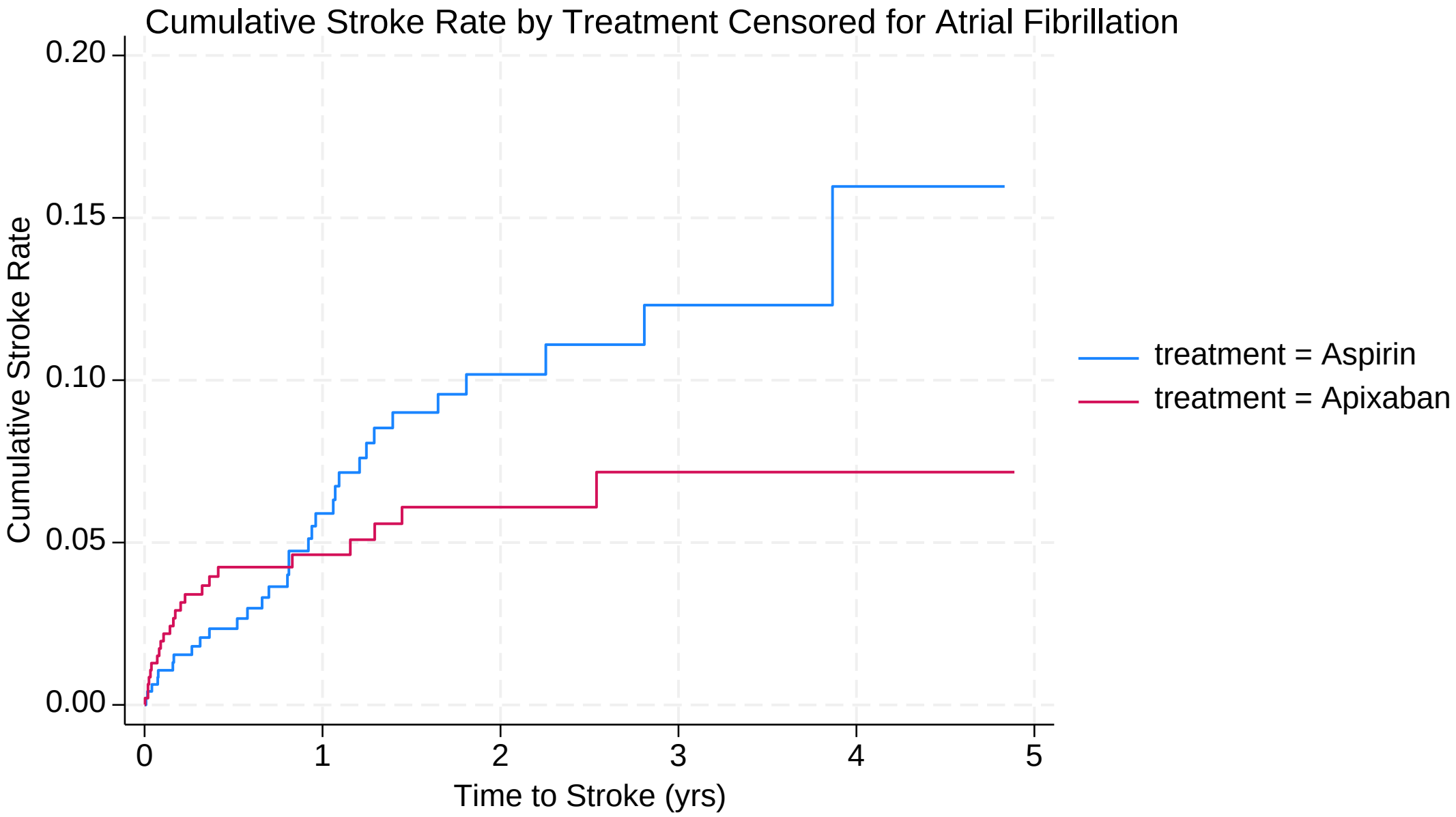
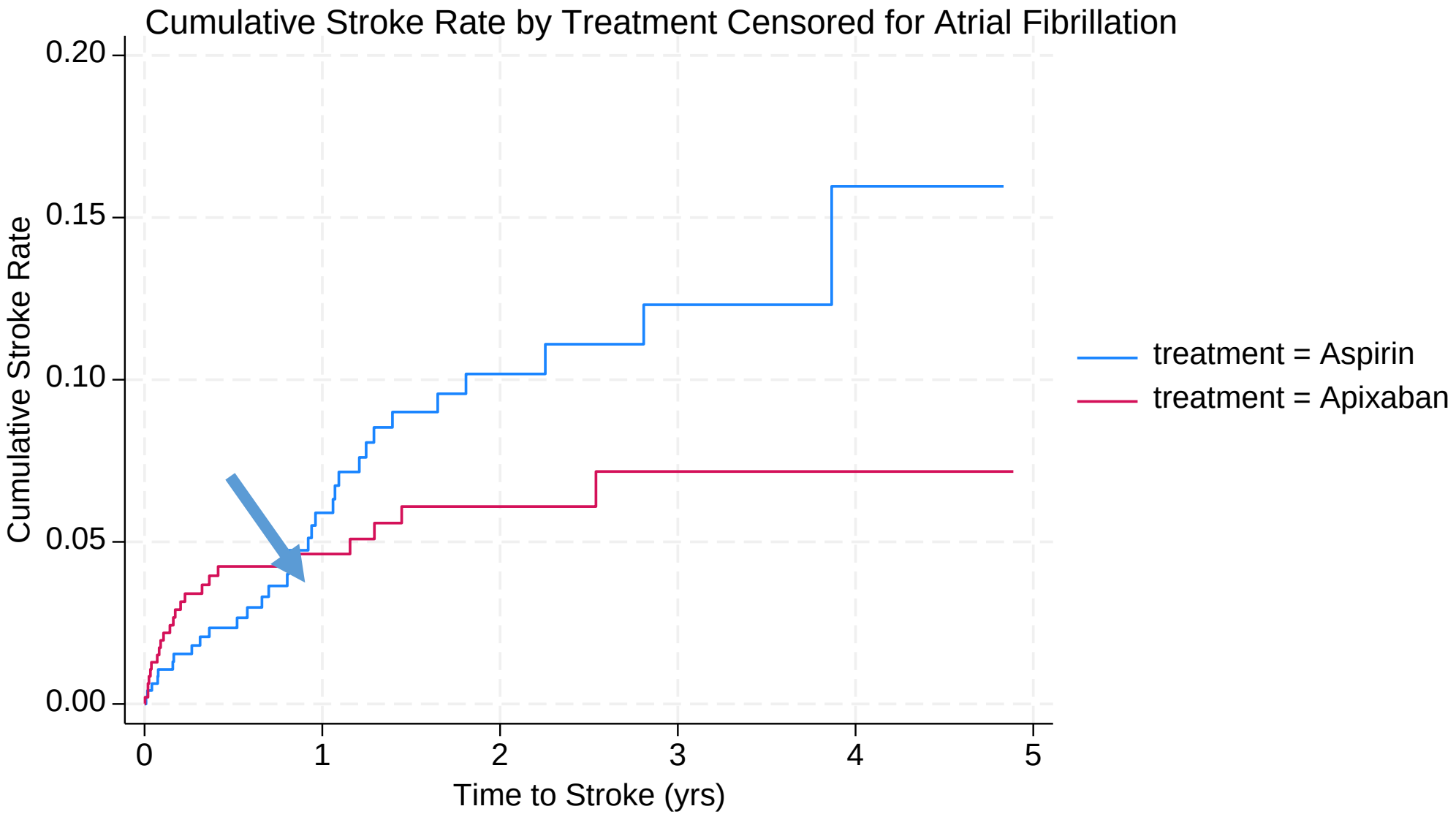
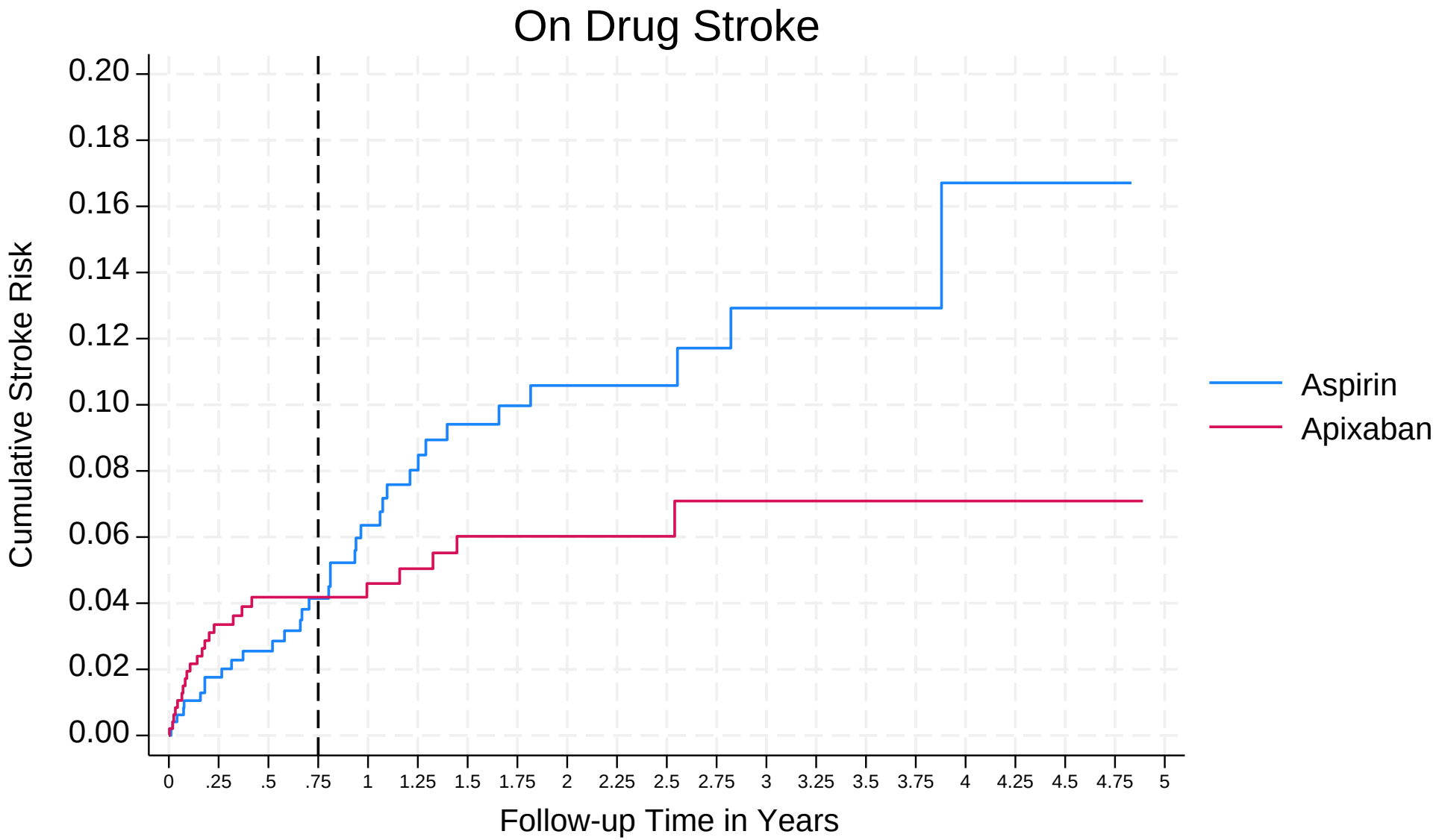
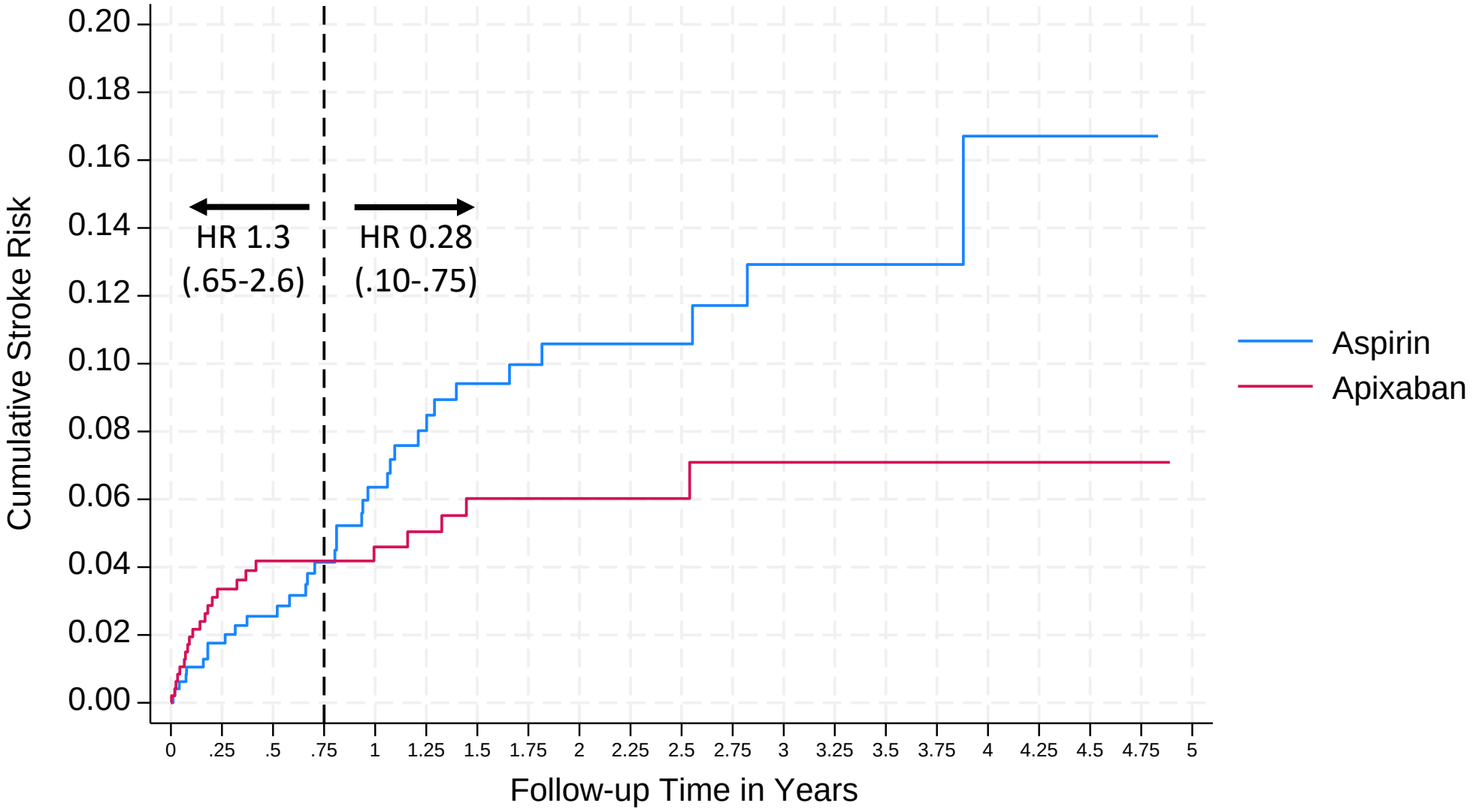

Cumulative Stroke Rate by Treatment Censored for Atrial Fibrillation
Cumulative Stroke Rate
0.20
0.15
0.10
0.05
0.00
0
1
2
3
4
5
Time to Stroke (yrs)
treatment = Aspirin
treatment = Apixaban


Cumulative Stroke Rate by Treatment Censored for Atrial Fibrillation
Cumulative Stroke Rate
0.20
0.15
0.10
0.05
0.00
0
1
2
3
4
5
Time to Stroke (yrs)
treatment = Aspirin
treatment = Apixaban


On Drug Stroke
Cumulative Stroke Risk
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0
.25
.5
.75
1
1.25
1.5
1.75
2
2.25
2.5
2.75
3
3.25
3.5
3.75
4
4.25
4.5
4.75
5
Follow-up Time in Years
Aspirin
Apixaban

On Drug Stroke



Main Off Treatment Survival Analysis (254 pyrs)

Table. Primary efficacy outcomes during period when the patients were off study drug with censoring for atrial fibrillation

Outcome	*number (rate per person years)* Aspirin Group (N = 160)	Apixaban Group (N = 156)	Hazard Ratio (95% CI)
Off Study Drug			
Primary Outcome: Recurrent stroke of any type	3 (0.024)	12 (0.094)	4.32 (1.22, 15.32)
Components of primary efficacy outcome			
Ischemic stroke	3 (0.024)	11 (0.086)	3.96 (1.10, 14.20)
Hemorrhagic stroke	0 (0.000)	1 (0.008)	
Stroke of undetermined type	0	0	
Secondary efficacy outcomes			
Recurrent ischemic stroke or systemic embolism	5 (0.040)	11 (0.086)	2.36 (0.82,6.80)
Recurrent stroke of any type or death from any cause	16 (0.13)	27 (0.21)	1.72 (0.93,3.21)
Death	13 (0.10)	15 (0.12)	1.14 (0.54,2.40)

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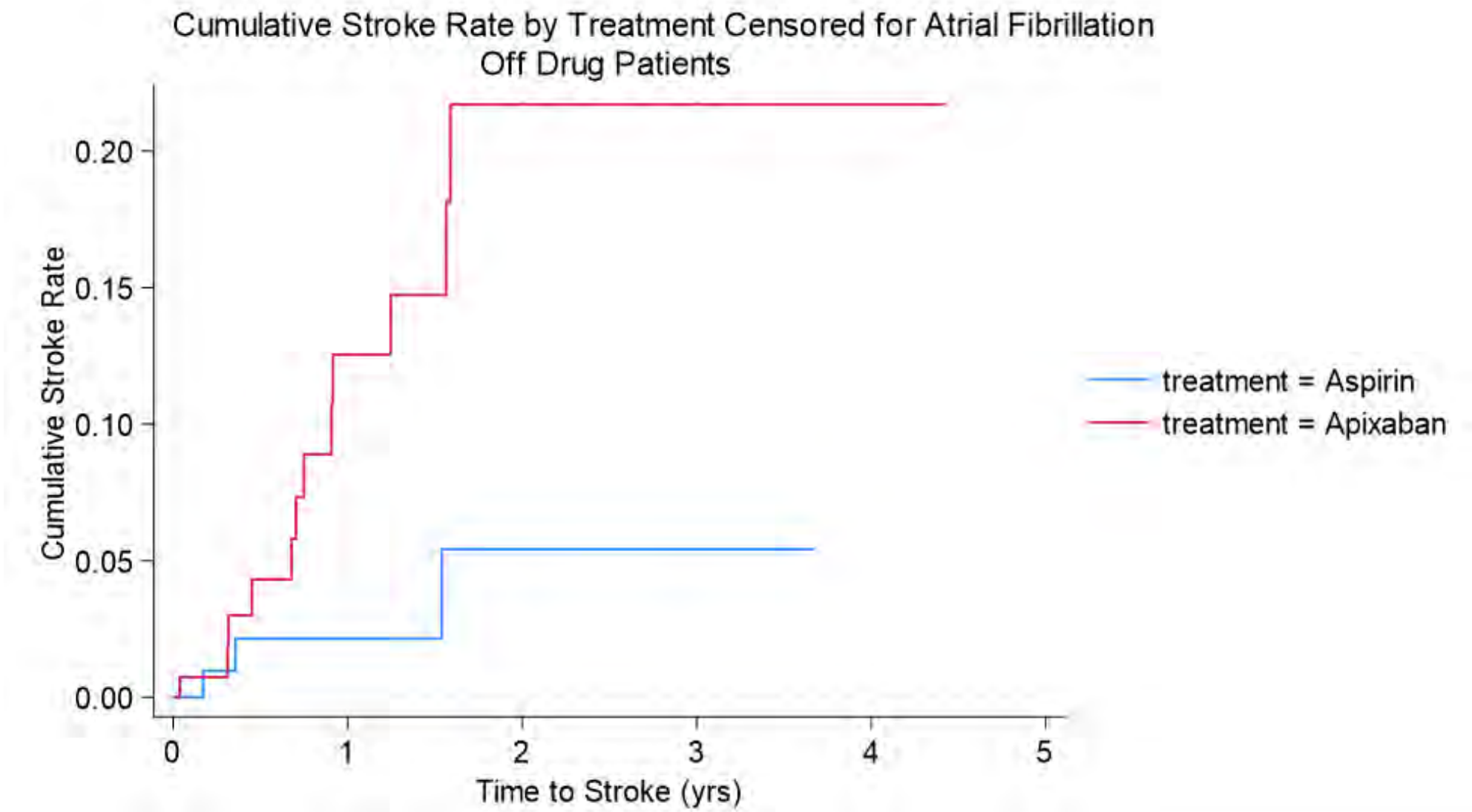

Cumulative Stroke Rate by Treatment Censored for Atrial Fibrillation
Off Drug Patients
Cumulative Stroke Rate
0.00
0.05
0.10
0.15
0.20
0
1
2
3
4
5
Time to Stroke (yrs)
treatment = Aspirin
treatment = Apixaban

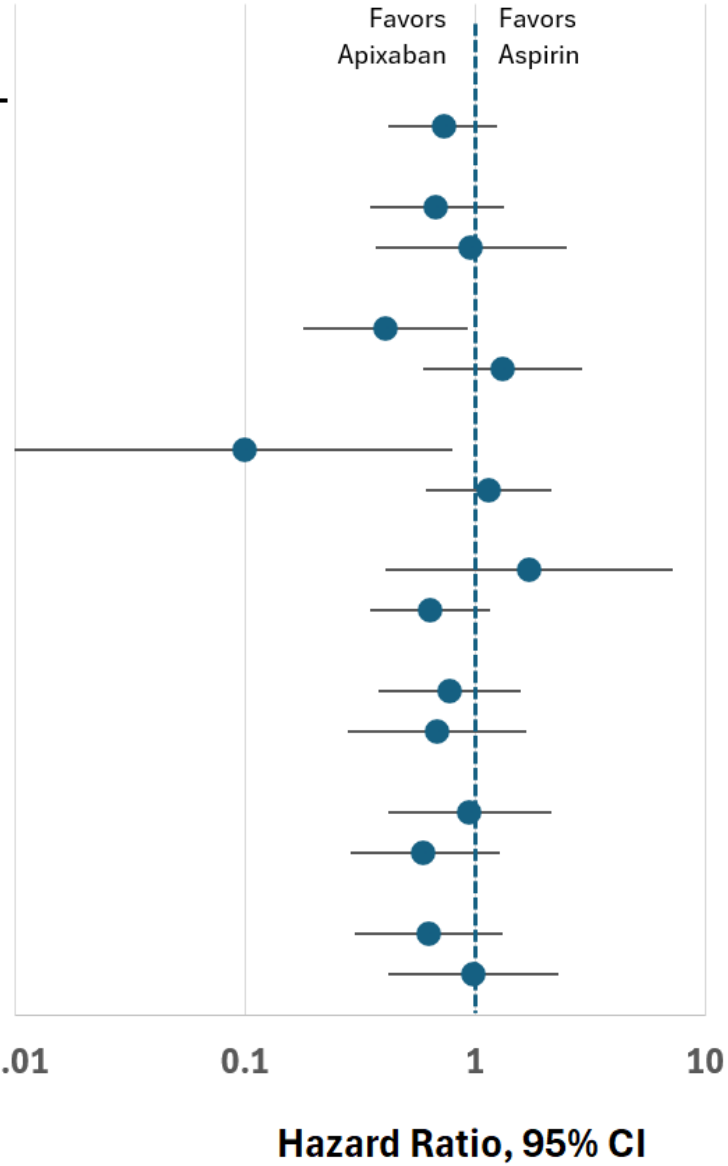
Adherence On Treatment

- Data difficult to work with, contain errors
- Good/poor adherence = 90-110% of pills taken/<90%
  - 206 cases dropped due to values >110%

Group	HR (95% CI)	Interaction P value
Good adherence	0.56 (0.25 – 1.3)	0.046
Poor adherence	5.6 (0.67 – 46.2)	

- Small N in poor adherence group
- Hypothesis: Aspirin half life longer, so poor adherence retains protection better

Subgroup	HR	95% CI lower/	upper	Interaction P value
All Patients	0.73	0.42	1.25	
Age, yrs				
<75	0.68	0.35	1.34	0.6
≥75	0.96	0.37	2.5	
Sex				
Male	0.41	0.18	0.93	0.044
Female	1.32	0.6	2.92	
Race				
Asian, Black, Other	0.1	0.01	0.8	0.021
White	1.15	0.61	2.16	
Weight, kg				
<70	1.73	0.41	7.25	0.21
≥70	0.64	0.35	1.17	
NT-proBNP level, pg/mL				
Below median (<304)	0.78	0.38	1.58	0.81
Above median (≥304)	0.69	0.28	1.67	
PTFV1, μV × ms				
Below median (<5200)	0.95	0.42	2.16	0.42
Above median (≥5200)	0.6	0.29	1.28	
Left atrial diameter index, cm/m2				
Below median (<1.89)	0.63	0.3	1.32	0.46
Above median (≥1.89)	0.98	0.42	2.31	



Summary

- 71%/29% of observed person years On/Off Treatment
- On Treatment
  - HR suggests possible benefit, underpowered
  - Proportional Hazards assumption violation: effect varies over time
- Off Treatment
  - Increased rate in apixaban group: previously protective?
- Adherence: better lowers HR
- Subgroups: sex

Discussion points…

- Many hypotheses generated, all exploratory
- ITT v PP/on treatment, explanatory vs pragmatic, efficacy vs effectiveness
  - Both approaches have value, and should be considered for reporting
  - ITT: generalizable, industry std, but may be biased if much lack of adherence
  - OT: more directly tests hypothesis, less generalizable, may need adjustment
- Even stronger focus on adherence
  - Pandemic – did us no favors
  - How much Off Treatment is acceptable?
- Should PP/On Treatment analysis be part of standard SAP, DSMB monitoring?
  - Especially relevant if no safety issues?
- Better markers of atrial cardiopathy needed?
- Is the development of Afib a special censoring event?
  - How to deal with a loss of equipoise for some patients during trial
- How to move forward…

Thank you

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ARCADIA-CSI

Cognition and Silent Infarcts

MUSC

MEDICAL UNIVERSITY of SOUTH CAROLINA

NIH

Funded by a grant from the National Institutes of Health

UNIVERSITY OF Cincinnati

Acknowledgements

- ARCADIA-CSI patients and their families
- Study site coordinators and investigators
- Project managers: Stephanie Kemp, Tashia Harris, Laura Benken, Kalli Beasley
- Imaging Core at MD Anderson
- StrokeNet NCC and NDMC teams
- ARCADIA study team
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Stanford University Coordinating Center

Maarten Lansberg

Stephanie Kemp

MD Anderson Imaging Core

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MUSC - StrokeNet DCC

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Kali Beasley

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UAB Cognitive and Stats Core

Ron Lazar

George Howard

Mike Brewer

Terina Meyers

Yale University Enrollment

Kevin Sheth

U. Washington ARCADIA Trial

David Tirschwell

Overview

Study population

ARCADIA-MRI

ARCADIA-Cognition

Overview

Study population

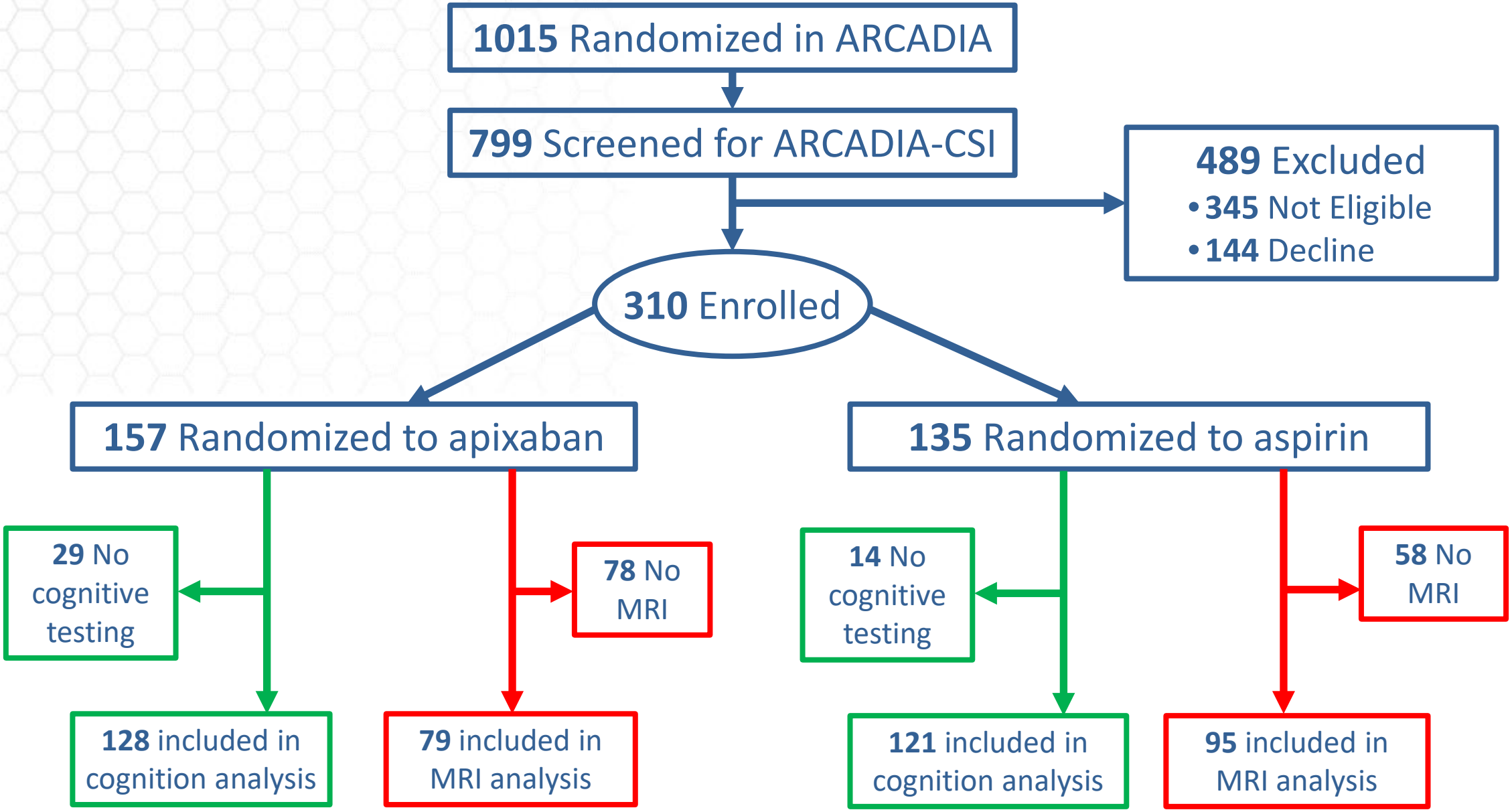
Inclusion and Exclusion

Inclusion Criteria

- Randomized in ARCADIA
- Able to undergo MRI
- Able to provide informed consent

Exclusion Criteria

- ARCADIA study drug permanently discontinued
- Diagnosis of dementia
- Active illicit drug use
- Admission for depression
- <8 years of education
- TBI with >30 min loc


1015 Randomized in ARCADIA
799 Screened for ARCADIA-CSI
489 Excluded
• 345 Not Eligible
• 144 Decline
310 Enrolled
157 Randomized to apixaban
135 Randomized to aspirin
29 No cognitive testing
78 No MRI
14 No cognitive testing
58 No MRI
128 included in cognition analysis
79 included in MRI analysis
121 included in cognition analysis
95 included in MRI analysis

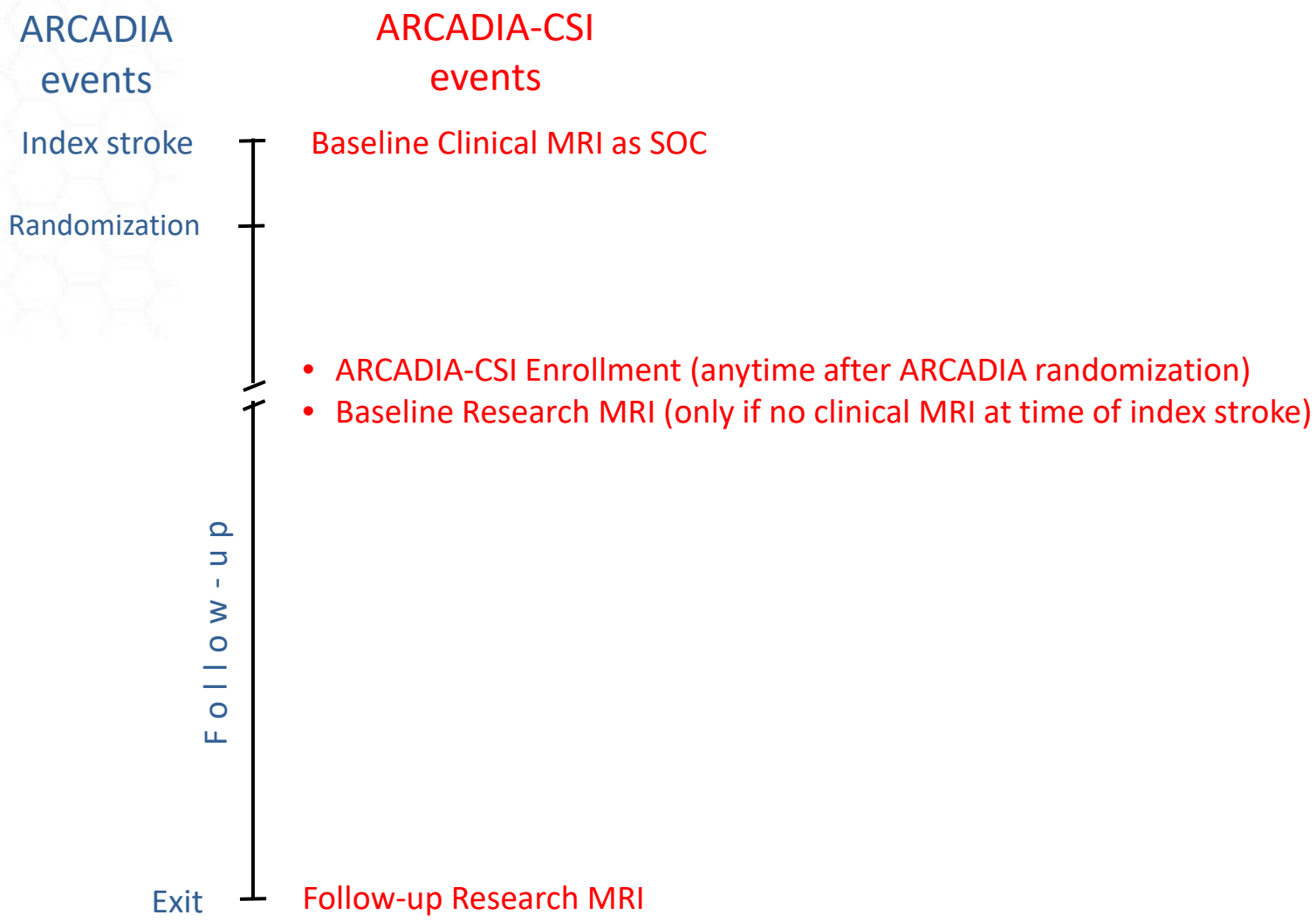
Part 1

ARCADIA-MRI

Background

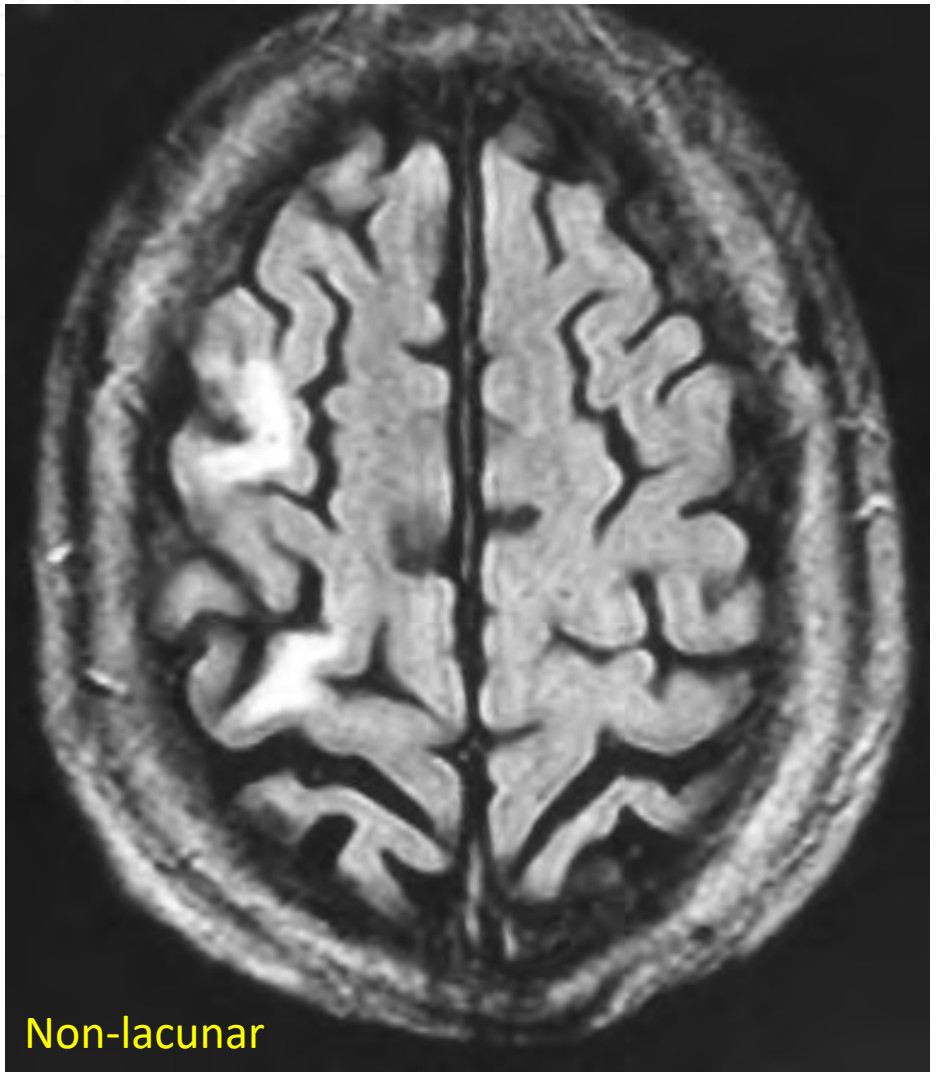
- Covert infarcts are common
  - Prevalence 30-50%
  - Incidence up to 19% annually after TIA
- Covert infarcts are important
  - Associated with increased risk of cognitive impairment and dementia
  - Associated with increased risk of clinical stroke
- Two secondary stroke prevention studies have focused on covert infarcts
  - NAVIGATE-ESUS and PACIFIC-Stroke
  - Annual rate of covert infarcts 10-22%

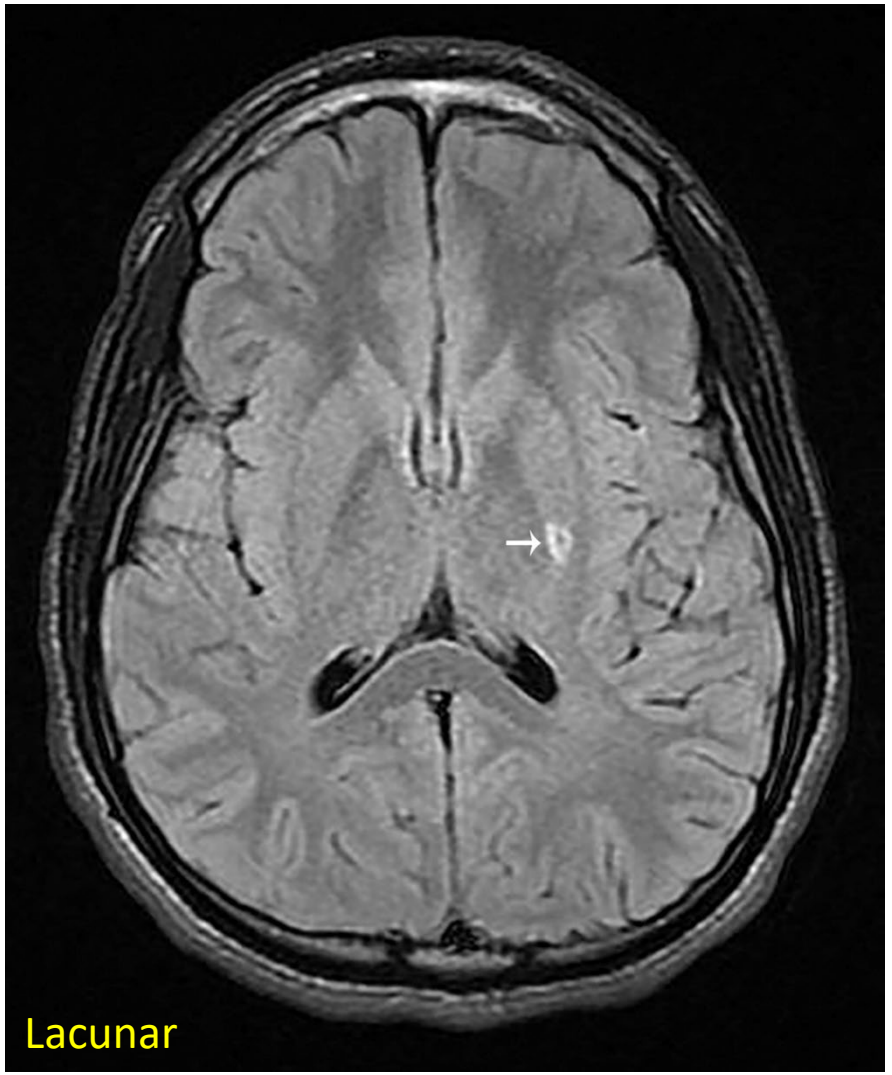
Timing of MRI Scans



MRI Interpretation

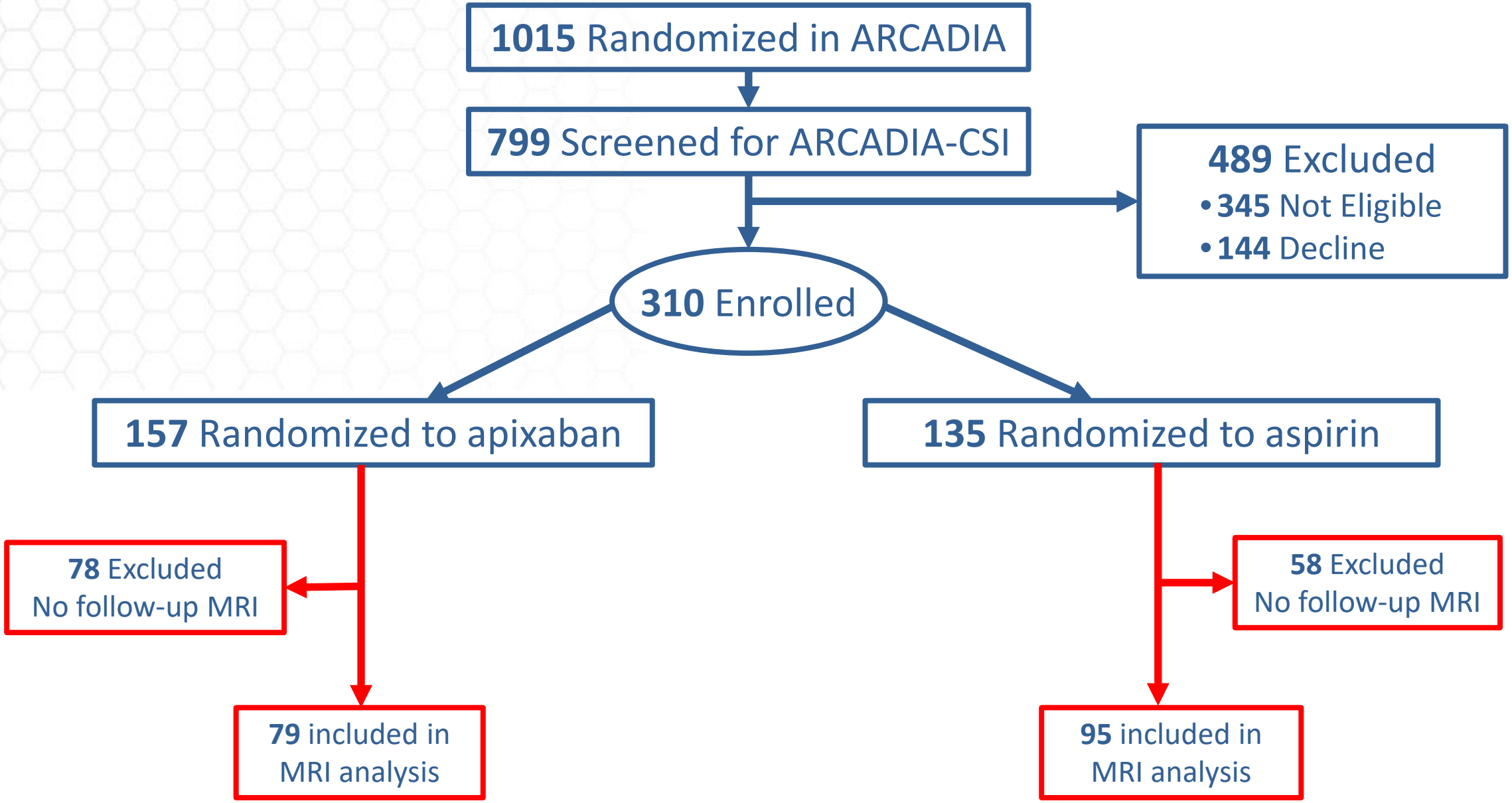
- Follow-up scans rated for the presence of new silent infarcts
- Lacunar infarcts defined as round or ovoid subcortical lesions <15 mm in diameter





Statistical Analysis

- The relative risk of the incidence of one or more new non-lacunar covert infarcts during follow-up was estimated using Poisson regression with adjustment for follow-up time and inverse probability weighting to account for missing follow-up MRI studies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310 Enrolled
157 Randomized to apixaban
135 Randomized to aspirin
78 Excluded
No follow-up MRI
58 Excluded
No follow-up MRI
79 included in
MRI analysis
95 included in
MRI analysis

Baseline Characteristics of Enrolled Patients

	Included (n=174)	Excluded (n=136)
Age, Mean (SD)	66.3 (10.6)	67.2 (9.7)
Female, no. (%)	83 (47.7)	72 (52.9)
Black, no. (%)	33 (19.0)	30 (22.1)
Hypertensive, no. (%)	128 (73.6)	104 (76.5)
Diabetic, no. (%)	44 (25.3)	43 (31.6)
Prior stroke or TIA (before index), no. (%)	36 (20.7)	27 (19.9)
Modified Rankin Scale, Median (IQR)	1 (0-2)	1 (0-2)
NIHSS, Median (IQR)	0 (0-2)	1 (0-3)
Fazekas score, Median (IQR)	2 (1-3)	2 (1-3)

Baseline Characteristics of Included Patients

	Apixaban (n=79)	Aspirin (n=95)
Age, Mean (SD)	66.3 (10.2)	66.3 (11.0)
Female, no. (%)	37 (46.8)	46 (48.4)
Black, no. (%)	13 (16.5)	20 (21.1)
Hypertensive, no. (%)	57 (72.2)	71 (74.7)
Diabetic, no. (%)	16 (20.3)	28 (29.5)
Prior stroke or TIA (before index), no. (%)	12 (15.2)	24 (25.3)
Modified Rankin Scale, Median (IQR)	1 (0-2)	1 (0-2)
NIHSS, Median (IQR)	0 (0-2)	1 (0-2)
Fazekas score, Median (IQR)	2 (1-3)	2 (1-3)

Study Characteristics of Included Patients

	Apixaban (n=79)	Aspirin (n=95)	P-value
Time from ARCADIA randomization to ARCADIA-CSI consent, median (IQR), days	179 (48, 364)	93 (37, 362)	0.47
Time from baseline to follow-up MRI, median (IQR), days	800 (479-1311)	822 (487-1238)	0.65
Discontinued study drug prematurely, no. (%)*	14 (17.7)	13 (13.7)	0.46

*A subject was considered to have “Discontinued study drug prematurely” if they discontinued study drug permanently before the date that sites were notified of trial end (12/21/22) and more than seven days before their censor date in the parent trial.

Primary Analysis

Difference in non-lacunar covert infarcts between treatment arms

Primary Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct				

Primary Analysis

Difference in non-lacunar covert infarcts between treatment arms

Primary Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)			

Primary Analysis

Difference in non-lacunar covert infarcts between treatment arms

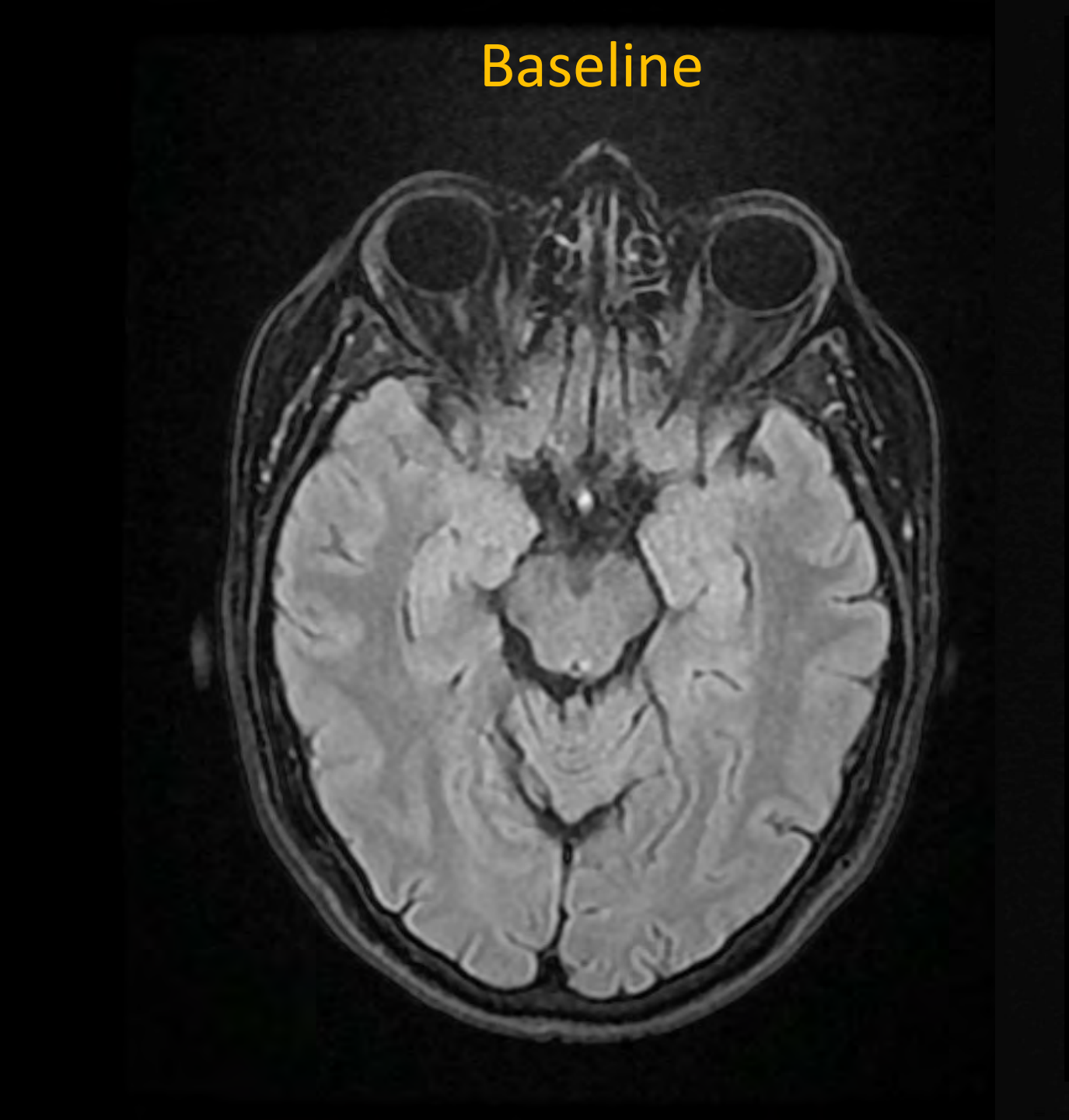
Primary Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)	17 (18%)		

Primary Analysis

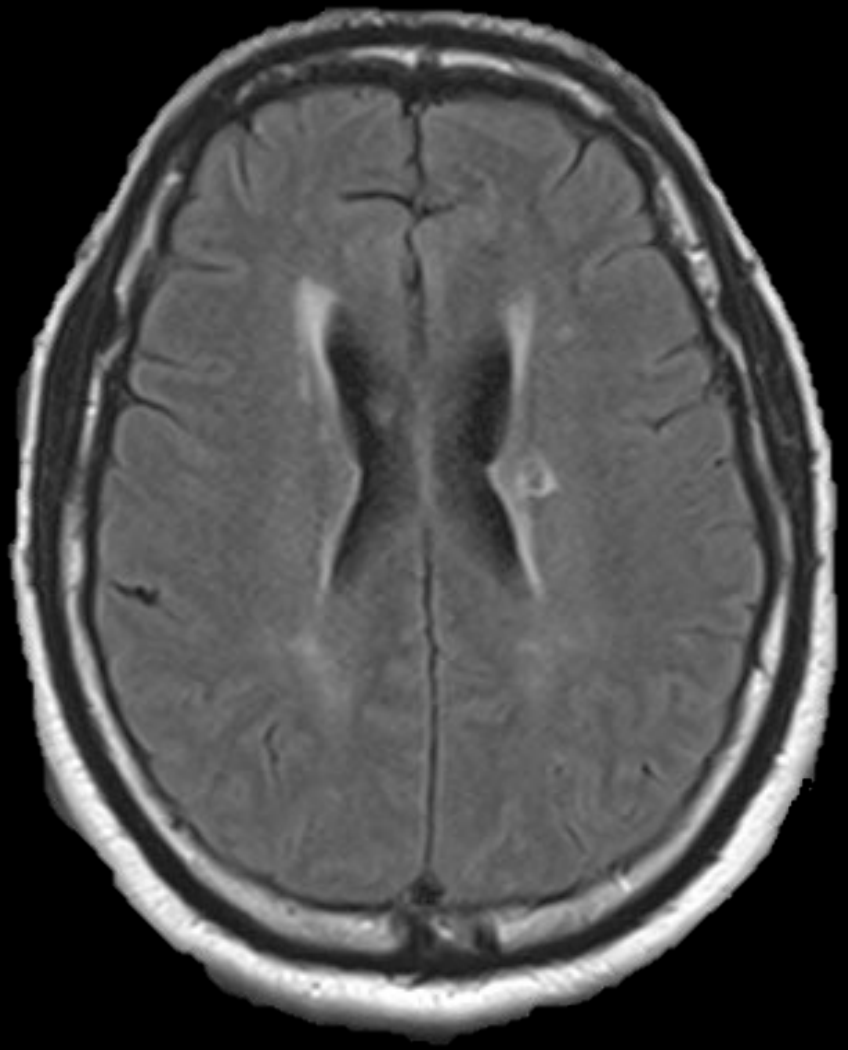
Difference in non-lacunar covert infarcts between treatment arms

Primary Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)	17 (18%)	0.29 (0.10 – 0.83)	0.02

Baseline



Baseline



Secondary Outcome

Composite of ≥1 non-lacunar covert infarct or a non-lacunar clinical stroke

Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)	17 (18%)	0.29 (0.10 – 0.83)	0.02
≥1 non-lacunar covert infarct or a non-lacunar clinical stroke	7 (9%)	25 (26%)	0.36 (0.17 – 0.79)	0.01

Additional Outcomes

Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)	17 (18%)	0.29 (0.10 – 0.83)	0.02
≥1 non-lacunar covert infarct or a non-lacunar clinical stroke	7 (9%)	25 (26%)	0.36 (0.17 – 0.79)	0.01
Additional Outcomes				
Non-lacunar clinical stroke	3 (4%)	8 (8%)	0.52 (0.15 – 1.77)	0.30

Additional Outcomes

Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)	17 (18%)	0.29 (0.10 – 0.83)	0.02
≥1 non-lacunar covert infarct or a non-lacunar clinical stroke	7 (9%)	25 (26%)	0.36 (0.17 – 0.79)	0.01
Additional Outcomes				
Non-lacunar clinical stroke	3 (4%)	8 (8%)	0.52 (0.15 – 1.77)	0.30
≥1 lacunar covert infarct	8 (10%)	12 (13%)	0.80 (0.34 – 1.86)	0.60

Additional Outcomes

Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)	17 (18%)	0.29 (0.10 – 0.83)	0.02
≥1 non-lacunar covert infarct or a non-lacunar clinical stroke	7 (9%)	25 (26%)	0.36 (0.17 – 0.79)	0.01
Additional Outcomes				
Non-lacunar clinical stroke	3 (4%)	8 (8%)	0.52 (0.15 – 1.77)	0.30
≥1 lacunar covert infarct	8 (10%)	12 (13%)	0.80 (0.34 – 1.86)	0.60
≥1 lacunar or non-lacunar covert infarct	12 (15%)	25 (26%)	0.57 (0.31 – 1.07)	0.08

Limitations / Discussion

- High percentage (44%) of enrolled patients did not return for their follow-up MRI
- Patients included in the ARCADIA-MRI analysis were less likely to discontinue study drug prematurely (15.5%) than patients who were screened but not enrolled (50.8%)

Conclusion

Among patients with a cryptogenic stroke and atrial cardiopathy, apixaban as compared to aspirin:

- prevents non-lacunar covert infarcts
- does not prevent lacunar covert infarcts

Part 2

ARCADIA-Cognition

ARCADIA – CSI: (Cognition Substudy)

Cognition and Covert Infarction

Vermeer SE et al. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke. Jan 2002;33(1):21-5.

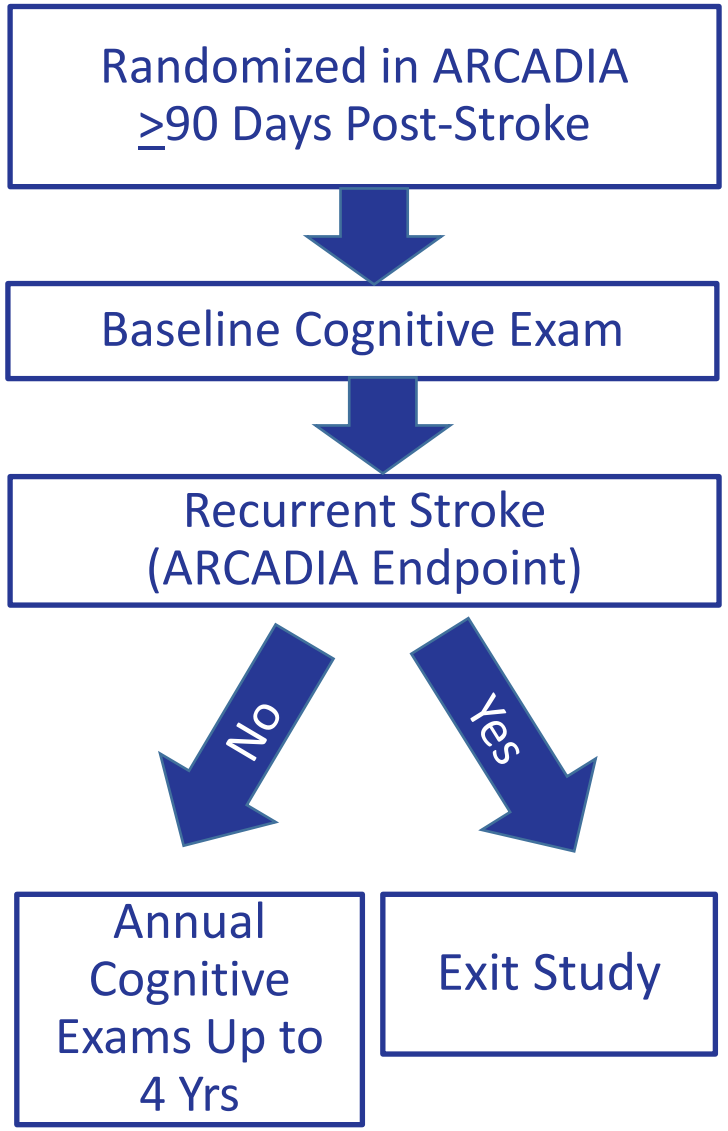
Vermeer SE, Longstreth WT, Jr., Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol. Jul 2007;6(7):611-9. doi:10.1016/S1474-4422(07)70170-9

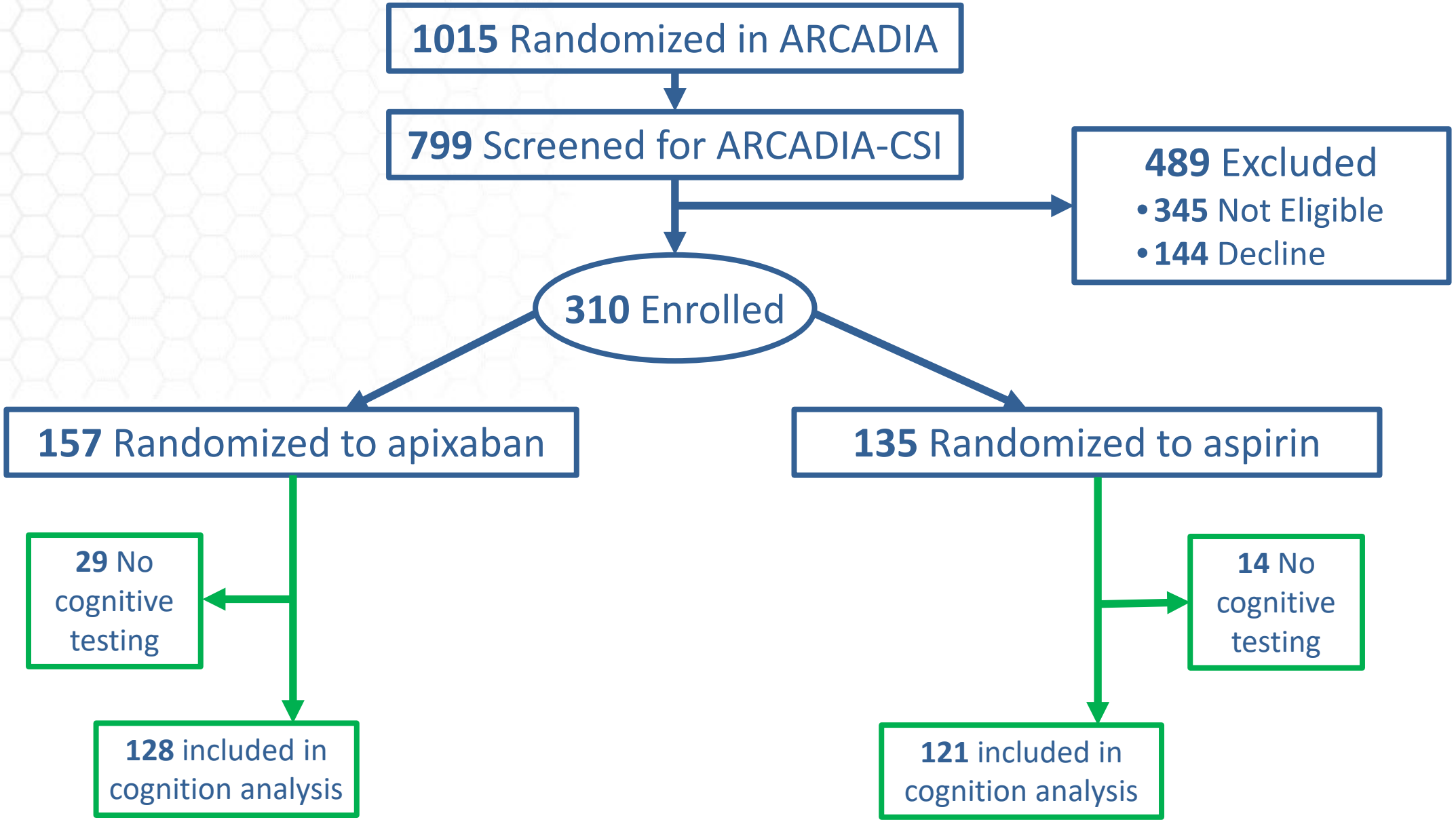
Iatrogenic Etiology: CABG (Tachibana, 2021), TAVR (Lazar, 2018), AF Ablation (Hahne, 2016)

Specific Aim 2: Determine the effect of apixaban (vs aspirin) on the longitudinal rate of change (i.e., slope) of global cognitive function after stroke (primary clinical outcome).

ARCADIA – CSI: (Cognition Substudy)

ARCADIA-CSI Cognitive Test Battery (Administered via Phone by the UAB Survey Research Unit)	
Test	**Domain**
CERAD Word List Learning	Learning
Digit Span	Attention
CERAD Delayed Recall	Memory
Animal Fluency	Executive Function
Letter Fluency	
Oral Trail Making*	

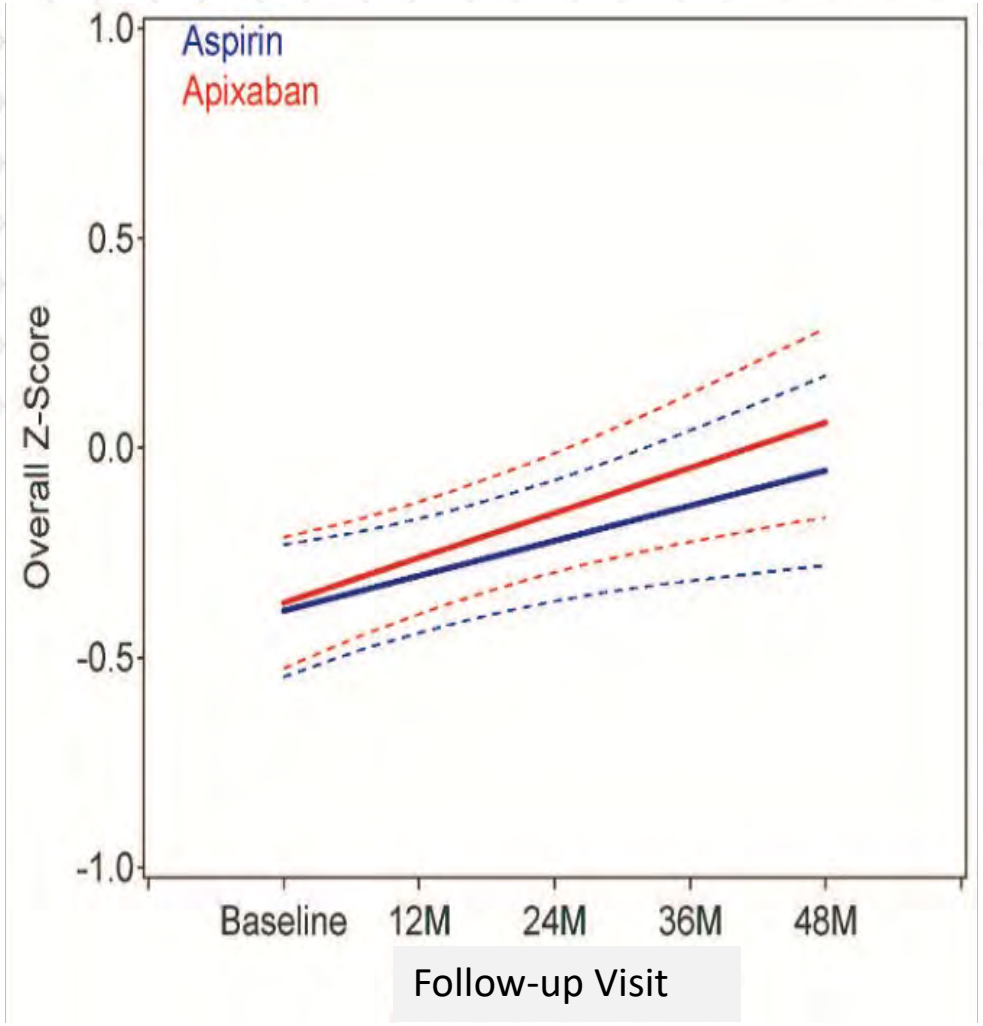



1015 Randomized in ARCADIA
799 Screened for ARCADIA-CSI
489 Excluded
• 345 Not Eligible
• 144 Decline
310 Enrolled
157 Randomized to apixaban
135 Randomized to aspirin
29 No cognitive testing
14 No cognitive testing
128 included in cognition analysis
121 included in cognition analysis

ARCADIA – CSI: (Cognition Substudy)

Baseline Characteristics/Follow-up Visits	Apixaban (n = 128)	Aspirin (n = 121)
Age at time of CSI consent, Mean (SD)	66.7 (10.3)	66.8 (10.6)
Female, no. (%)	64 (50.0)	65 (53.7)
Black, no. (%)	20 (15.6)	28 (23.1)
Hypertensive, no. (%)	96 (75.0)	89 (73.6)
Diabetic, no. (%)	31 (24.2)	35 (28.9)
Education n (%)	- - -	- - -
<High School	3 (2.3)	5 (4.1)
High School Graduate or GED	34 (26.6)	26 (21.5)
Partial College or Specialized Training	40 (31.3)	30 (24.8)
College Graduate	26 (20.3)	31 (25.6)
Graduate Professional Degree	25 (19.5)	29 (24.0)
Cognitive Exams Completed (%)		
Baseline	127 (99.2)	120 (99.2)
Follow-Up Visit 1	95 (74.2)	93 (76.9)
Follow-Up Visit 2	53 (41.4)	55 (45.5)
Follow-Up Visit 3	18 (14.1)	20 (16.5)
Follow-Up Visit 4		1 (1.0)

ARCADIA – CSI: (Cognition Substudy)



	Apixaban (n=128)	Aspirin (n=121)
ARCADIA Index stroke to first Cognitive exam (days), median (IQR)	264 (IQR: 141, 539)	249 (IQR: 138, 504)
First cognitive exam to last cognitive Exam (days), median (IQR)	374 (IQR: 0, 738)	413 (IQR: 225, 734)

Estimated Annual Change	
Aspirin	Apixaban
0.084 (0.018 – 0.149)	0.107 (0.041– 0.174)
P = 0.62	

ARCADIA – CSI: (Cognition Substudy)

Estimated Annual Change by Cognitive Test

	Aspirin	Apixaban	P-value
Verbal Fluency	0.089 (0.022 – 0.156)	0.109 (0.040 – 0.177)	0.69
Digit Span	0.069 (-0.008 – 0.147)	0.046 (-0.033 – 0.124)	0.67
Animal Naming	0.026 (-0.053 – 0.104)	0.109 (0.030 – 0.189)	0.14
Word List Learning	0.096 (0.008 – 0.185)	0.094 (0.005 – 0.183)	0.97
Word List Recall	0.057 (-0.038 – 0.153)	0.060 (-0.036 – 0.156)	0.97

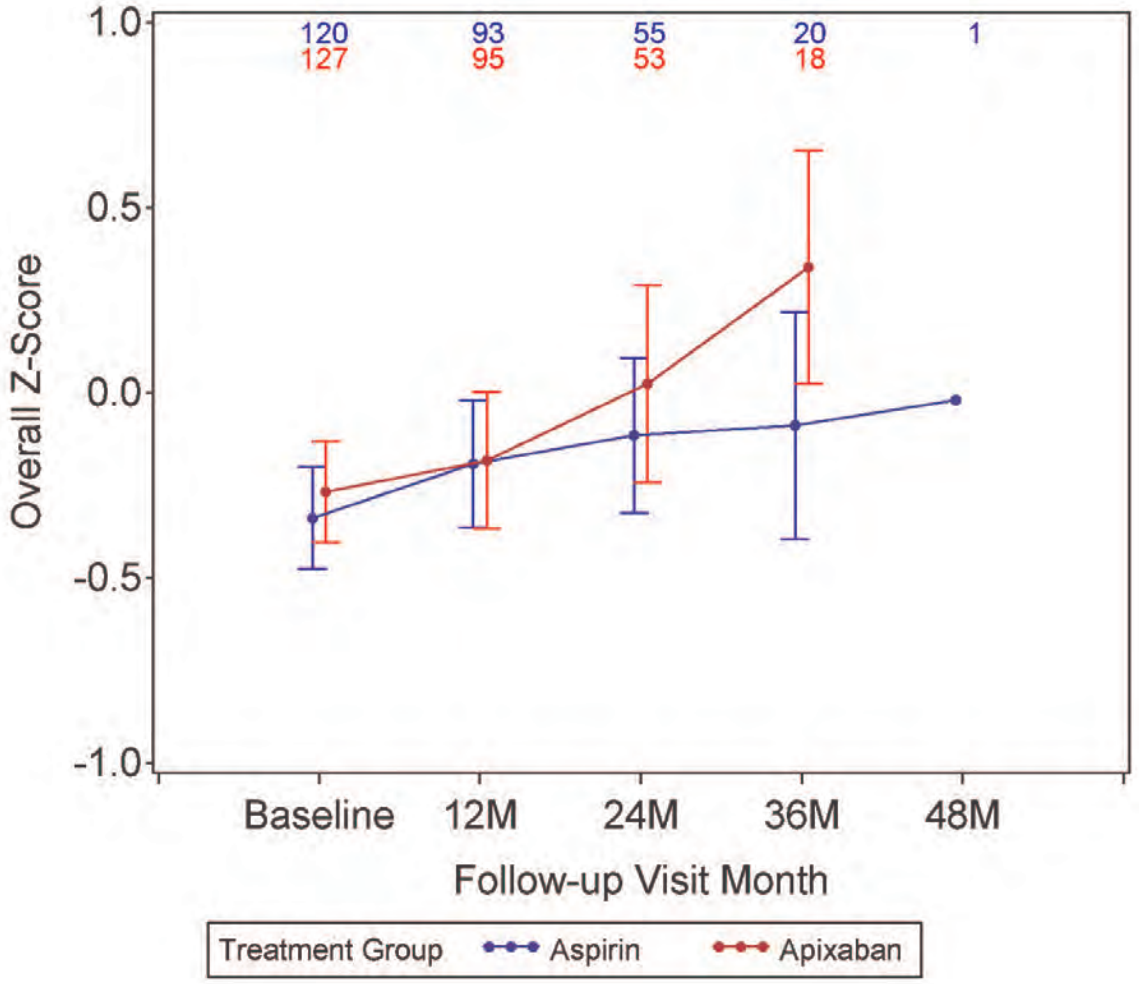
ARCADIA – CSI: (Cognition Substudy)

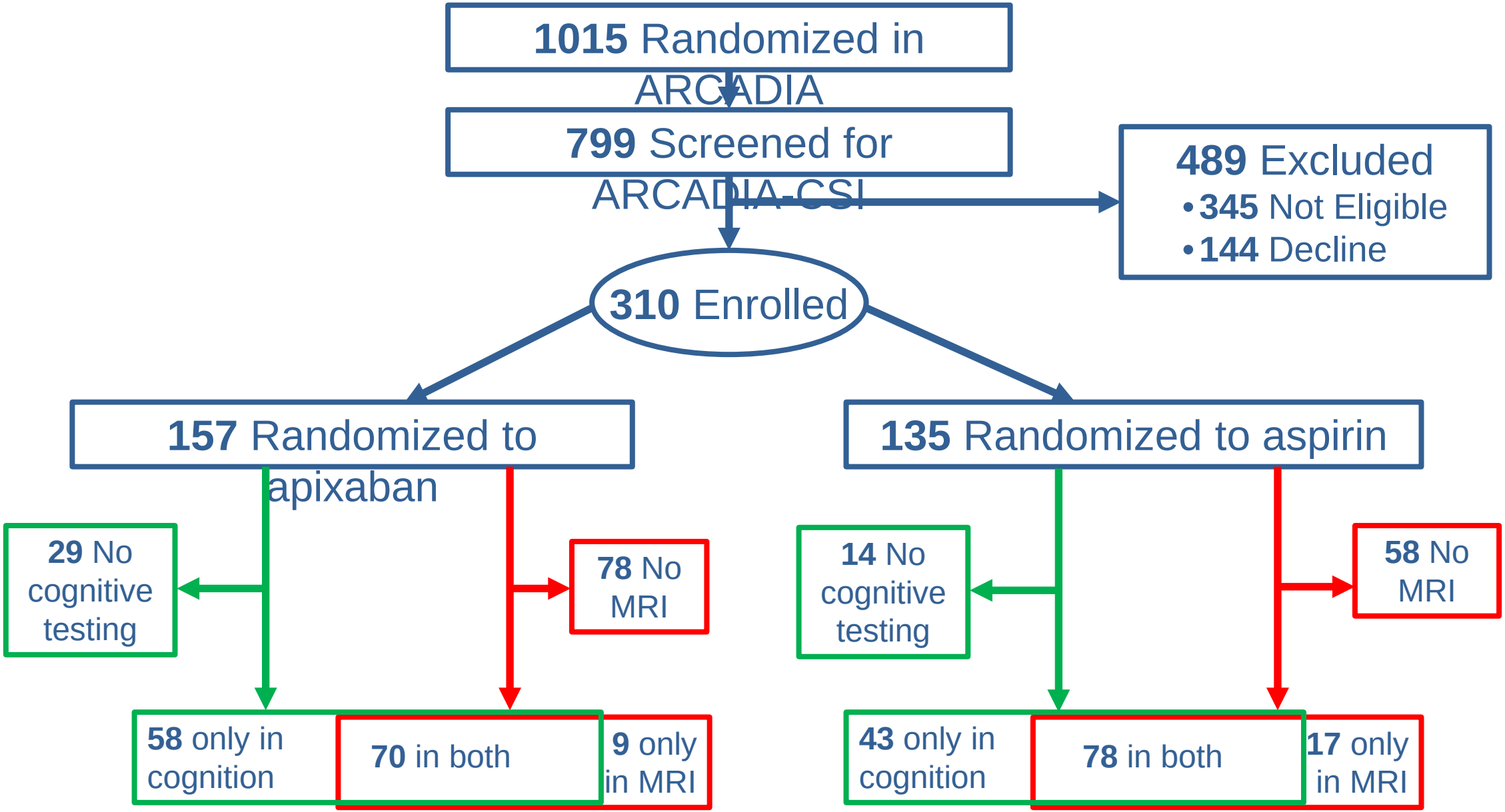
Factor Affecting Cognitive Effects

- Duration of Follow-Up
- Number of Covert Infarcts
- Volume of Covert Infarcts
- Location of Covert Infarcts
- Time since index stroke

ARCADIA – CSI: (Cognition Substudy)

What if….

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•144 Decline
310 Enrolled
157 Randomized to apixaban
135 Randomized to aspirin
29 No cognitive testing
78 No MRI
14 No cognitive testing
58 No MRI
58 only in cognition
70 in both
9 only in MRI
43 only in cognition
78 in both
17 only in MRI

Atrial Fibrillation in the ARCADIA Trial

Hooman Kamel for the ARCADIA Investigators

Disclosures

NIH (R01HL144541, R01NS123576, R01NS135205, U01NS095869, U01NS106513)

BMS (in-kind study drug for ARCADIA trial)

Roche (ancillary study support for ARCADIA trial)

STROKE-AF, LIBREXIA-AF, LAAOS-4 (trial steering committees)

AbbVie, Arthrosi, AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Medtronic, Novo Nordisk (consulting, endpoint adjudication committees)

TETMedical, Spectrum Plastics, Ascential Technologies (ownership interest)

Deputy Editor, *JAMA Neurology*

Original Research Article

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Sage

Atrial cardiopathy biomarkers and atrial fibrillation in the ARCADIA trial

Hooman Kamel[1], Mitchell SV Elkind[2,3], Richard A Kronmal[4], WT Longstreth, Jr.[5,6,7], Pamela Plummer[8], Rebeca Aragon Garcia[2], Joseph P Broderick[8], Qi Pauls[9], Jordan J Elm[9], Fadi Nahab[10], L Scott Janis[11], Marco R Di Tullio[12], Elsayed Z Soliman[13], Jeff S Healey[14] and David L Tirschwell[5]; for the ARCADIA Investigators

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Table 1. Characteristics of patients screened for atrial cardiopathy in ARCADIA, stratified by subsequent detection of AF.

Characteristic[a]	Atrial fibrillation (*N* = 254)	No atrial fibrillation (*N* = 3491)
Age, mean (SD), years	71.7 (9.7)	65.8 (10.6)
Female, no. (%)	134 (52.8%)	1604 (45.9%)
Race, no. (%) [*N* = 3659][b]		
Asian	2 (0.8%)	68 (2.0%)
Black or African American	43 (17.1%)	649 (19.0%)
Other	205 (81.7%)	2645 (77.6%)
White	1 (0.4%)	46 (1.3%)
Ethnicity, no. (%) [*N* = 3724][b]		
Hispanic or Latino	15 (6.0%)	343 (9.9%)
Not Hispanic or Latino	237 (94.0%)	3129 (90.1%)
Medical comorbidities		
Hypertension	200 (78.7%)	2512 (72.0%)
Prior or current tobacco use	104 (40.9%)	1426 (40.8%)
Diabetes	76 (29.9%)	1052 (30.1%)
Coronary artery disease	26 (10.2%)	265 (7.6%)
Heart failure	18 (7.1%)	136 (3.9%)
Peripheral artery disease	5 (2.0%)	67 (1.9%)
Atrial cardiopathy biomarkers		
$PTFV_1$, mean (SD), μV*ms [*N* = 3673]	3798 (2,660)	3426 (2,259)
NT-proBNP, median (IQR), pg/mL [*N* = 3580]	416 (258–751)	96 (45–231)
LA diameter index, mean (SD), cm/m^2 [*N* = 3125]	2.1 (0.4)	1.8 (0.4)
Days from stroke to biomarker screening, mean (SD)	1.9 (4.3)	3.0 (25.3)

AF: atrial fibrillation; IQR: interquartile range; LA: left atrial; NT-proBNP: amino terminal pro-B-type natriuretic peptide; $PTFV_1$: P-wave terminal force in lead V_1; SD: standard deviation.

[a]Percentages may not total 100 because of rounding.

[b]Other race was defined as American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or more than one race. Site investigators and coordinators were instructed to directly ask participants to report their self-identified race and ethnicity, which were then categorized per NIH guidelines.

Table 2. Associations between baseline atrial cardiopathy biomarkers and subsequent detection of atrial fibrillation in ARCADIA.

Biomarker	Model 1	Model 2	Model 3
$PTFV_1$	1.15 (1.03–1.28)	1.03 (0.92–1.14)	-
NT-proBNP	1.99 (1.85–2.13)	1.83 (1.69–1.97)	1.88 (1.67–2.11)
LADI	1.34 (1.20–1.50)	1.25 (1.14–1.38)	1.25 (1.14–1.37)

LADI: left atrial diameter index; NT-proBNP: amino terminal pro-B-type natriuretic peptide; $PTFV_1$: P-wave terminal force in lead V_1.
Data are presented as risk ratios (95% confidence intervals) per standard-deviation increase in the atrial cardiopathy biomarker variables. Model 1 was unadjusted. Model 2 included all three biomarkers together. Model 3 additionally adjusted for age, sex, race, ethnicity, hypertension, diabetes, coronary artery disease, heart failure, peripheral artery disease, and tobacco use, with variables reduced using stepwise reverse selection with a *p*-value threshold of 0.2.

Table 3. Discrimination of baseline atrial cardiopathy biomarkers for predicting subsequent AF in ARCADIA.

Variables included in predictive model	C-statistic (95% CI)
$PTFV_1$, NT-proBNP, LADI	0.82 (0.79–0.85)
NT-proBNP, LADI	0.82 (0.79–0.85)
NT-proBNP, $LADI_{central}$	0.80 (0.77–0.83)
NT-proBNP, $LAVI_{central}$	0.81 (0.78–0.84)
NT-proBNP, LADI, age	0.82 (0.79–0.85)
NT-proBNP	0.80 (0.77–0.83)
LADI	0.67 (0.63–0.72)
$LADI_{central}$	0.67 (0.64–0.71)
$LAD_{central}$	0.66 (0.63–0.70)
$LAVI_{central}$	0.71 (0.67–0.74)
$PTFV_1$	0.54 (0.50–0.58)
Age	0.66 (0.63–0.70)

Figure 1. Calibration of atrial cardiopathy biomarkers for predicting AF in ARCADIA.

Each open circle represents 1 of 20 groups of ARCADIA trial participants. Patients were grouped by their predicted probability of atrial fibrillation (AF) based on a relative risk regression model comprised of NT-proBNP, left atrial dimension index, and P-wave terminal force in ECG lead V_1. The circle's position on the x-axis represents the group's predicted probability of atrial fibrillation. The circle's position on the y-axis represents the actual proportion of patients in the group who developed atrial fibrillation. The dashed blue line represents perfect calibration

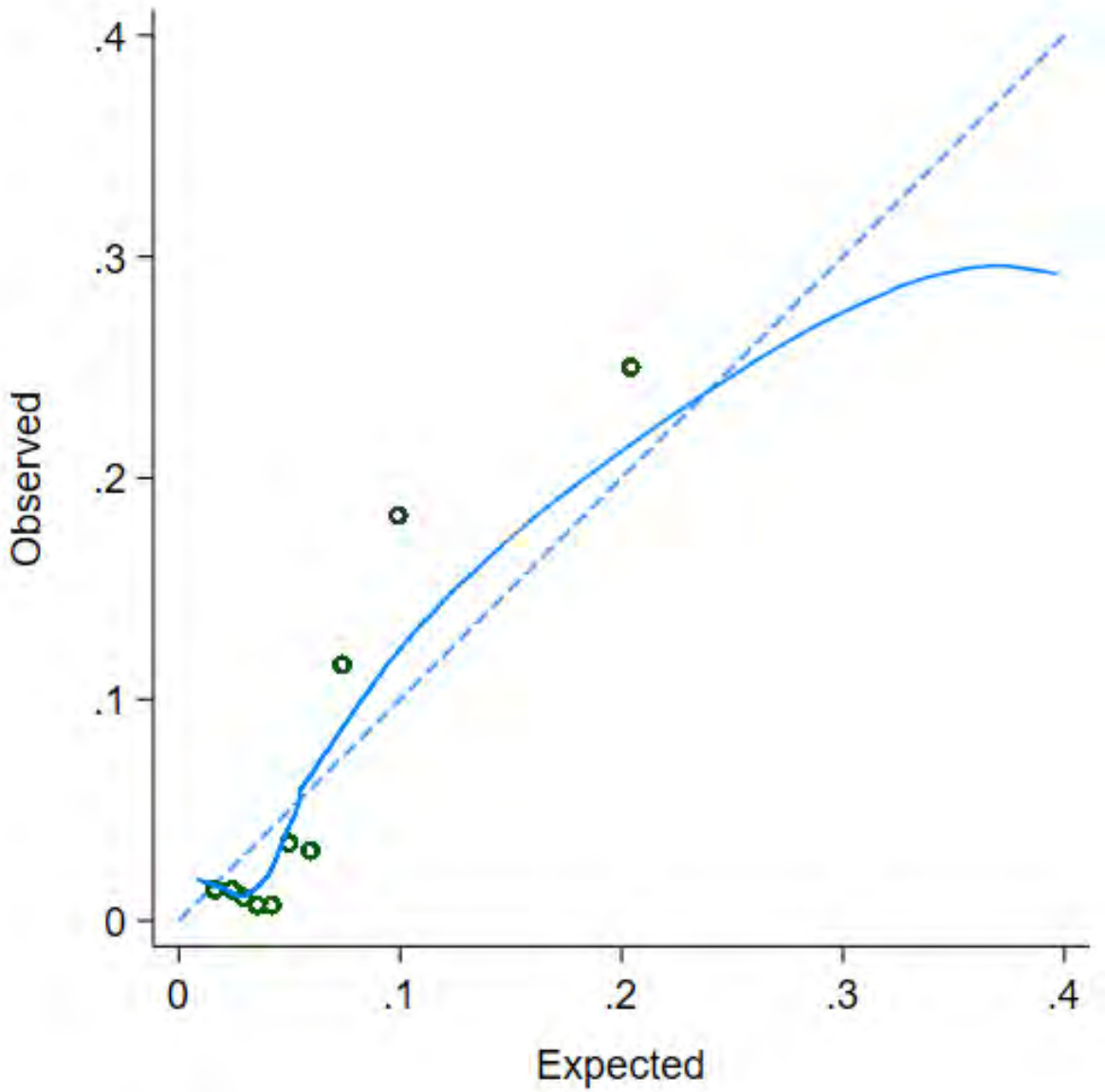

Table 4. Sensitivity analysis of associations between baseline atrial cardiopathy biomarkers and subsequent detection of atrial fibrillation in the ARCADIA trial.

Patient population	$PTFV_1$[a]	NT-proBNP[a]	LADI[a]	Discrimination[b]
Eligible	0.84 (0.74–0.95)	1.30 (1.15–1.47)	1.18 (1.10–1.26)	0.67
Randomized	0.81 (0.68–0.95)	1.38 (1.15–1.66)	1.25 (1.11–1.41)	0.69

LADI: left atrial diameter index; NT-proBNP: amino terminal pro-B-type natriuretic peptide; $PTFV_1$: P-wave terminal force in lead V_1.
[a]Data are presented as risk ratios (95% confidence intervals) or hazard ratios (95% confidence intervals) per standard-deviation increase in the atrial cardiopathy biomarker variables in a model that included all three biomarkers together.
[b]Data are presented as c-statistics or Harrell's C.

Limitations

- Differential ascertainment of AF based on eligibility for randomization
- Heterogeneity in AF monitoring and ascertainment

Conclusions

Biomarkers used to identify atrial cardiopathy in ARCADIA were associated with and predictive of subsequent AF detection, suggesting neutral results of trial not entirely due to suboptimal biomarkers of atrial cardiopathy

Predictive performance of biomarkers was modest, supporting further research to identify other measures that can identify a more severe form of atrial cardiopathy with a high risk of AF

Heart-Rhythm Monitoring Practices, Detection of Atrial Fibrillation, and Effect of Anticoagulation in the ARCADIA Trial

Figure 1. Flow Diagram of Patients Included in Analysis of Heart-Rhythm Monitoring Practices in the ARCADIA Trial.

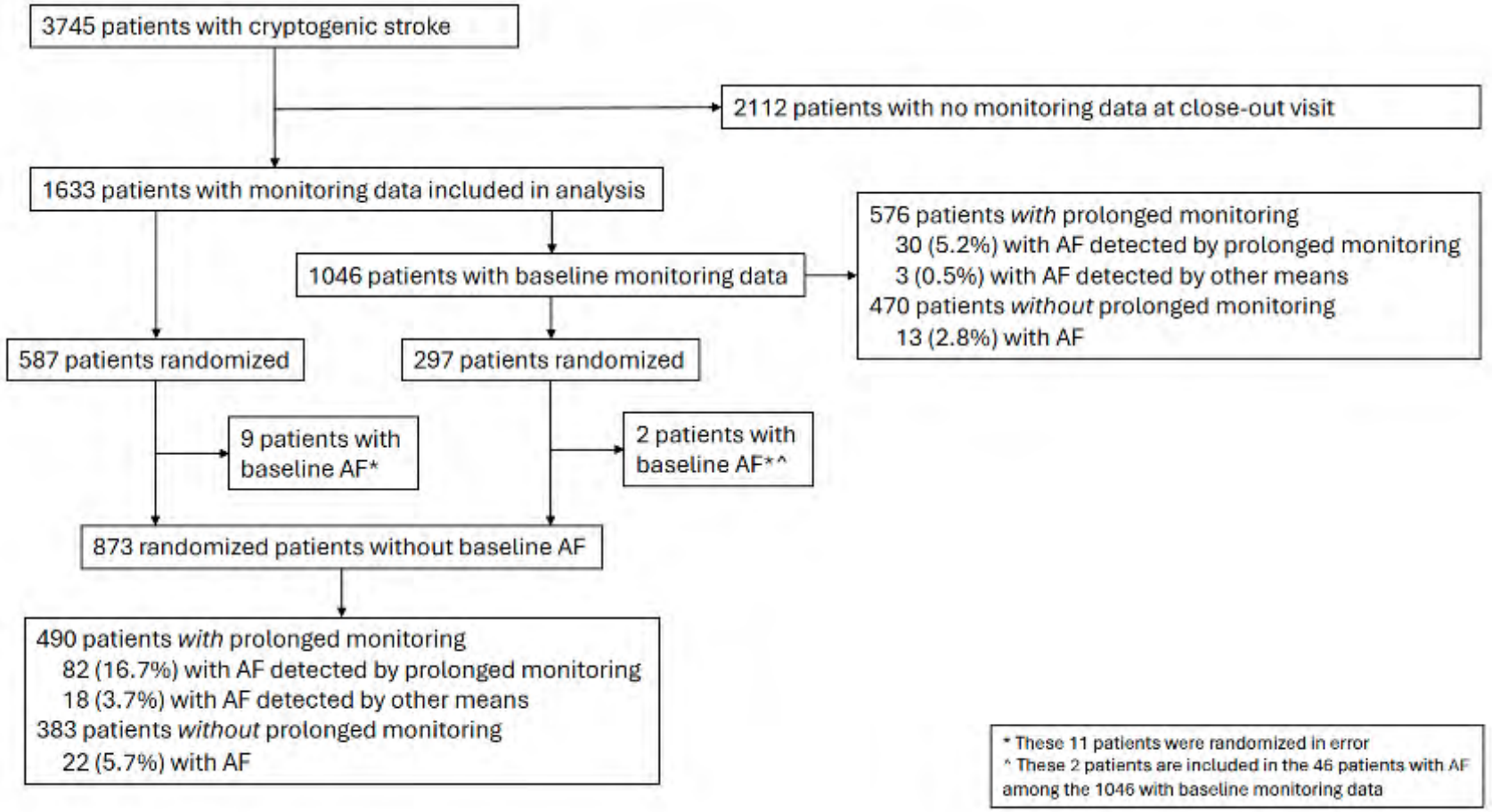

Table 1. Characteristics of patients screened for atrial cardiopathy in ARCADIA, stratified by subsequent detection of AF.

Characteristic[a]	Atrial fibrillation (*N* = 254)	No atrial fibrillation (*N* = 3491)
Age, mean (SD), years	71.7 (9.7)	65.8 (10.6)
Female, no. (%)	134 (52.8%)	1604 (45.9%)
Race, no. (%) [*N* = 3659][b]		
Asian	2 (0.8%)	68 (2.0%)
Black or African American	43 (17.1%)	649 (19.0%)
Other	205 (81.7%)	2645 (77.6%)
White	1 (0.4%)	46 (1.3%)
Ethnicity, no. (%) [*N* = 3724][b]		
Hispanic or Latino	15 (6.0%)	343 (9.9%)
Not Hispanic or Latino	237 (94.0%)	3129 (90.1%)
Medical comorbidities		
Hypertension	200 (78.7%)	2512 (72.0%)
Prior or current tobacco use	104 (40.9%)	1426 (40.8%)
Diabetes	76 (29.9%)	1052 (30.1%)
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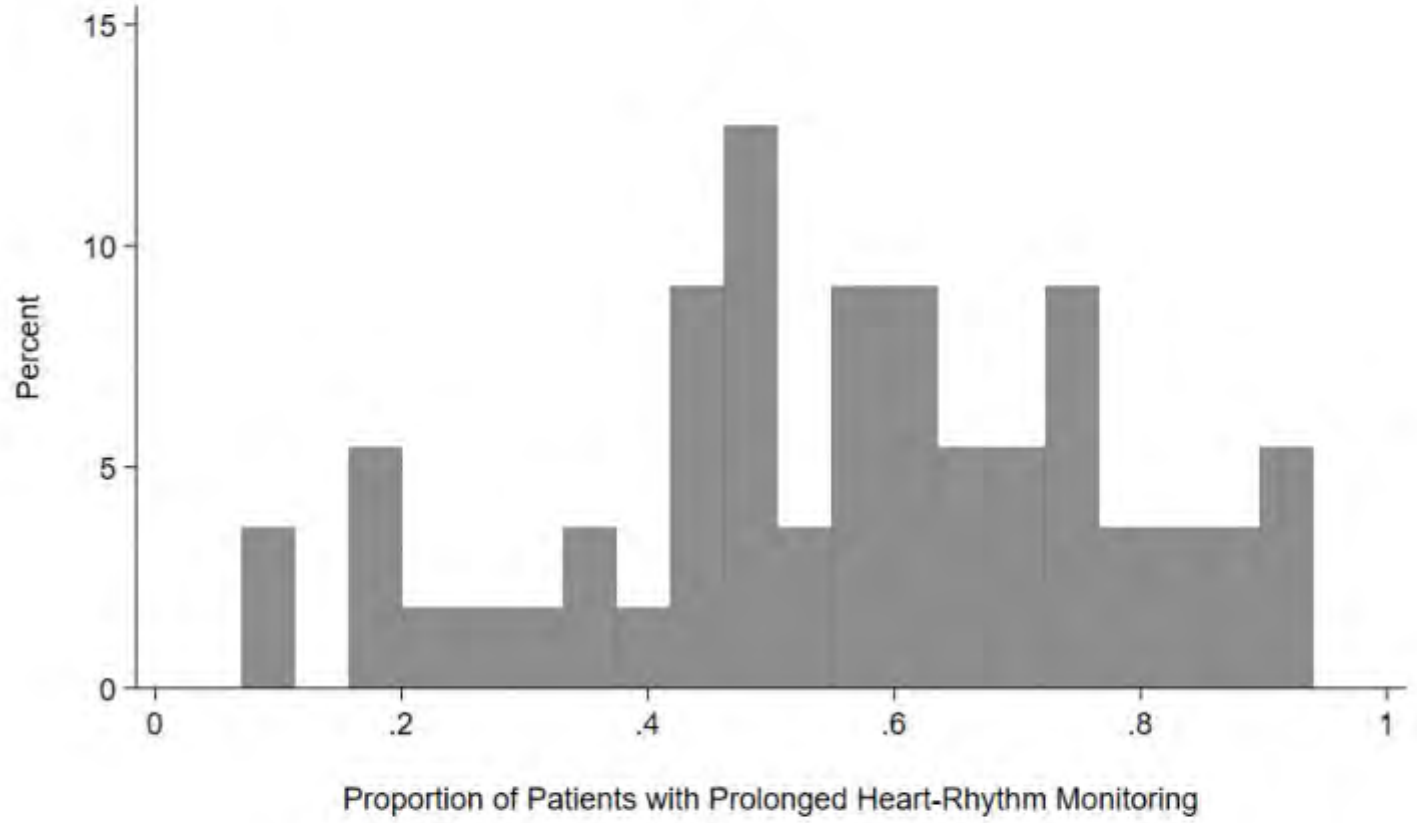
Table 2. Proportions of ARCADIA Patients Undergoing Prolonged Heart-Rhythm Monitoring.[a]

	Any Prolonged Monitoring	External Ambulatory Monitor	Implantable Loop Recorder	Both[b]
Overall (n = 1,633)	58.6%	34.7%	29.3%	5.5%
Before randomization (n = 1,046)	55.1%	39.0%	18.6%	2.6%
After randomization (n = 873)	56.2%	21.7%	39.4%	4.9%

Table 3. Factors Associated with Prolonged Heart-Rhythm Monitoring in the ARCADIA Trial.[a]

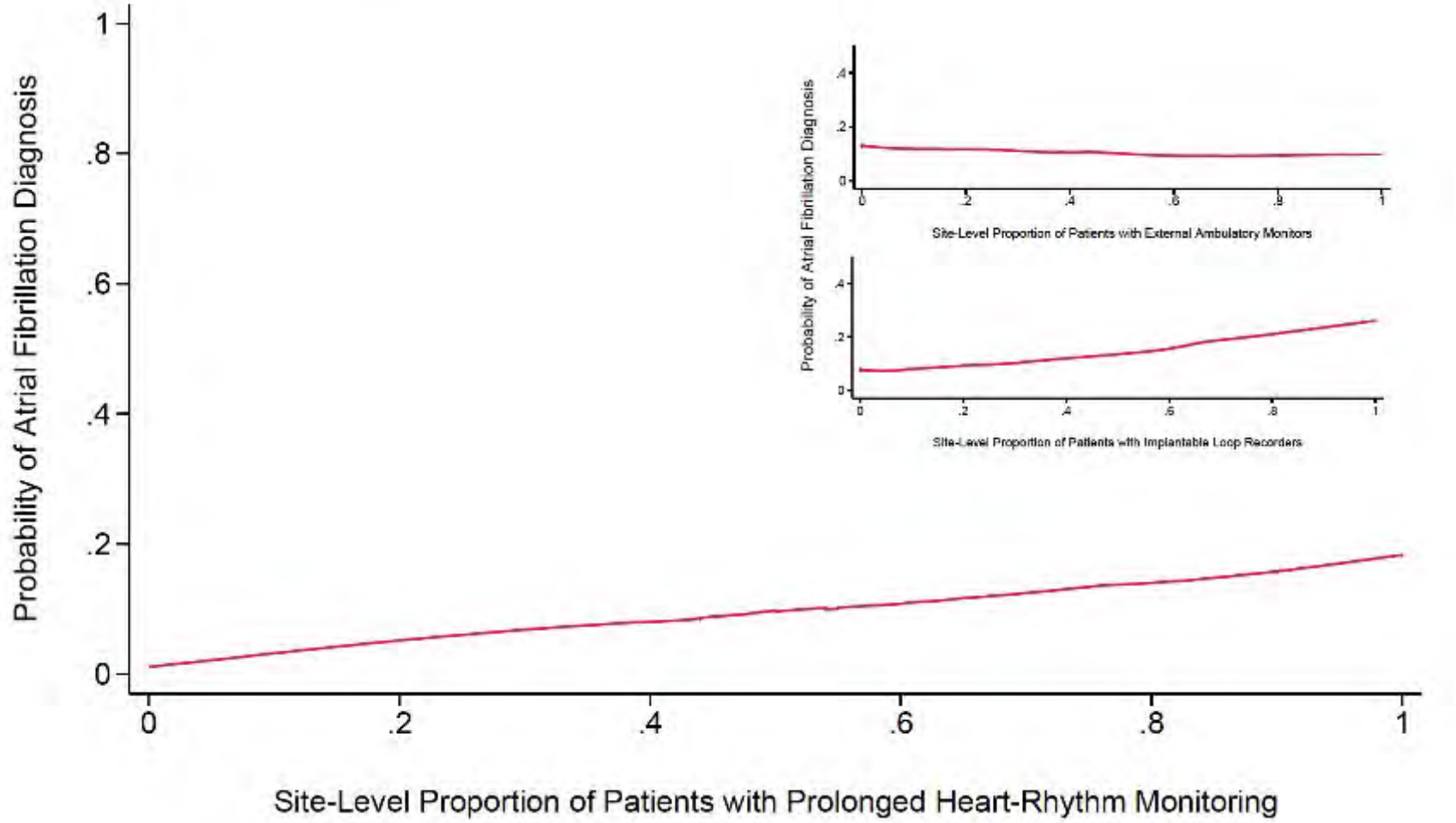
Characteristic	Risk Ratio (95% CI)	*P* value
Age (per decade)	1.04 (1.00-1.08)	0.047
Female sex	1.07 (0.98-1.17)	0.14
Asian, Black, Hispanic, or other race-ethnicity	0.84 (0.74-0.95)	0.006
Modified Rankin Scale (per point)	0.97 (0.93-1.01)	0.12
National Institutes of Health Stroke Scale (per point)	0.98 (0.96-1.00)	0.037
Peripheral artery disease	0.71 (0.49-1.05)	0.09

Figure 2. Distribution Across Sites of the Proportion of Patients Undergoing Prolonged Heart-Rhythm Monitoring.



Only sites with >10 patients in this sample are shown (96 sites had ≤10 patients and 55 had >10 patients).

Figure 3. Relationship between Site-Level Proportion of Patients Undergoing Prolonged Heart-Rhythm Monitoring and Detection of Atrial Fibrillation.



Limitations

- Lacked detail on precise type and duration of monitoring
- Data available for only a subset of trial participants
- Potential confounding in association between monitoring and AF

Conclusions

- Prolonged heart-rhythm monitoring appears fairly widespread at North American stroke centers participating in stroke trials
- More monitoring at site level associated with greater risk of AF detection
- Substantial practice variation and sociodemographic disparities
- Future studies needed to identify optimal and equitable strategies for assessing risk of cardioembolic stroke after cryptogenic stroke

Other Secondary Analyses of the ARCADIA Trial

Hooman Kamel for the ARCADIA Investigators

Pending paper topics

- Cancer
- LV injury
- Brain infarction in multiple arterial territories
- Vascular risk factors and effect of anticoagulation

JAMA Neurology | Original Investigation

Apixaban vs Aspirin in Patients With Cancer and Cryptogenic Stroke
A Post Hoc Analysis of the ARCADIA Randomized Clinical Trial

Babak B. Navi, MD, MS; Cenai Zhang, MS; Benjamin Miller, MD; Mary Cushman, MD, MSc; Scott E. Kasner, MD, MSCE; Mitchell S. V. Elkind, MD, MS; David L. Tirschwell, MD, MSc; W. T. Longstreth Jr, MD, MPH; Richard A. Kronmal, PhD; Morin Beyeler, MD; Jordan Elm, PhD; Richard M. Zweifler, MD; Joseph Tarsia, MD; Carlo W. Cereda, MD; Giovanni Bianco, MD; Gianluca Costamagna, MD; Patrik Michel, MD; Joseph P. Broderick, MD; David J. Gladstone, MD; Hooman Kamel, MD, MS; Christopher Streib, MD, MS

Table 3. Outcomes Among Participants With History of Cancer at Enrollment Stratified by Treatment Group

	Aspirin (n = 76)		Apixaban (n = 61)		
Outcome	No. (%)	Incidence rate, No./100 person-years (95% CI)	No. (%)	Incidence rate, No./100 person-years (95% CI)	HR (95% CI)
Primary outcome					
Major ischemic or major hemorrhagic event	16 (21.1)	12.8 (7.8-20.9)	8 (13.1)	7.8 (3.9-15.7)	0.61 (0.26-1.43)
Secondary efficacy outcome					
Recurrent ischemic stroke	7 (9.2)	5.3 (2.5-11.2)	5 (8.2)	4.7 (1.9-11.2)	0.87 (0.28-2.76)
Ischemic or hemorrhagic stroke	9 (11.8)	6.8 (3.6-13.2)	5 (8.2)	4.7 (1.9-11.2)	0.68 (0.23-2.03)
Major arterial ischemic event	9 (11.8)	7.0 (3.7-13.5)	6 (9.8)	5.6 (2.5-12.5)	0.79 (0.28-2.23)
Symptomatic DVT or PE	6 (7.9)	4.7 (2.1-10.4)	1 (1.6)	0.9 (0.1-6.7)	0.21 (0.02-1.71)
Major ischemic event	14 (18.4)	11.2 (6.6-18.9)	7 (11.5)	6.6 (3.1-13.9)	0.59 (0.24-1.47)
Secondary safety outcome					
All-cause mortality	4 (5.3)	3.0 (1.1-8.1)	3 (4.9)	2.8 (0.9-8.7)	0.94 (0.21-4.19)
Symptomatic ICH	2 (2.6)	1.5 (0.4-6.1)	0	NA	NA
Major hemorrhagic event	2 (2.6)	1.5 (0.4-6.1)	1 (1.6)	1.0 (0.1-6.9)	0.61 (0.06-6.73)

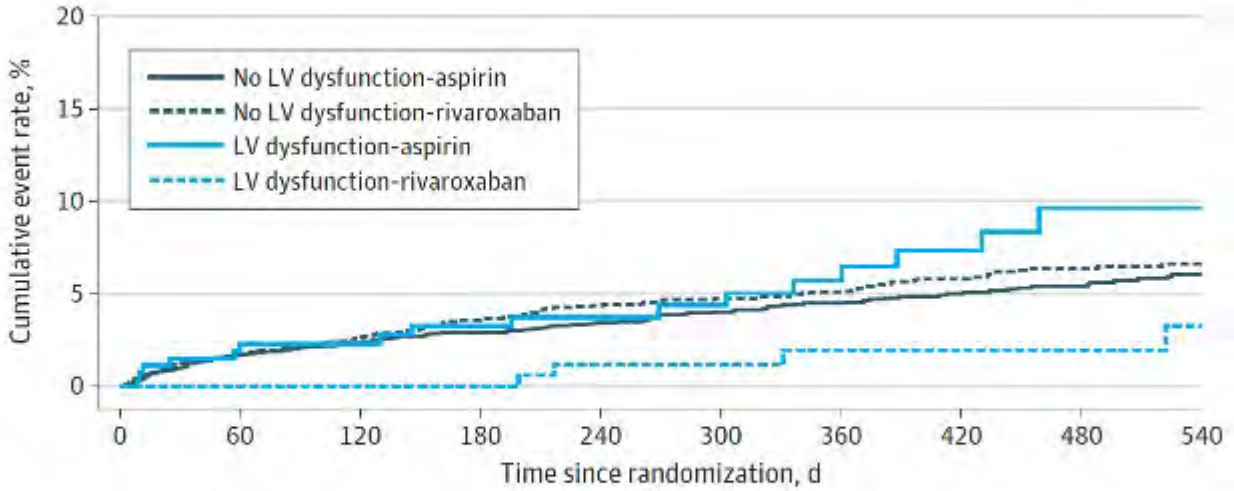
JAMA Neurology | Original Investigation

Left Ventricular Dysfunction Among Patients With Embolic Stroke of Undetermined Source and the Effect of Rivaroxaban vs Aspirin

A Subgroup Analysis of the NAVIGATE ESUS Randomized Clinical Trial

Alexander E. Merkler, MD, MS; Lesly A. Pearce, MS; Scott E. Kasner, MD; Ashkan Shoamanesh, MD; Lee A. Birnbaum, MD; Hooman Kamel, MD, MS; Kevin N. Sheth, MD; Richa Sharma, MD, MPH

Figure 2. Kaplan-Meier Curves for Time to Primary Outcome Event by Left Ventricular Dysfunction and Assigned Treatment



No. at risk

No LV dysfunction-aspirin	3282	2910	2594	2302	1972	1709	1426	1201	958	721
No LV dysfunction-rivaroxaban	3323	2935	2600	2311	1967	1708	1430	1181	941	697
LV dysfunction-aspirin	273	242	220	195	166	149	120	96	63	47
LV dysfunction-rivaroxaban	229	213	197	178	156	141	121	102	85	70

LV injury and anticoagulation in ARCADIA

- EF, fractional shortening, and WMA from echo lab
- Analysis led by Alex Merkler, Richa Sharma, Fadi Nahab, and others
- Directly informed RESOLVE trial proposal
- Results submitted for ISC 2025

Acknowledgements

ARCADIA patients and their families

Study site investigators and coordinators

Project managers: Rebeca Aragon-Garcia and Pam Plummer

StrokeNet NCC and NDMC teams and Canadian Coordinating Center

Central Pharmacy

ECG, Echo, and Laboratory Cores

Outcome Adjudication Core and Medical Safety Monitor

NIH/NINDS

The BMS-Pfizer Alliance

Roche Diagnostics

Priority Setting Conferences

NIH StrokeNet initiative to guide stroke research priorities

Pooja Khatri, MSc

GOAL: Conferences on Dedicated Scientific Themes

Comprehensive Review

A full consideration of a single scientific theme, drawing insights from key stakeholders and experts in an open forum, to develop research priorities and opportunities within that theme.

Diverse Perspectives

This includes perspectives from clinical researchers, preclinical scientists, patient representatives, DEI experts, and methodologists.

Resulting White Paper

The paper will guide trial proposers, peer review and funders.

.

Themes Proposed by Working Groups To Date

Emphasizing scientific themes over methodology was the guiding principle.

Acute

- Addressing barriers in rural and underserved communities
- Ultra-early interventions including pre-hospital treatments and diagnosis
- Neuroprotection

Prevention

- Cerebral small vessel disease (CAA, hypertensive ICH, etc.)
- Novel approaches to vascular risk factor management (obesity, microbiome, diet, cardiometabolic)

Recovery/Rehab

- Very high-dose rehabilitation
- Combining rehab with neuromodulation (brain stimulation, drugs)
- Rehab models for rural settings
- Technology-based interventions and long-term sustainability

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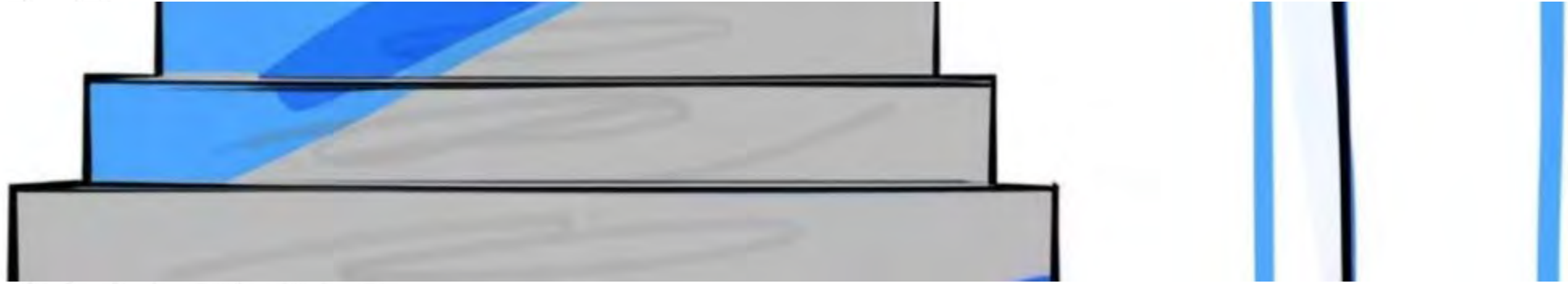

Next Steps

1

Current Meeting

Breakout rooms according to domain. Seeking diverse of thought.

2

Working Group and Executive Committee Review

Working Groups and Executive Committee will consider input from fall meeting.

3

Theme Selection

Themes will be presented to the NINDS for review and consideration. A theme will be selected by NINDS for the first conference.

4

Conference Development

Volunteers from StrokeNet community will be sought for a Task Force to develop the first conference grant proposal for that particular scientific theme.

Breakout Room Activity

1

Review Themes

Carefully examine the **scientific themes proposed by each working group.**

2

Prioritize Themes

Identify the **most important and impactful themes for future stroke research.**

3

Refine Suggestions

Narrow down the **list of suggested themes** or propose **alternate priorities** that emerge from the discussion.

4

Share Findings

Provide a **summary of your group's discussion and recommendations** to larger group.

A StrokeNet trainee in each room has been asked to take notes

WG Chair(s) will also be in respective breakout room to hear and participate in discussions

Moderators will provide 10-min summaries to larger group to weigh in

Consider the following aspects for each potential scientific theme:

Reasons that theme may be timely

Challenges in bridging evidence and practice

Opportunities for pragmatic and decentralized approaches

Challenges related to race/ethnic, geographic, and socioeconomic disparities

Types of stakeholders needed for the conference

More on Themes Proposed by Working Groups:

RECOVERY/REHAB: Steve Cramer

ACUTE: Karen Johnston

PREVENTION: Hooman Kamel

Themes for priority setting conferences

Recovery and Rehabilitation Group

MUSC Medical University of South Carolina

NIH

UNIVERSITY OF Cincinnati

Complexities of stroke recovery/rehabilitation research

(1) Some positive trials (EXCITE, L-Dopa, FLAME, TR, VNS)

(2) Many treatment targets, many endpoints

(3) Multidisciplinary teams, in patient care and in clinical research

(4) Patients are scattered to the 4 winds

The StrokeNet Recovery & Rehabilitation Group

Steve Cramer (Chair)	MD	UCLA
Steve Wolf (Co-Chair)	PhD, PT	Emory University
Oluwole Awosika	MD	University of Cincinnati
Jonathan Beall	PhD	MUSC
Amy Boos	MSBME, OTR/L	University of Pittsburgh
Michael Borich	DPT, PhD	Emory University
Devin Brown	MD	University of Michigan
Cassandra Cardenas	MS	UC Irvine
Patricia Coker-Bolt	PhD, OTR/L	MUSC
Daofen Chen	PhD	NINDS
Mary Carter Denny	MD	Medstar Health
Jordan Elm	PhD	MUSC
Wayne Feng	MD	Duke University
Cathra Halabi	MD	UCSF
Scott Janis	PhD	NINDS
Lorelei Phillip Johnson	PhD	Atrium Health
Pooja Khatri	MD	University of Cincinnati
Cassandra List	MD	Brooks Rehabilitation
Jenny Majersik	MD	University of Utah
Sue Marden	PhD, RN	NICHD
Caitlyn Meinzer	PhD	MUSC
Eva Mistry	MD	University of Cincinnati
Susan Murphy	BS	Emory University
Michael Obel-Omia	MA	Patient representative
Ela Plow	PhD	Cleveland Clinic
Vivek Prabhakaran	MD, PhD	University of Wisconsin
Jessica Richardson	Ph.D., CCC-SLP	University of New Mexico
Kelly Sloane	MD	University of Pennsylvania
Peter Turkeltaub	MD, PhD	Georgetown University
George Wittenberg	MD, PhD	University of Pittsburgh

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There were 90 votes across 18 people

Level	Count
AFB	4
CC	3
CH	5
CML	5
EP	5
GFW	12
JDR	7
KLS	3
LB	5
LPJ	5
MCD	5
OA	5
PCB	6
PET	6
SCC	3
SLW	5
SM	2
VP	4
Total	90

Therapy or biomarker idea	Your initials	# votes
Very very very high doses of rehab therapy	SCC, SM, PCB, AFB, SLW, PET, EP, CH, CML	9
Combining intensive therapies with neuromodulation (i.e. taVNS, TMS, including pharmacological interventions)	PCB, SLW, JDR, OA, CH, LB, GFW, LPJ	8
Rehabilitation models for clients in rural settings or geographically remote areas and other marginalized groups	PCB, JDR, KLS, PET, CC, LB, MCD, LPJ	8
Technology based interventions; long-term effects, sustainability	PCB, SLW, KLS, PET, OA, GFW, MCD, VP	8
Participation focused interventions in stroke rehabilitation	PCB, SLW, JDR, PET, EP, CC, LPJ	7
Artificial Intelligence based stroke rehabilitation	VP, SM, PCB, AFB, SCC, GFW	6
Broadening access to interventional trials for patients with communication/language or cognitive impairments	CH, LB, JDR, CML, MCD, LPJ	6
Partner/community training for interventions, maintenance, accessible communities	JDR, KLS, CC, MCD	4
Customization of Rehabilitation–less one size fits all approach	OA, EP, JDR, LB	4
Understanding priorities of patients with stroke (from Ranking of Importance on Stroke Topics)	EP, LB, GFW, MCD	4
Invasive procedures (ex: spinal cord stimulation, tendon release) combined with functional training	AFB, CH, GFW	3
Developing sensitive and reliable measures to assess clinically meaningful outcomes	PET, JDR, GFW	3
Recruitment & Retention of Next Generation of Trialists in Stroke Recovery/Rehabilitation (from Ranking of Importance on Stroke Topics)	EP, GFW, LPJ	3
Gut Brain Axis and Brain Health Research	OA, VP	2
Biometric monitors and other technologies for ecologically valid, accessible, and rich outcome measurement	PET, GFW	2
Accurate assessments/pathways/resources for successful return to work after stroke	CML, GFW	2
Accurate assessments/pathways/resources for successful return to driving after stroke	CML, GFW	2
Advanced Connectome Stroke MR Imaging	VP, GFW	2
Aerobic and strength training exercise	AFB, CH	2
Mesenchymal stromal cell therapy	SCC	1
Duration of “intense” rehabilitation	CML	1
Machine based learning including data transmission from home environment	SLW	1
Pre-enrollment conditioning for intervention trials to better delineate true effects	OA	1
Biomarkers (-omics) in rehabilitation	GFW	1

- Very very very high doses of rehab therapy
- Combining intensive therapies with neuromodulation (i.e., taVNS, TMS, and pharmacological interventions)
- Rehabilitation models for clients in rural settings or geographically remote areas and other marginalized groups
- Technology-based interventions; long-term effects, sustainability

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Why it's timely: Increased momentum in recovery/rehab therapeutics

Challenges in bridging the gap between evidence and changing practice: mounting evidence, weak translation to clinical practice

Opportunities for pragmatic and decentralized approaches: needed, but complex given variability in clinical practice

Challenges related to geographic and socioeconomic disparities: wide geographic variation in rehab practice, high impact of socioeconomic factors

Types of stakeholders needed: numerous, e.g., patients, OT, PT, SLP, RN, MD, neuropsych, hospital CEOs, industry, etc

- Very very very high doses of rehab therapy
- Combining intensive therapies with neuromodulation (i.e., taVNS, TMS, and pharmacological interventions)
- Rehabilitation models for clients in rural settings or geographically remote areas and other marginalized groups
- Technology-based interventions; long-term effects, sustainability

Themes for priority setting conferences

Acute Stroke Working Group

On behalf of the ASWG

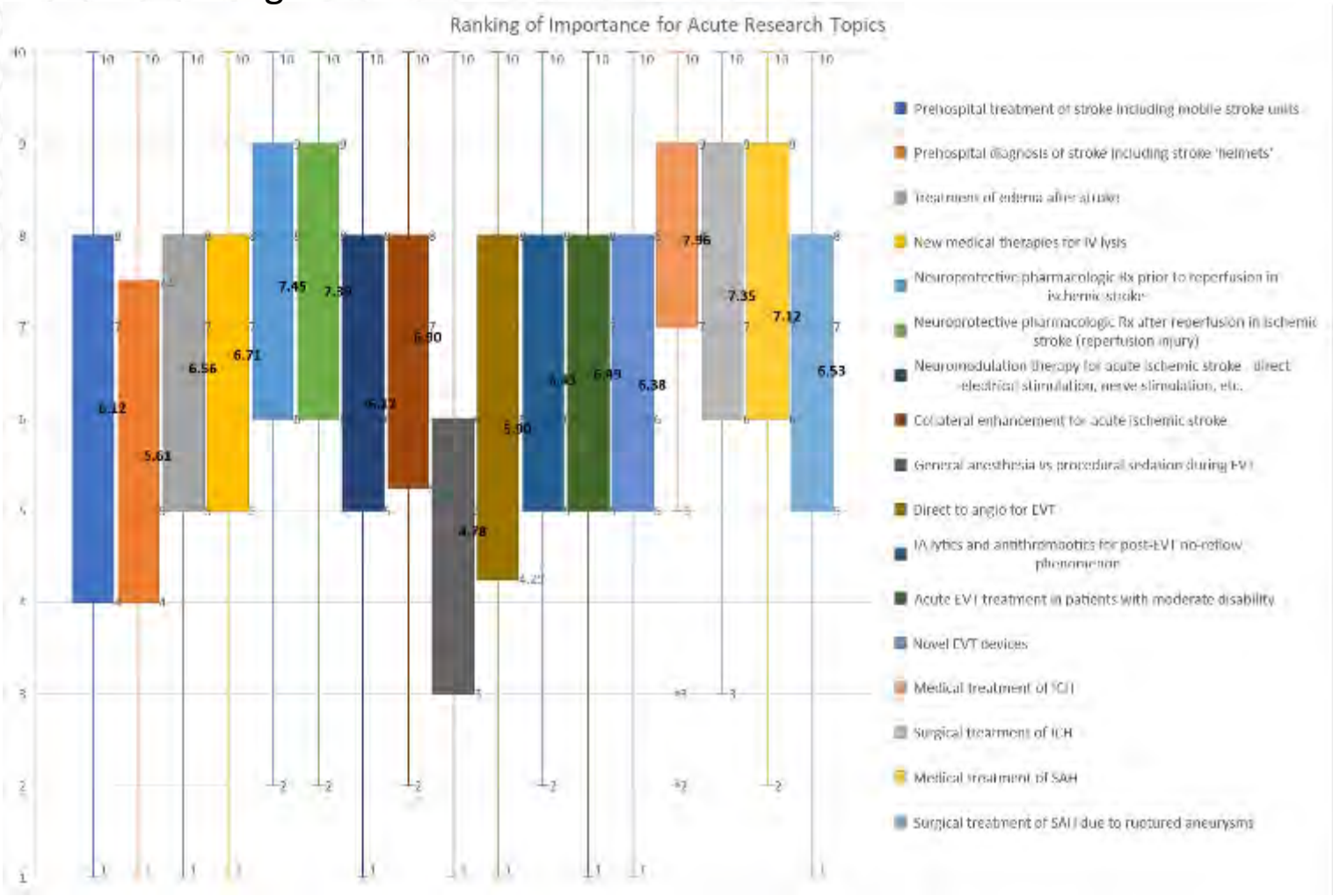
MUSC Medical University of South Carolina

NIH

University of Cincinnati

StrokeNet Acute Stroke Priorities in 2023

1. Medical Treatment for ICH
2. Neuroprotection
3. Medical and Surgical Treatment for SAH



2024 Acute Stroke Themes for Discussion

- 1. Address barriers to getting acute stroke trials and treatments to rural and underserved communities
- 2. Ultra-early intervention (Prehospital diagnosis and treatment of acute stroke)
- 3. Neuroprotection

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PREVENTION | TREATMENT | RECOVERY

Acute Stroke Rx to Rural & Underserved Patients

- EVT and many of our research interventions are not available at rural (geographically challenged) and underserved hospitals
- Longer times to treatment and reduced treatment options for rural and underserved patients contribute to disparities in outcomes
- Transfer to a stroke center is more common
- Pragmatic and decentralized trials could contribute to the StrokeNet portfolio
- **How can StrokeNet leverage our network to address treatment gaps for rural and underserved communities?**

Ultra Early, Pre-Hospital Interventions

- Mobile stroke units (MSU) can facilitate prehospital diagnosis, treatment and research efforts
- By far, the majority of stroke patients will not be transported by MSU
- Healthcare technologies (e.g., phone apps, wearable technology, point of care testing) and AI analytic technologies (ML, NLP, LLM) are ripe to be used in innovative ways for acute stroke detection and/or subtyping
- **How can StrokeNet utilize new technologies to transform prehospital care in the fleet of regular ambulances?**

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Neuroprotection

- New opportunities for neuroprotection exist with EVT, the STEP platform, and the SPAN network
- Pre-EVT – Preservation of salvageable ischemic tissue during transport to thrombectomy center
  - Initial transport from field (MSU or standard ambulance)
  - Secondary transport from rural and underserved hospital
- Post-EVT - Post thrombectomy treatment to reduce reperfusion injury

How can we leverage our StrokeNet, STEP, and SPAN infrastructure to implement the next phase of neuroprotection trials?

Acute Stroke Working Group

- Kinga Aitken
- Andrew Barreto
- Tim Coyne
- Stacie Demel
- Mustapha Ezzeddine
- Toby Gropen
- Thomas Hemmen
- Christine Holmstedt
- Christopher Kellner
- Maarten Lansberg
- Shraddah Mainali
- Flannery O’Neil
- Peter Panagos
- Alejandro Rabinstein
- Edgar Samaniego
- Philip Scott
- Aneesh Singhal
- Sarah Lee – Peds Advisory
- Sherita Chapman - DEI
- Keiko Fukuda - DEI
- Romo Elida – DEI
- Renee Martin - Biostats
- Jeff Saver – Co Chair
- Karen Johnston - Chair

Themes for priority setting conferences

Prevention Group

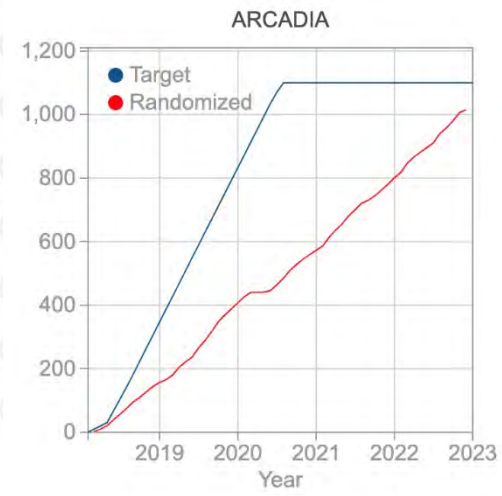
Hooman Kamel on behalf of the Prevention Working Group

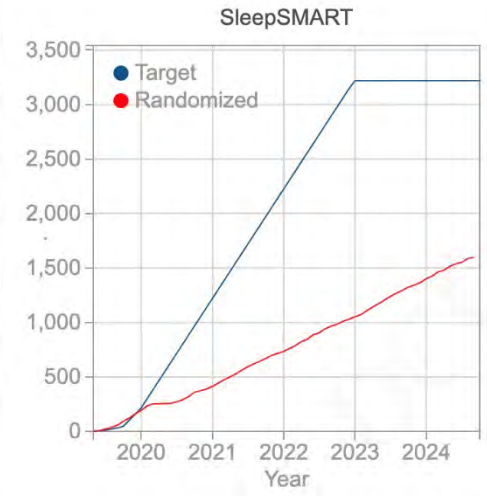
MUSC Medical University of South Carolina

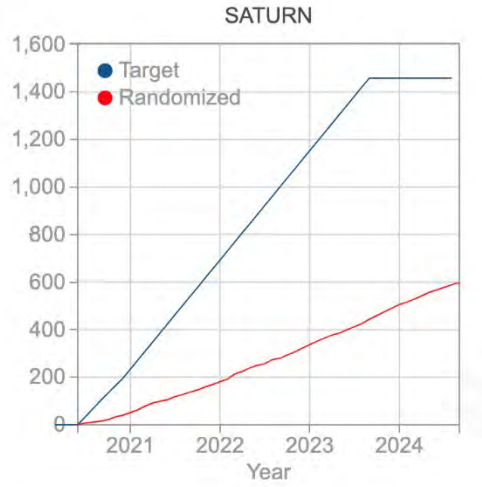
NIH

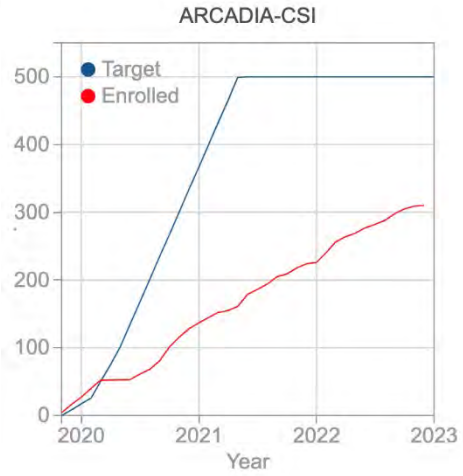
University of Cincinnati

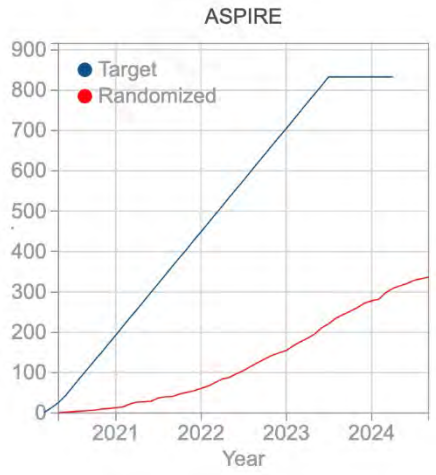
StrokeNet experience with prevention trials

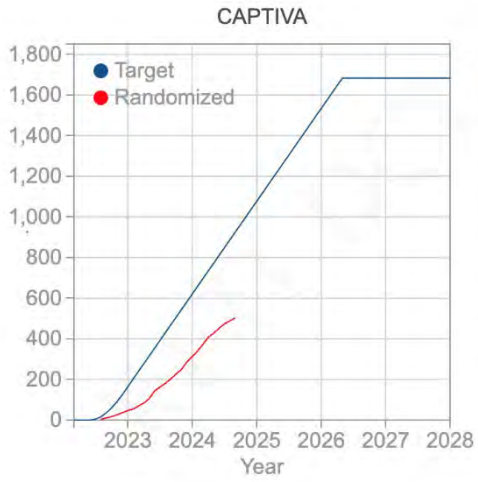










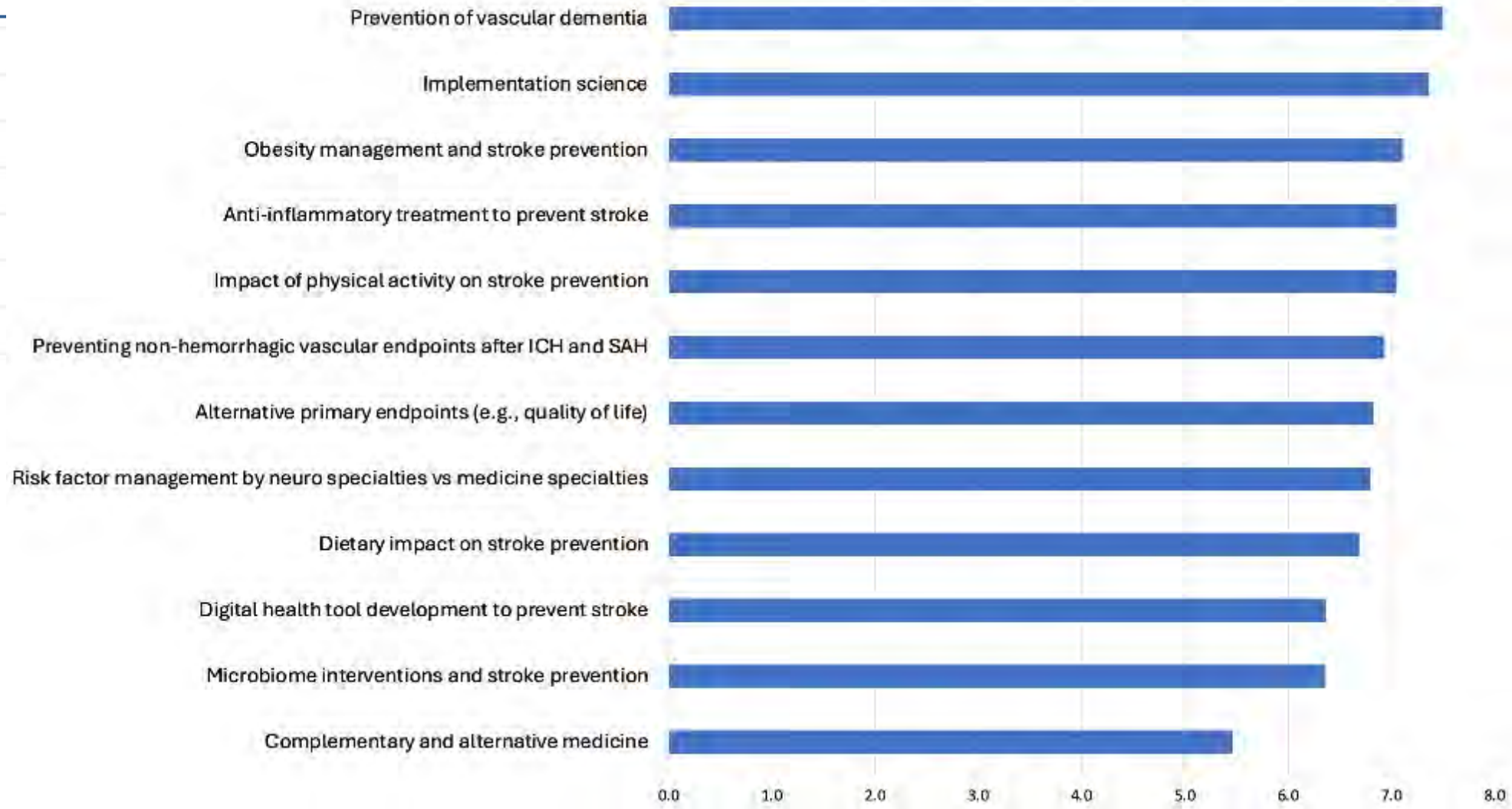


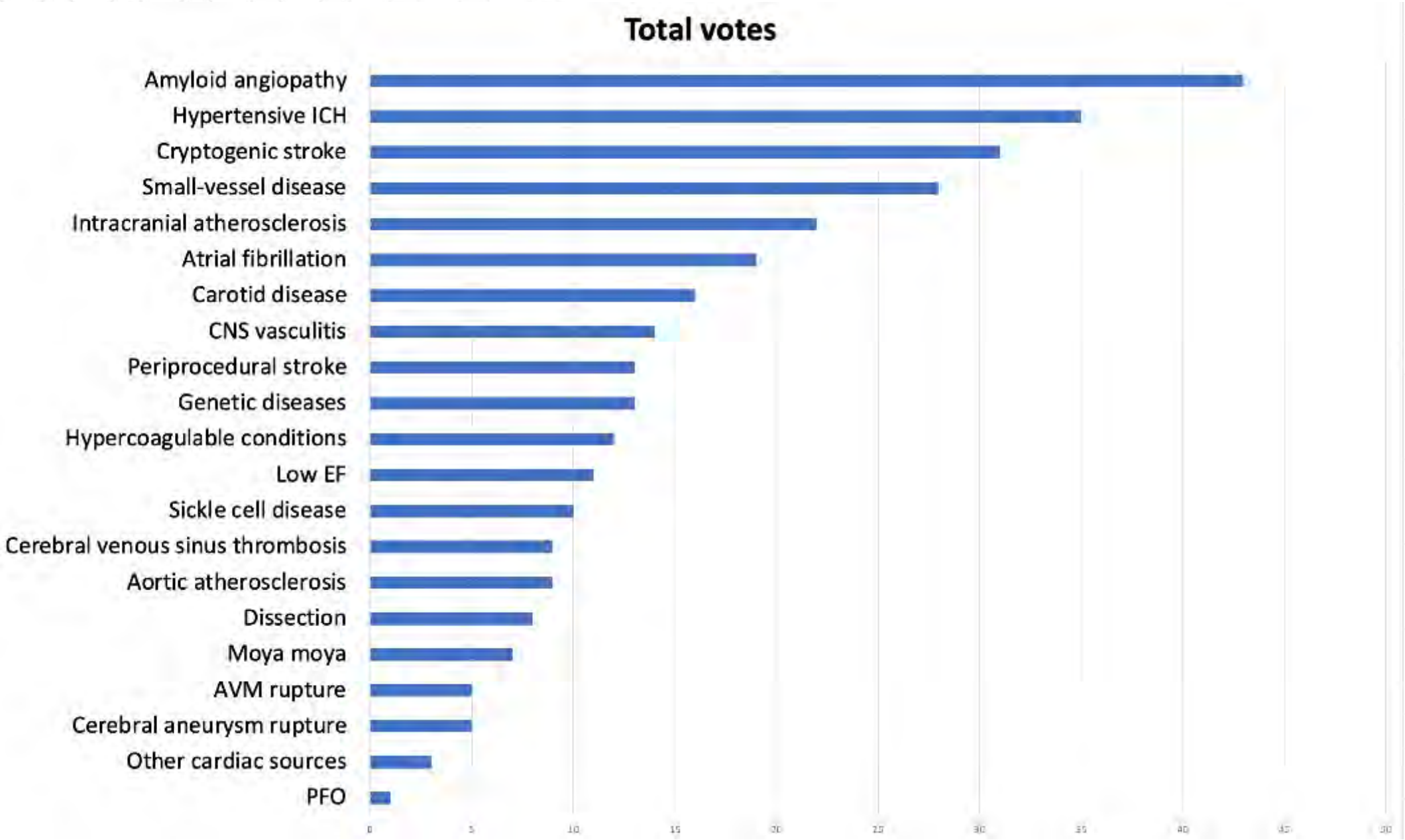
Survey of StrokeNet community

Summer 2023

~100 respondents

Average Score




Total votes
Amyloid angiopathy
Hypertensive ICH
Cryptogenic stroke
Small-vessel disease
Intracranial atherosclerosis
Atrial fibrillation
Carotid disease
CNS vasculitis
Periprocedural stroke
Genetic diseases
Hypercoagulable conditions
Low EF
Sickle cell disease
Cerebral venous sinus thrombosis
Aortic atherosclerosis
Dissection
Moya moya
AVM rupture
Cerebral aneurysm rupture
Other cardiac sources
PFO
0
5
10
15
20
25
30
35
40
45
50

Themes emerging during PWG discussion

1. Cerebral small-vessel disease (CAA, hypertensive ICH, and small-vessel disease)
2. Broadened focus on fundamental vascular risk factors, most notably obesity/microbiome/diet and cardiometabolic factors such as aldosteronism

Themes emerging during PWG discussion

1. Cerebral small-vessel disease (CAA, hypertensive ICH, and small-vessel disease)

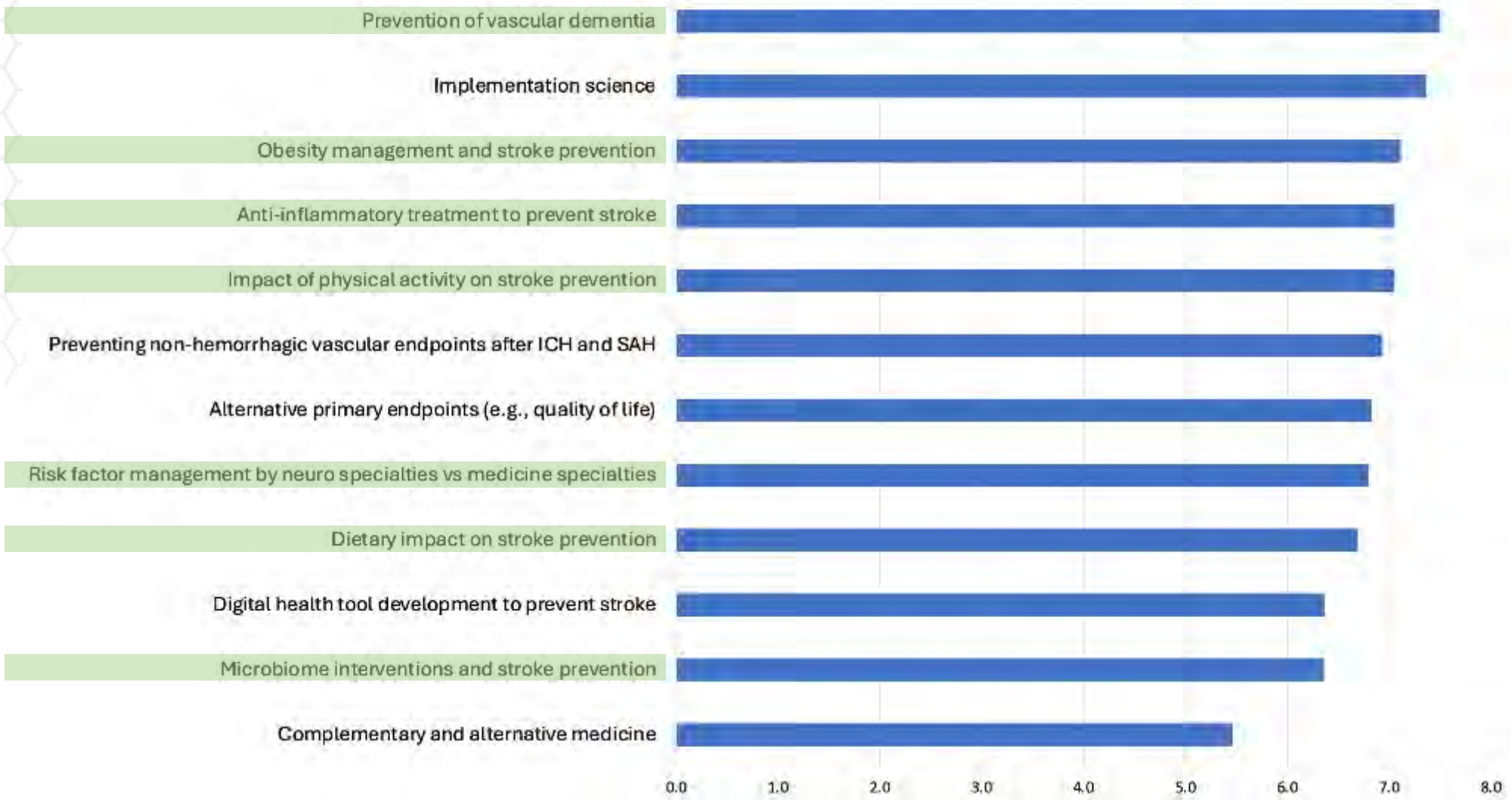
Ties in with other important topics of AD immunotherapies and post-stroke cognitive impairment and dementia

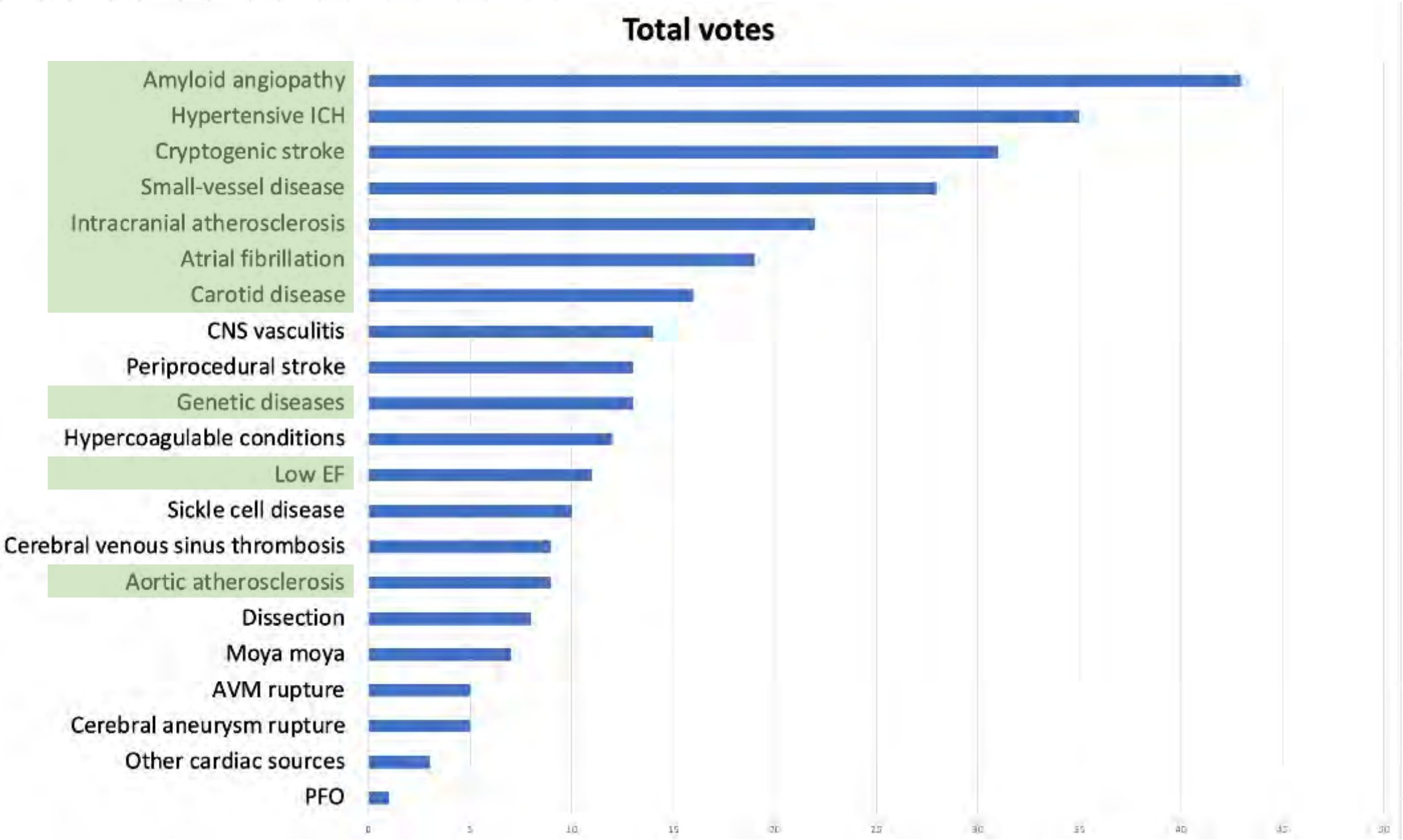
Themes emerging during PWG discussion

2. Broadened focus on fundamental vascular risk factors, most notably obesity/microbiome/diet and cardiometabolic factors such as aldosteronism

Ties in with traditional risk factors (AF, atherosclerosis), cryptogenic stroke, novel obesity and other CV drugs, neuro vs medicine management of risk factors, racial and ethnic disparities and SDOH

Average Score

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Atrial fibrillation
Carotid disease
CNS vasculitis
Periprocedural stroke
Genetic diseases
Hypercoagulable conditions
Low EF
Sickle cell disease
Cerebral venous sinus thrombosis
Aortic atherosclerosis
Dissection
Moya moya
AVM rupture
Cerebral aneurysm rupture
Other cardiac sources
PFO
0
5
10
15
20
25
30
35
40
45
50

Challenges in Priority Area #1

Low rates of recurrent stroke after small-vessel occlusion

Broader outcomes that are relevant, feasible, acceptable?

Combined populations (e.g., deep ICH + lacunar stroke)?

	Higher-target group (n=1519)		Lower-target group (n=1501)	
	Number of patients	Rate (% per patient-year)	Number of patients	Rate (% per patient-year)
Stroke				
All stroke	152	2·77%	125	2·25%

Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial

*The SPS3 Study Group**

Challenges in Priority Area #2

What will shift guidelines? Do we always need stroke-specific trials?

4.4. Glucose

Recommendations for Glucose
Referenced studies that support recommendations are summarized in online Data Supplements 14 and 15.

COR	LOE	Recommendations
1	B-R	2. In patients with an ischemic stroke or TIA who also have diabetes, treatment of diabetes should include glucose-lowering agents with proven cardiovascular benefit to reduce the risk for future major adverse cardiovascular events (ie, stroke, MI, cardiovascular death).[231–236]

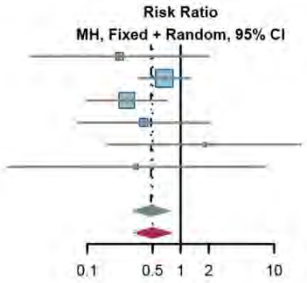
Challenges in Priority Area #2

What will shift guidelines? Do we always need stroke-specific trials?

C Stroke

Study	colchicine Events	colchicine Total	control Events	control Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
Nidorf SM, et al.–2013	1	282	4	250	7.7%	4.8%	0.22 [0.02, 1.97]
Stefan M Nidorf–2020	16	2762	24	2760	43.9%	57.1%	0.67 [0.35, 1.25]
Jean–Claude Tardif–2019	5	2366	19	2379	34.6%	23.4%	0.26 [0.10, 0.71]
Tong DC–2020	2	396	5	399	9.1%	8.5%	0.40 [0.08, 2.07]
Mewton N–2019	2	101	1	91	1.9%	4.0%	1.80 [0.17, 19.54]
Nina C Raju–2012	0	40	1	40	2.7%	2.3%	0.33 [0.01, 7.95]
Total (fixed effect, 95% CI)		**5947**		**5919**	**100.0%**	--	**0.48 [0.30, 0.76]**
Total (random effects, 95% CI)					--	**100.0%**	**0.50 [0.31, 0.80]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 4.20$, df = 5 (P = 0.52); $I^2 = 0\%$
Test for overall effect (fixed effect): Z = −3.09 (P < 0.01)
Test for overall effect (random effects): Z = −2.85 (P < 0.01)



Colchicine and coronary heart disease risks: A meta-analysis of randomized controlled clinical trials

Zijun Ma[1], Jun Chen[1]*, Kaiqin Jin[2] and Xin Chen[1]*

Colchicine and usual care (n=1569)		Usual care alone (n=1575)		Hazard ratio (95% CI)
n (%)	Events per 100 person-years	n (%)	Events per 100 person-years	
153 (9·8%)	3·33	185 (11·7%)	3·92	0·84 (0·68–1·05)

Long-term colchicine for the prevention of vascular recurrent events in non-cardioembolic stroke (CONVINCE): a randomised controlled trial

Peter Kelly, Robin Lemmens, Christian Weimar, Cathal Walsh, Francisco Purroy, Mark Barber, Ronan Collins, Simon Cronin, Anna Czlonkowska, Philippe Desfontaines, Adinda De Pauw, Nicholas Richard Evans, Urs Fischer, Catarina Fonseca, John Forbes, Michael D Hill, Dalius Jatuzis, Janika Kõrv, Peter Kraft, Christina Kruuse, Catherine Lynch, Dominick McCabe, Robert Mikulik, Sean Murphy, Paul Nederkoorn, Martin O'Donnell, Peter Sandercock, Bernadette Schroeder, Gek Shim, Katrina Tobin, David J Williams, Christopher Price

Challenges in Priority Area #2

Guidelines vs actual practice

4.4. Glucose

Recommendations for Glucose
Referenced studies that support recommendations are summarized in online Data Supplements 14 and 15.

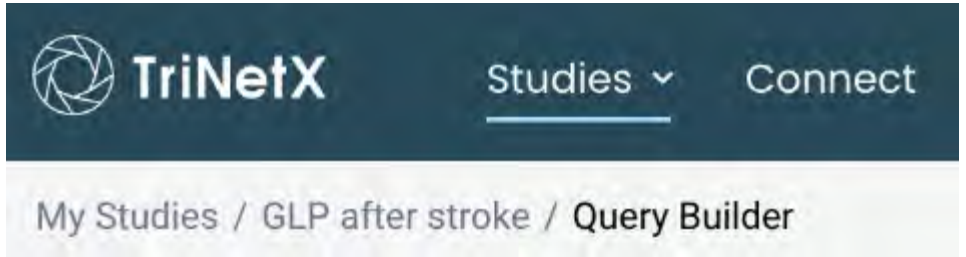
COR	LOE	Recommendations
1	B-R	2. In patients with an ischemic stroke or TIA who also have diabetes, treatment of diabetes should include glucose-lowering agents with proven cardiovascular benefit to reduce the risk for future major adverse cardiovascular events (ie, stroke, MI, cardiovascular death).[231–236]

Challenges in Priority Area #2

Guidelines vs actual practice

Across 24 U.S. healthcare systems:

- 398,177 patients with diabetes and ischemic stroke
- 80,128 (**20%**) receiving GLP-1 agonists or SGLT2 inhibitors



Opportunities

More holistic preventive care

More integration with other specialties

NETWORK MEETING

LUNCH BREAK

Reassemble in Salon at 12:00pm for working lunch

Embedding Pragmatic Trials Within Emergency and Critical Care

Matthew W. Semler, MD, MSc

Associate Professor of Medicine, Anesthesiology and Biomedical Informatics

Associate Director of the Medical Intensive Care Unit

Director, Center for Learning Healthcare

Vanderbilt University, Nashville, TN

MUSC Medical University of South Carolina

NIH

UNIVERSITY OF Cincinnati

Overview

- **Part 1 – Me convincing you to do pragmatic trials**
  - What qualifies me to talk about pragmatic trials?
  - What does “pragmatic trial” even mean, really?
  - Why do a pragmatic trial?

- **Part 2 – Now convinced, key aspects of conducting a pragmatic trial**
  - What questions are a good fit for a pragmatic trial?
  - What are the key tools for pragmatic trials in emergency and critical care?
  - How to deal with grant reviewer #2

What qualifies me to talk about pragmatic trials?

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NECTAR
Novel Experimental COVID Therapies Affecting Host Response

Insight
STRIVE
ACTIV INSIGHT018

JAMA | Original Investigation
Renin-Angiotensin System Modulation With Synthetic Angiotensin (1-7) and Angiotensin II Type 1 Receptor–Biased Ligand in Adults With COVID-19
Two Randomized Clinical Trials

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT
Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis
The VICTAS Randomized Clinical Trial

NHLBI ARDS Network

PETAL NETWORK
Prevention & Early Treatment of Acute Lung Injury

ORIGINAL ARTICLE
Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension
The National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network*

ORIGINAL ARTICLE
Early High-Dose Vitamin D_3 for Critically Ill, Vitamin D–Deficient Patients

ORIGINAL ARTICLE
Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

JAMA | Original Investigation
Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19
A Randomized Clinical Trial

PRAGMATIC CRITICAL CARE RESEARCH GROUP

ORIGINAL ARTICLE
Balanced Crystalloids versus Saline in Noncritically Ill Adults

ORIGINAL ARTICLE
Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation

ORIGINAL ARTICLE
Video versus Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT
Individualized Treatment Effects of Oxygen Targets in Mechanically Ventilated Critically Ill Adults

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT
Effect of Use of a Bougie vs Endotracheal Tube With Stylet on Successful Intubation on the First Attempt Among Critically Ill Patients Undergoing Tracheal Intubation
A Randomized Clinical Trial

ORIGINAL ARTICLE
Balanced Crystalloids versus Saline in Critically Ill Adults

ORIGINAL ARTICLE
Noninvasive Ventilation for Preoxygenation during Emergency Intubation

ORIGINAL ARTICLE
Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT
Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection
The ACORN Randomized Clinical Trial

JAMA | Original Investigation
Effect of Fluid Bolus Administration on Cardiovascular Collapse Among Critically Ill Patients Undergoing Tracheal Intubation
A Randomized Clinical Trial

EXPLANATORY ⟷ **PRAGMATIC**

What does a “pragmatic trial” even mean, really?

- Is pragmatic a dirty word?
- What is does NOT mean:
  - Less rigorous
  - Making design choices because they make life easier *for the trialist*
  - Evaluating only nudges, decision support, or other implementation interventions
  - Poor separation between groups
  - Poor data on the delivery of the intervention
  - Lack of granularity in the outcome
  - Loss to follow up in outcome assessment
  - Analysis using methods that don’t account for biases
  - Imbalance in importance covariates or cointerventions

Password to the PCCRG website since 2014 = “Pragmatic_does_not_mean_crappy”

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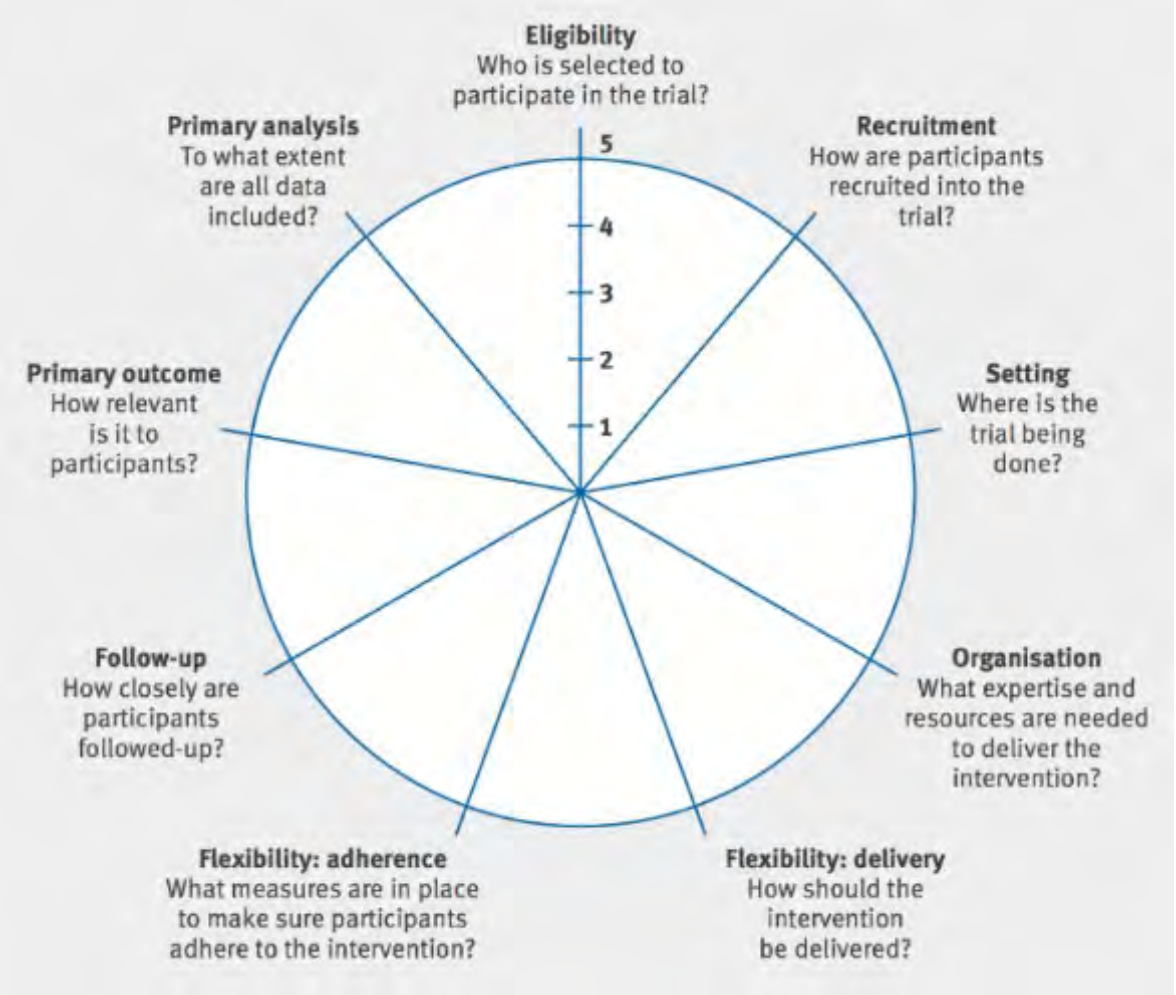
What does “pragmatic trial” even mean, really?

NIH Collaboratory defines a pragmatic clinical trial as a study that takes place in real-world healthcare settings to evaluate the benefits and risks of treatment options. The goal of a PCT is to provide evidence that can be applied to real-world practice and inform policy.

	What is the purpose?	What question does it answer?	Who is enrolled?	Who collects data?	What is studied?	What is compared?	What is the setting?	Adherence to the intervention	Outcomes
Explanatory Trial	Create generalizable knowledge; determine causes and effects	Can this intervention work under ideal conditions?	Selected patients who meet strict inclusion and exclusion criteria	Researchers; data collection occurs outside of clinical care	A biological or mechanistic hypotheses	Treatment vs placebo or non-treatment	Medical centers designated as research sites	Strictly enforced	May be surrogates or process measures
Pragmatic Trial	Create generalizable knowledge, improve care locally, and inform clinical and policy decisions	Does this intervention work under usual conditions?	Diverse, representative populations who meet broad eligibility criteria	Clinicians at the point of care; EHRs; registries	The comparative balance of benefits, burdens and risks of an intervention	The comparative effectiveness of real-world alternatives	Multiple, heterogeneous settings	Flexible (as it would be in usual care)	Directly relevant to participants, funders, communities, and healthcare practitioners

What does a “pragmatic trial” even mean, really?

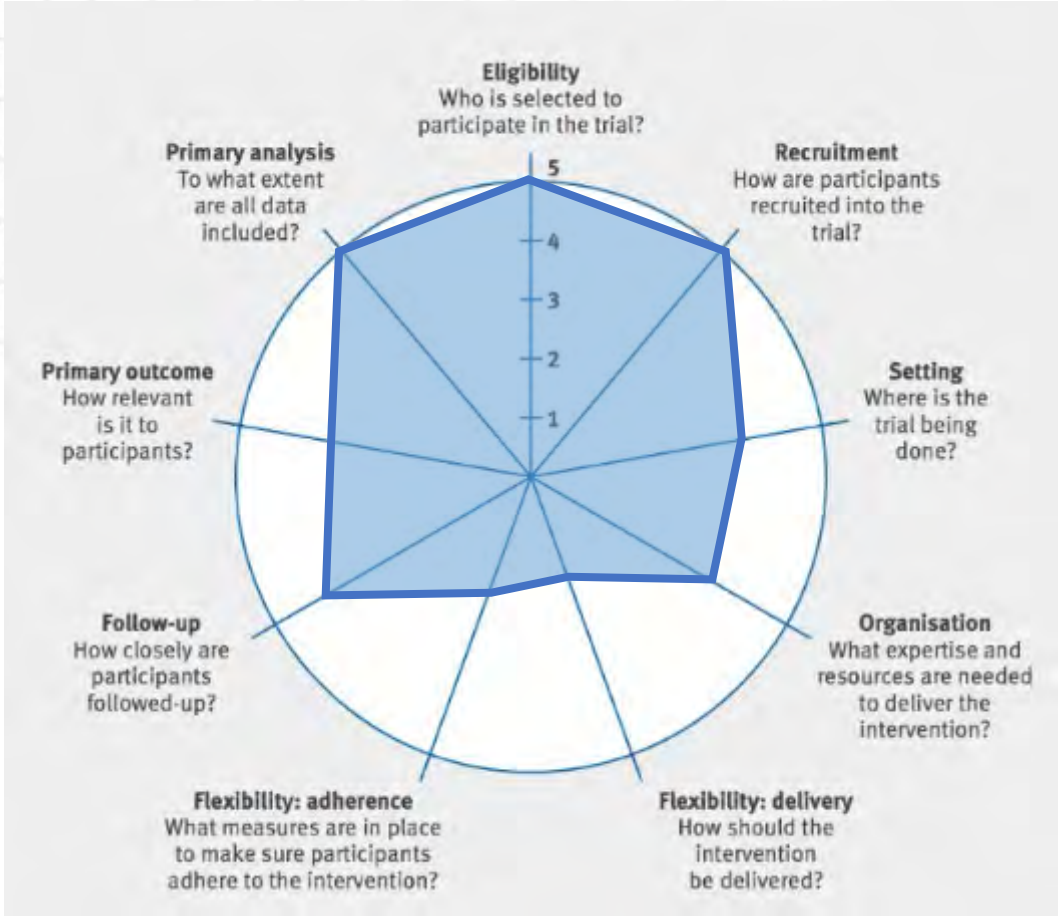
No trial is “pragmatic” or “explanatory” –
In every trial, investigators must choose where each trial procedure should lie on the spectrum.



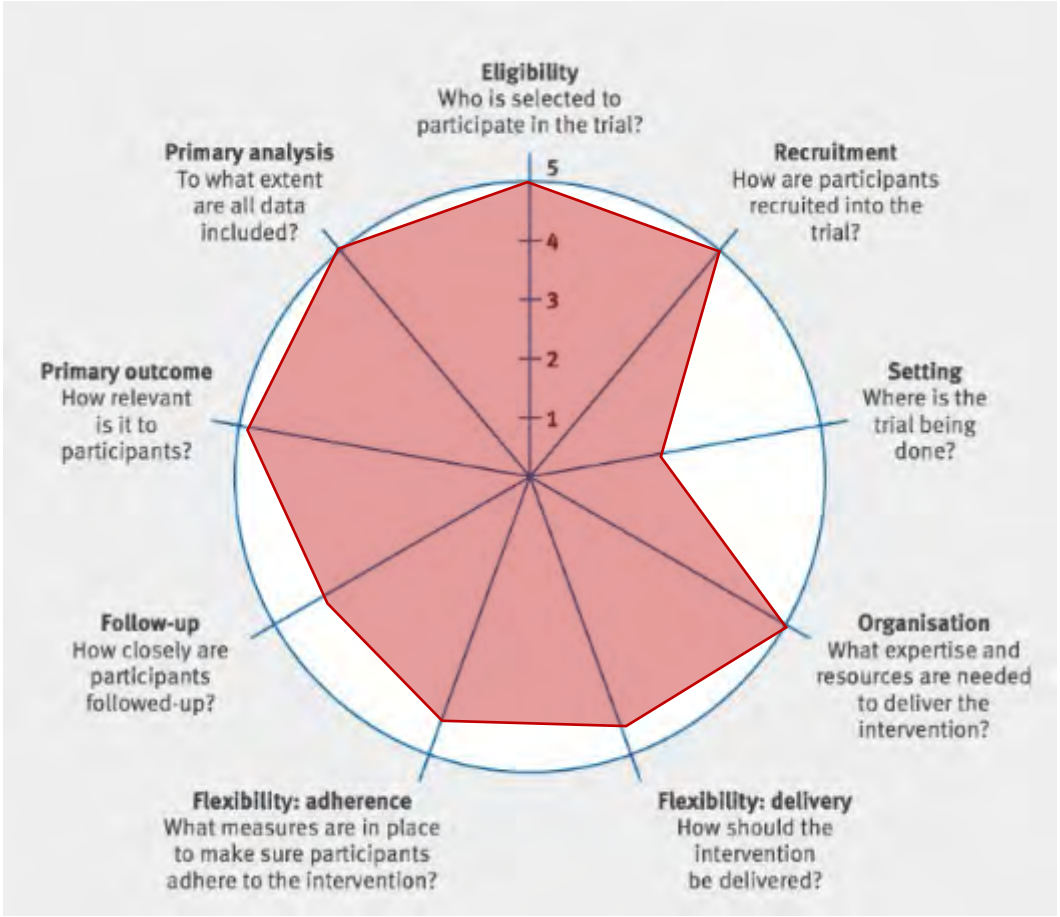
https://www.precis-2.org/

What does a “pragmatic trial” even mean, really?

PREOXI Trial



SMART Trial



https://www.precis-2.org/

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Why do a pragmatic trial?

Sometimes a pragmatic trial may be:

- “Better”
- “More efficient”

"**Better**" – Patients represent full diversity of clinical care

ORIGINAL ARTICLE

Comparison of Two Fluid-Man
Strategies in Acute Lung In

11,512 Patients screened

91%

10,511 Excluded
21% Had a pulm
artery cathe
16% Had their p
refuse
14% Had chroni
disease
11% Had high ri
within 6 mo
9% Required di
8% Exceeded ti
8% Had chroni
disease
6% Had acute
infarction
6% Were unabl
consent
4% Declined to
consent
4% Were not c
to full supp
3% Had neuro
disease

1001 Underwent randomization

9% included

Study	Trial Demographics Black	Trial Demographics Non-Black	City Demographics Black	City Demographics Non-Black	RD with 95% CI	Weight (%)
Billings 2016	26	589	166,549	436,889	-0.23 [-0.25, -0.22]	4.89
Casey 2019	108	290	1,048,575	2,782,077	-0.00 [-0.05, 0.04]	4.75
Curtis 2016	12	217	105,749	1,342,861	-0.02 [-0.05, 0.01]	4.84
Delorme 2017	0	12	14,102	691,001	-0.02 [-0.02, -0.02]	4.91
Festic 2017	3	79	515,488	1,771,974	-0.19 [-0.23, -0.15]	4.77
Girard 2019	76	491	4,285,875	9,026,116	-0.19 [-0.22, -0.16]	4.84
Heyland 2020	2	153	1,259,367	17,925,156	-0.05 [-0.07, -0.03]	4.88
Jaiswal 2019	11	109	91,739	1,332,112	0.03 [-0.02, 0.08]	4.69
Janz 2016	19	130	166,549	436,889	-0.15 [-0.20, -0.09]	4.67
Janz 2018	72	219	901,808	2,204,539	-0.04 [-0.09, 0.01]	4.70
Janz 2019	75	259	2,255,348	9,913,752	0.04 [-0.01, 0.08]	4.74
Limaye 2017	17	143	1,496,934	4,544,802	-0.14 [-0.19, -0.09]	4.72
Moss 2016	9	111	195,188	1,483,453	-0.04 [-0.09, 0.01]	4.72
Schell-Chaple 2017	2	39	49,367	832,182	-0.01 [-0.07, 0.06]	4.56
Semler 2016	19	130	166,549	436,889	-0.15 [-0.20, -0.09]	4.67
Semler 2017	72	219	908,047	2,264,110	-0.04 [-0.09, 0.01]	4.70
Semler 2018	2,165	13,637	183,195	480,555	-0.14 [-0.14, -0.13]	4.91
Sims 2019	82	18	694,454	889,610	0.38 [0.31, 0.46]	4.46
Skrobik 2018	1	99	355,804	2,108,575	-0.13 [-0.15, -0.11]	4.88
STARRT-AKI 2020	27	967	1,410,655	19,921,926	-0.04 [-0.05, -0.03]	4.90
Swan 2016	42	283	524,381	1,795,887	-0.10 [-0.13, -0.06]	4.80
Overall					-0.06 [-0.11, -0.01]	

Heterogeneity: $\tau^2 = 0.01$, $I^2 = 99.71\%$, $H^2 = 339.77$
Test of $\theta_i = \theta_j$: Q(20) = 3066.49, p = 0.00
Test of $\theta = 0$: z = -2.27, p = 0.02

-2 0 2 4

Youmbi, CJA 2023

oscopy for
lly Ill Adults

criteria
routinely perform intubation in the
e was not orotracheal intubation
as not video or direct laryngoscope

27% excluded

exclusion criterion
intubation too urgently to complete trial
es
ngoscope or direct laryngoscope required
deo laryngoscope required*
rect laryngoscope required†
oners
than 18 years old
nant
not enrolled
ng clinician decline enrollment
sonnel error
fied
udy personnel available
udy materials available
surrogates declined enrollment

NIH

1,420 Patients underwent randomization

73% included

"**Better**" – Delivery of intervention mirrors clinical care

Video laryngoscopy vs. direct laryngoscopy: Which should be chosen for endotracheal intubation during cardiopulmonary resuscitation? A prospective randomized controlled study of experienced intubators

Randomized trial of 140 patients at 1 ED
Unit of randomization: intubating clinician
Total of **7 expert clinicians in each group**

VS

ORIGINAL ARTICLE

Video versus Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults

Randomized trial of 1,417 patients in 17 ED/ICU
Unit of randomization: patient
Total of **~400 unique clinicians**

Characteristic	Video Laryngoscope (N=705)	Direct Laryngoscope (N=712)
Operator*		
Clinical specialty — no. (%)		
Emergency medicine	496 (70.4)	497 (69.8)
Critical care medicine	177 (25.1)	182 (25.6)
Anesthesiology	18 (2.6)	25 (3.5)
Other†	14 (2.0)	8 (1.1)
Level of training — no. (%)		
Resident physician	513 (72.8)	502 (70.5)
Fellow physician	164 (23.3)	173 (24.3)
Attending physician	9 (1.3)	18 (2.5)
Other clinician‡	19 (2.7)	19 (2.7)
Median no. of previous intubations performed (IQR)	50 (25–90)	50 (26–99)

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“More efficient”

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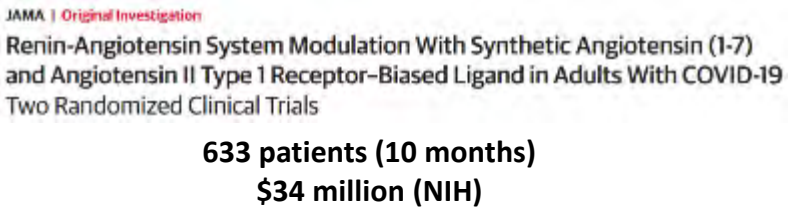
NECTAR
Novel Experimental COVID Therapies Affecting Host Response

1 RCT enrolled 633 patients at direct cost of $34 million


JAMA | Original Investigation

Renin-Angiotensin System Modulation With Synthetic Angiotensin (1-7) and Angiotensin II Type 1 Receptor–Biased Ligand in Adults With COVID-19
Two Randomized Clinical Trials

633 patients (10 months)
$34 million (NIH)

PRAGMATIC CRITICAL CARE RESEARCH GROUP

9 RCTs enrolled ~40,000 patients at total cost of $3.7 million


ORIGINAL ARTICLE

Video versus Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults

1,417 patients (8 months)
$1.8 million (DoD)


ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

15,802 patients (22 months)
UNFUNDED


ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

13,347 patients (16 months)
UNFUNDED


ORIGINAL ARTICLE

Noninvasive Ventilation for Preoxygenation during Emergency Intubation

1,301 patients (19 months)
$1.6 million (DoD)


ORIGINAL ARTICLE

Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults

401 patients (14 months)
UNFUNDED


JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection
The ACORN Randomized Clinical Trial

2,511 patients (11 months)
UNFUNDED


ORIGINAL ARTICLE

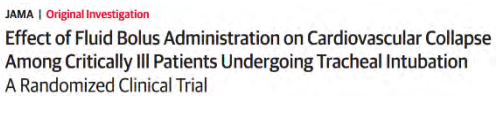
Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation

2,541 patients (36 months)
$50,000 per year (NIH K23)


JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Use of a Bougie vs Endotracheal Tube With Stylet on Successful Intubation on the First Attempt Among Critically Ill Patients Undergoing Tracheal Intubation
A Randomized Clinical Trial

1,106 patients (21 months)
UNFUNDED


JAMA | Original Investigation

Effect of Fluid Bolus Administration on Cardiovascular Collapse Among Critically Ill Patients Undergoing Tracheal Intubation
A Randomized Clinical Trial

1,067 patients (25 months)
UNFUNDED

EXPLANATORY ⟷ **PRAGMATIC**

"More efficient" – why is it important for patients that our trials be more efficient?

Treatments administered to millions of critically ill patients each year in routine clinical care that would never have been examined in an explanatory randomized trial.

Higher vs lower SpO2 targets

HFNC vs NIV vs COT in AHRF

Mode of ventilation

Saline vs balanced crystalloids

albumin vs crystalloids in septic shock

Restrictive vs liberal fluid management in sepsis

fluid responsiveness measures to guide fluid therapy

etomidate vs ketamine

sedative-first vs NMB-first

video vs direct laryngoscopy

hyperangulated vs standard geometry

Bag-mask ventilation vs none during intubation

NIV vs HFNC vs BMV

neuromuscular blocker vs none

"apneic oxygenation" vs none

fluid bolus vs none

bougie vs stylet

vasopressor vs none

ramped vs sniffing position

Traditional explanatory trials focus on new drugs and devices and neglect the comparison of existing therapies that patients are exposed to in care – "a profound moral problem"

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Part 2

Now that you're completely convinced to do pragmatic trials, what are some key aspects of designing and conducting a pragmatic trial?

#1 What questions are a good fit for pragmatic trials?

- **Trials comparing the effectiveness of existing treatment alternatives (A vs B designs)**
- **Trials evaluating a new approach to care delivery (A vs A+ design)**
- **NOT trials evaluating a new drug or device (A vs placebo design)**

Higher vs lower SpO2 targets

HFNC vs NIV vs COT in AHRF

Mode of ventilation

Saline vs balanced crystalloids

albumin vs crystalloids in septic shock

Restrictive vs liberal fluid management in sepsis

fluid responsiveness measures to guide fluid therapy

etomidate vs ketamine

sedative-first vs NMB-first

video vs direct laryngoscopy

hyperangulated vs standard geometry

Bag-mask ventilation vs none during intubation

NIV vs HFNC vs BMV

neuromuscular blocker vs none

"apneic oxygenation" vs none

fluid bolus vs none

bougie vs stylet

vasopressor vs none

ramped vs sniffing position

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#2 What are some key tools for a pragmatic trial?

Characteristic of Emergency & Critical Care Environment	RCT Procedure	Tool for Pragmatic Trial
Brief therapeutic window	Screening Enrollment Randomization Intervention Delivery	Embed RCT procedures within people & systems of clinical care
Low ‘signal-to-noise’ from complex acute and chronic conditions (low attributable risk) and limited time to phenotype	Sample size	Leveraging information technology tools and the EHR to facilitate each RCT procedure
Lack of decisional capacity & surrogates	Informed consent process	EFIC, waiver, and ‘the gray space’ for comparative effectiveness RCTs
Heterogeneity of patients in response to therapy	Analysis of treatment effect	Large sample size & analysis of ‘heterogeneity of treatment effect’ and ‘individual treatment effect’

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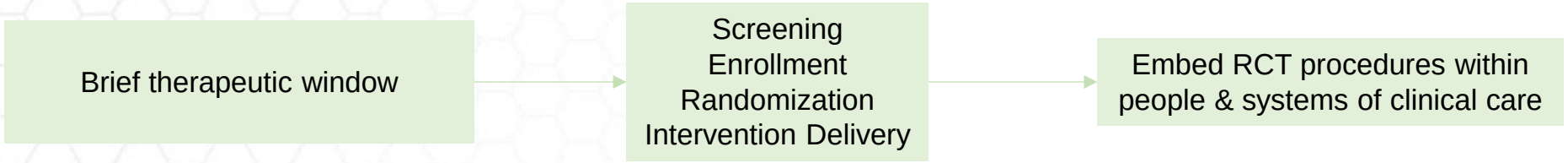

Embedding Screening, Enrollment, Randomization, and Delivery of the Intervention in an RCT within the People and Systems of Clinical Care

Or ‘how to do trials when trial personnel cannot be present’

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Emergency Tracheal Intubation

- 2-5 million adults intubated in ED and ICU each year
- 75% of patients are comatose or delirious
- 5% of patients are in cardiac arrest
- Median **5 min** from decision-to-intubate to procedure

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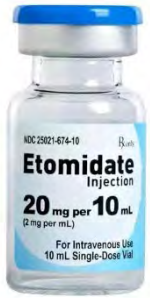
Decisions a clinician must make during every emergency tracheal intubation

or



or

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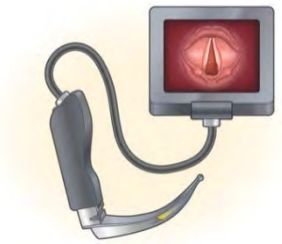

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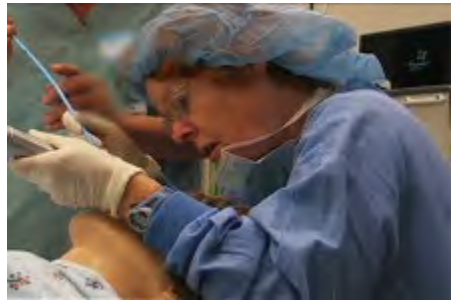

or

5 million emergency tracheal intubations each year in US.

0 randomized trials to inform best approach to emergency tracheal intubation.

PREO2XI

PRagmatic trial Examining OXygenation prior to Intubation

- Multicenter, parallel-group, randomized trial
- 24 EDs and ICUs across the US
- Eligibility Criteria
  - Inclusion
    1. Undergoing tracheal intubation in a participating unit using a laryngoscope and sedation
  - Exclusion
    1. Patient is <18 years old, pregnant, or a prisoner
    2. Patients is already receiving positive pressure ventilation
    3. Immediate need for tracheal intubation precludes safe performance of study procedures
    4. Clinician has determined that preoxygenation with non-invasive positive pressure ventilation or preoxygenation with a facemask is required or contraindicated for optimal care of the patient

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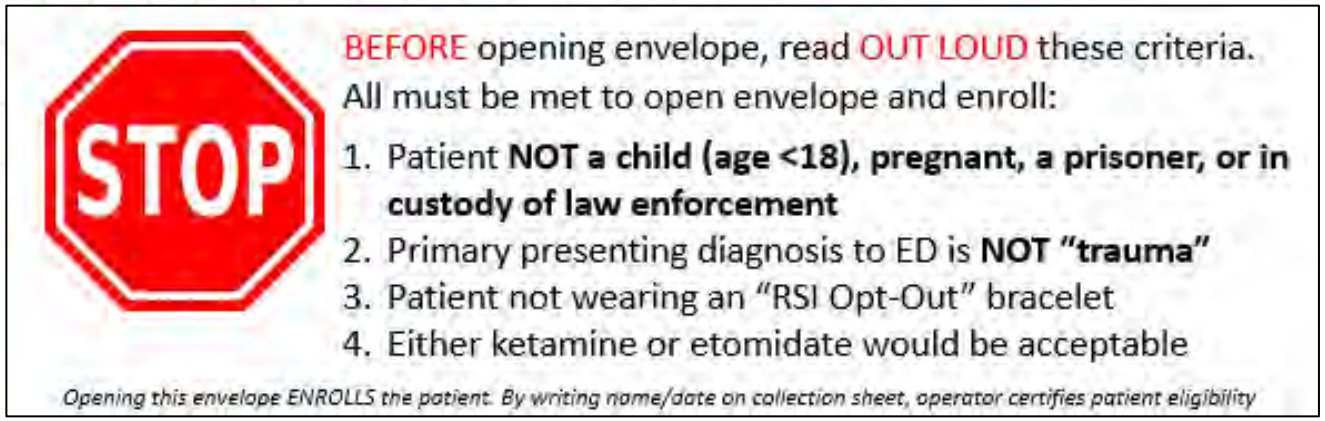
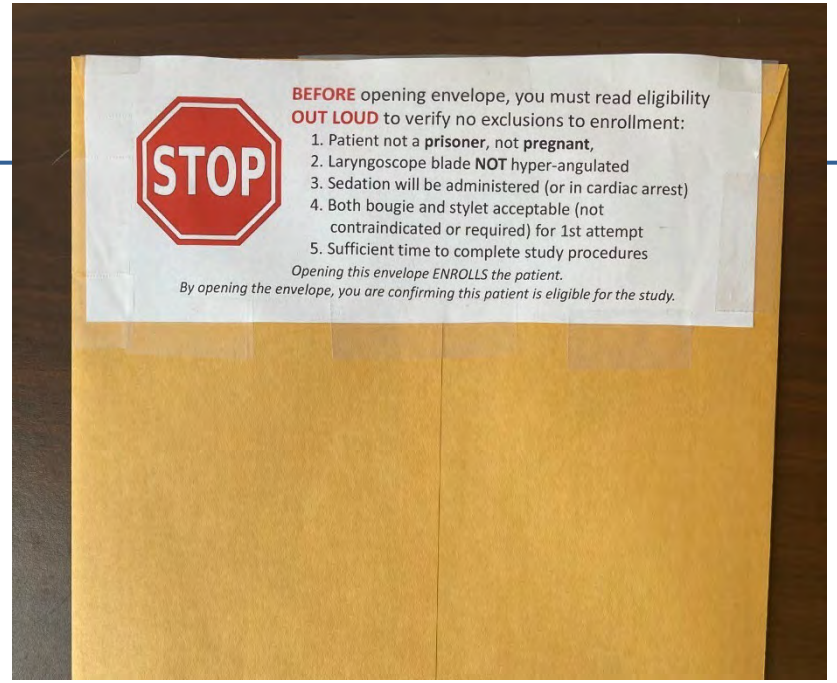
Bougie Study
Completed Envelopes
BOUGIE Trial
VS
Bougie Study
New Envelopes
Before opening one envelope to enroll,
record the device you plan to use:
Direct laryngoscope
Video laryngoscope
TRAUMA BAY 3
1453
CLEAN/STOCK
COMPRESSED GAS
ECOLAB





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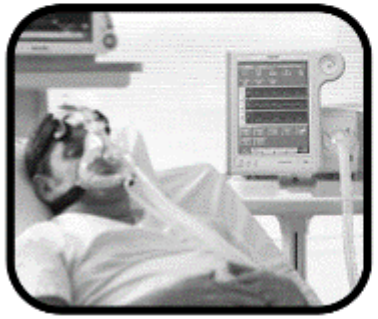
PREO_2XI

PRagmatic trial Examining OXygenation prior to Intubation

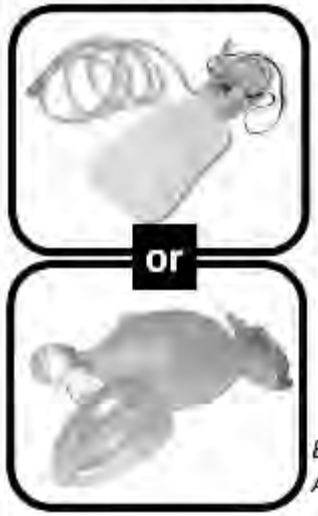
- Clinician perform , Criteria)
- Clinician opens envelope (Trial Enrollment)
- Envelope contains trial group assignment (Randomization)
- Clinician delivers assigned intervention (Delivery of the Intervention)

Non-Invasive Positive Pressure Ventilation



1. Apply BiPAP or ventilator via mask
2. Set
   - FiO2 = 100%
   - Expiratory pressure ≥ 5
   - Inspiratory pressure ≥ 10
   - Respiratory rate ≥ 10
3. Preoxygenate ≥ 3 min (if feasible)
4. Remove mask only as the laryngoscope blade enters mouth

Facemask Oxygen

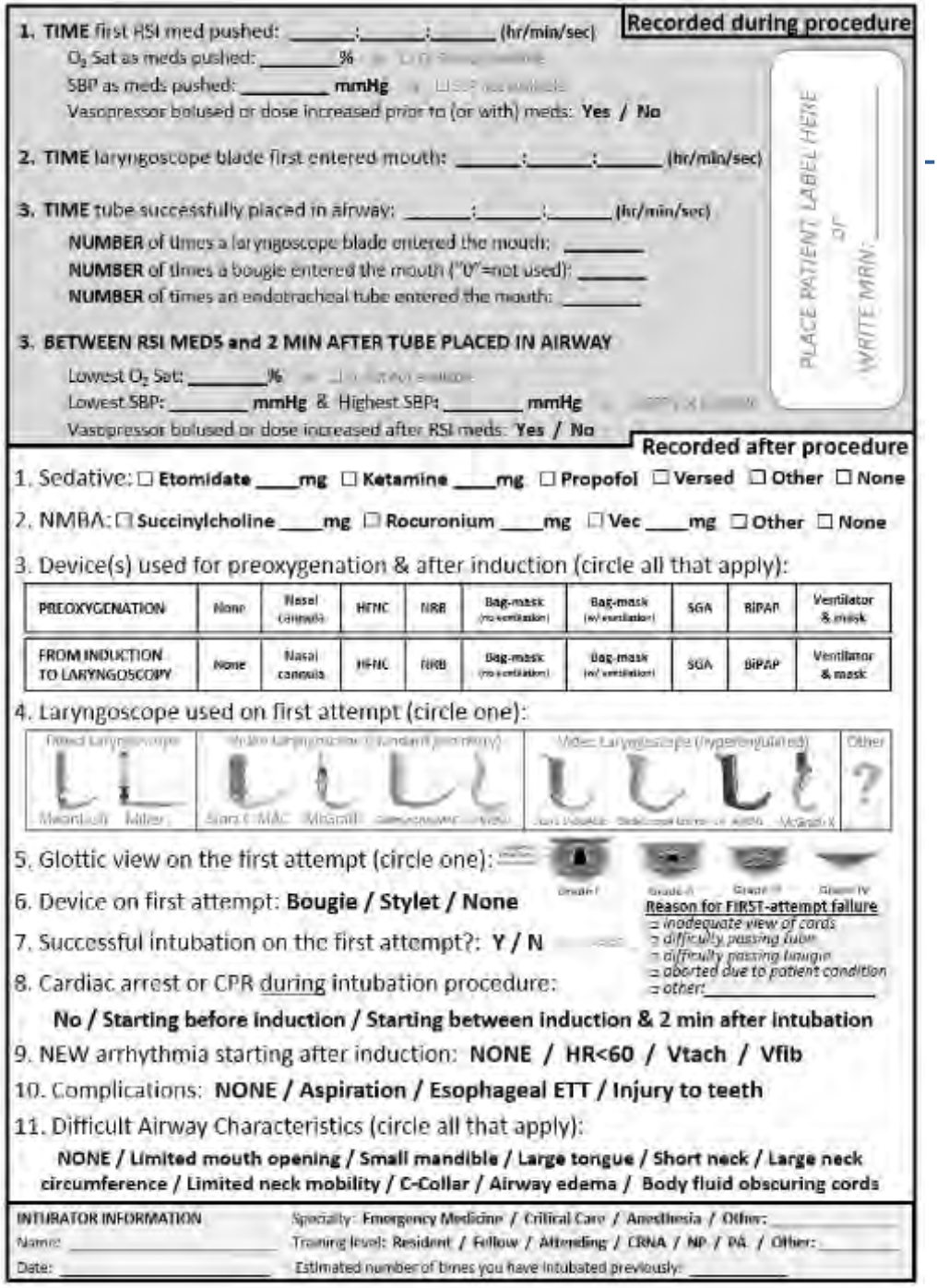


1. Apply non-rebreather or bag-mask
2. Set O_2 flow rate to max (≥ 15 LPM)
3. Preoxygenate ≥ 3 min (if feasible)
4. Remove mask only as the laryngoscope blade enters mouth

BEFORE INDUCTION – do NOT ventilate (squeeze bag)
AFTER INDUCTION – OK to ventilate (squeeze bag)

Data Collection

A second clinician not involved with the performance of the procedure collects data



Recorded during procedure

1. **TIME** first RSI med pushed: _____:_____:_____ (hr/min/sec)
   O_2 Sat as meds pushed: _____%
   SBP as meds pushed: _____ **mmHg**
   Vasopressor bolused or dose increased prior to (or with) meds: **Yes / No**
2. **TIME** laryngoscope blade first entered mouth: _____:_____:_____ (hr/min/sec)
3. **TIME** tube successfully placed in airway: _____:_____:_____ (hr/min/sec)
   NUMBER of times a laryngoscope blade entered the mouth: _____
   NUMBER of times a bougie entered the mouth ("0"=not used): _____
   NUMBER of times an endotracheal tube entered the mouth: _____
3. **BETWEEN RSI MEDS and 2 MIN AFTER TUBE PLACED IN AIRWAY**
   Lowest O_2 Sat: _____%
   Lowest SBP: _____ **mmHg** & Highest SBP: _____ **mmHg**
   Vasopressor bolused or dose increased after RSI meds: **Yes / No**

PLACE PATIENT LABEL HERE
OR
WRITE MRN: _____

Recorded after procedure

1. Sedative: ☐ **Etomidate** ____**mg** ☐ **Ketamine** ____**mg** ☐ **Propofol** ☐ **Versed** ☐ **Other** ☐ **None**
2. NMBA: ☐ **Succinylcholine** ____**mg** ☐ **Rocuronium** ____**mg** ☐ **Vec** ____**mg** ☐ **Other** ☐ **None**
3. Device(s) used for preoxygenation & after induction (circle all that apply):

PREOXYGENATION	None	Nasal (already)	HFNC	NRB	Bag-mask (no ventilation)	Bag-mask (w/ ventilation)	SGA	BiPAP	Ventilator & mask
FROM INDUCTION TO LARYNGOSCOPY	None	Nasal cannula	HFNC	NRB	Bag-mask (no ventilation)	Bag-mask (w/ ventilation)	SGA	BiPAP	Ventilator & mask

4. Laryngoscope used on first attempt (circle one):
   Other ?
5. Glottic view on the first attempt (circle one):
6. Device on first attempt: **Bougie / Stylet / None**
7. Successful intubation on the first attempt?: **Y / N**
8. Cardiac arrest or CPR during intubation procedure:
   No / Starting before induction / Starting between induction & 2 min after intubation

Reason for FIRST-attempt failure
- inadequate view of cords
- difficulty passing tube
- difficulty passing bougie
- aborted due to patient condition
- other: _____

9. NEW arrhythmia starting after induction: **NONE / HR<60 / Vtach / Vfib**
10. Complications: **NONE / Aspiration / Esophageal ETT / Injury to teeth**
11. Difficult Airway Characteristics (circle all that apply):
    NONE / Limited mouth opening / Small mandible / Large tongue / Short neck / Large neck circumference / Limited neck mobility / C-Collar / Airway edema / Body fluid obscuring cords

INTUBATOR INFORMATION
Name: _____
Date: _____
Specialty: **Emergency Medicine / Critical Care / Anesthesia / Other:** _____
Training level: **Resident / Fellow / Attending / CRNA / NP / PA / Other:** _____
Estimated number of times you have intubated previously: _____

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Patient Characteristics	Noninvasive Ventilation (N= 645)		Oxygen Mask (N= 656)	
Age, years	61	[47-71]	61	[47-70]
Female sex	255	(39.5%)	260	(39.6%)
Body mass index, kg/m²	27.6	[23.2-32.9]	26.6	[22.5-32.4]
Active conditions				
Altered mental status	402	(62.3%)	390	(59.5%)
Sepsis or Septic Shock	301	(46.7%)	312	(47.6%)
Gastrointestinal bleeding	107	(16.6%)	102	(15.5%)
Location: Intensive Care Unit	476	(73.8%)	476	(72.6%)
In the hour prior to enrollment				
Receipt of vasopressors	178	(27.6%)	178	(27.1%)
Receipt of high-flow nasal cannula	150	(23.3%)	165	(25.2%)
Lowest oxygen saturation	95	[92-98]	95	[92-98]
Highest fraction of inspired oxygen	0.33	[0.21-0.66]	0.36	[0.21-0.70]

Data given as no. (%) or median [IQR]

Separation between Trial Groups

	Noninvasive Ventilation (N= 645)		Oxygen Mask (N= 656)	
Noninvasive Ventilation	**616**	**(95.5%)**	4	(0.6%)
Oxygen Mask	22	(3.4%)	**648**	**(98.8%)**
Other	7	(1.1%)	4	(0.6%)

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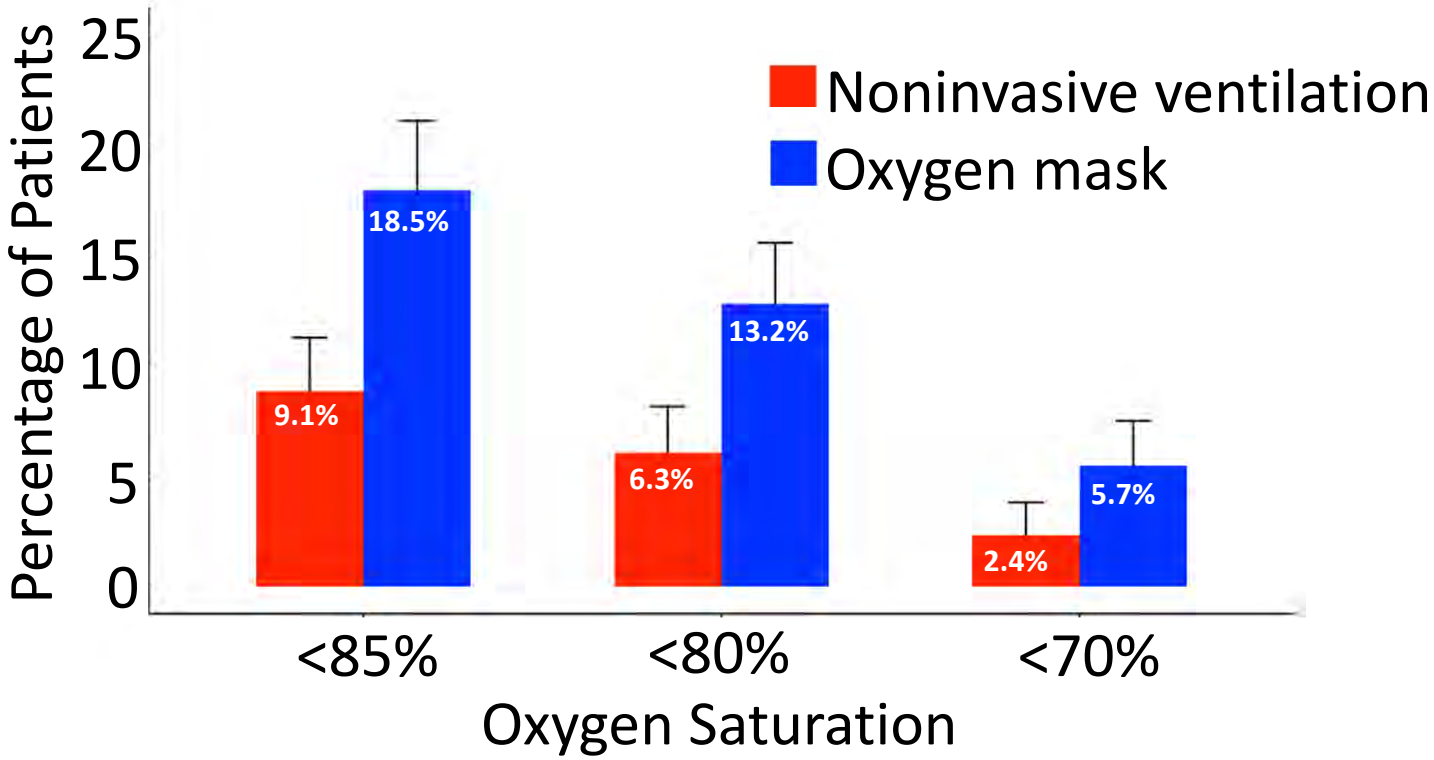
PREVENTION | TREATMENT | RECOVERY

Data given as no. (%)

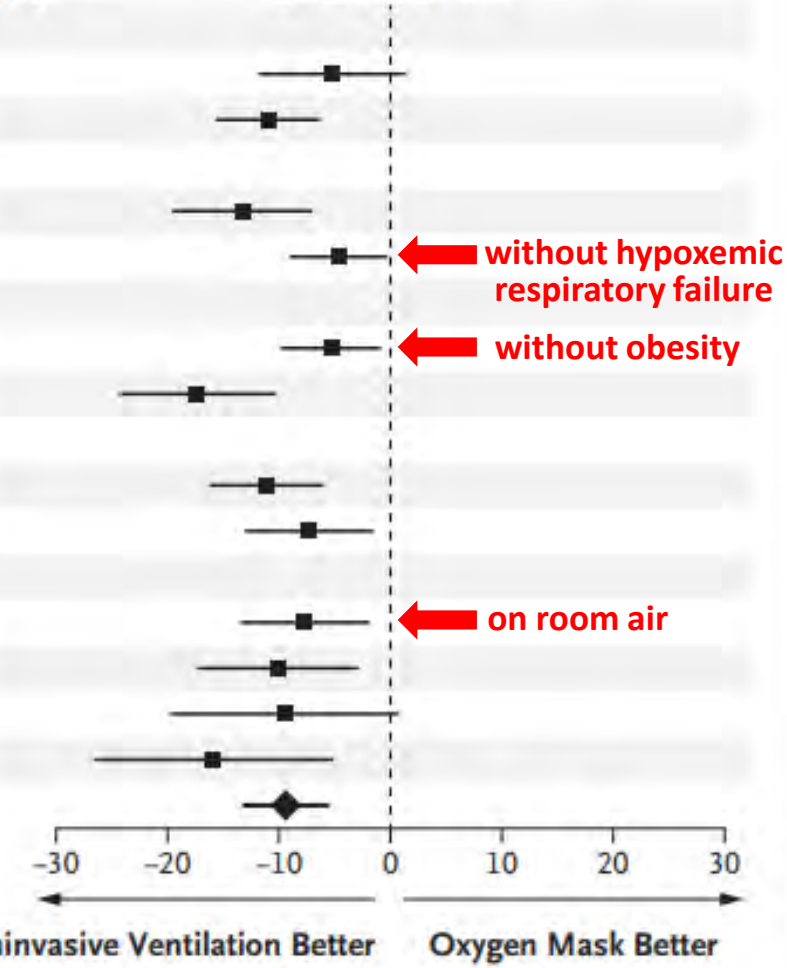
	Noninvasive Ventilation (N= 645)	Oxygen Mask (N= 656)	Absolute risk difference (95% CI)	P value
Primary outcome: Incidence of Hypoxemia (SpO2<85%)	57 (9.1%)	118 (18.5%)	**-9.4%** (-13.2% to -5.6%)	<0.001



Noninvasive ventilation cut in <u>half</u> the risk of hypoxemia during intubation (no matter how hypoxemia was defined)

NIV improved outcomes in all subgroups

Subgroup	Noninvasive Ventilation	Oxygen Mask
	no. of patients with event/total no. of patients (%)	
Location		
Emergency department	13/165 (7.9)	23/175 (13.1)
Intensive care unit	44/459 (9.6)	95/462 (20.6)
Acute hypoxemic respiratory failure		
Yes	36/282 (12.8)	84/322 (26.1)
No	21/342 (6.1)	34/315 (10.8)
Body-mass index		
<30	36/397 (9.1)	59/410 (14.4)
≥30	20/222 (9.0)	58/220 (26.4)
APACHE II score		
<17	27/337 (8.0)	67/350 (19.1)
≥17	30/287 (10.5)	51/287 (17.8)
FIO_2 in previous 1 hr		
0.21	4/142 (2.8)	15/143 (10.5)
0.22–0.40	18/192 (9.4)	35/180 (19.4)
0.41–0.70	9/100 (9.0)	15/81 (18.5)
>0.70	18/106 (17.0)	45/137 (32.8)
Overall	**57/624 (9.1)**	**118/637 (18.5)**



Exploratory Procedural Outcomes	Noninvasive Ventilation (N= 645)	Oxygen Mask (N=656)	Absolute Difference or Median Difference (95% CI)
Successful intubation on the first attempt	534 (82.8)	535 (81.6)	1.2 (-2.9 to 5.4)
Cardiovascular collapse	113 (17.5)	127 (19.4)	-1.8 (-6.1 to 2.4)
SBP <65 mm Hg	18/621 (2.9)	28/633 (4.4)	-1.5 (-3.6 to 0.6)
New or increased use of vasopressors	111 (17.2)	117 (17.8)	-0.6 (-4.8 to 3.5)
Cardiac arrest	**1 (0.2)**	**7 (1.1)**	**-0.9 (-1.8 to -0.1)**

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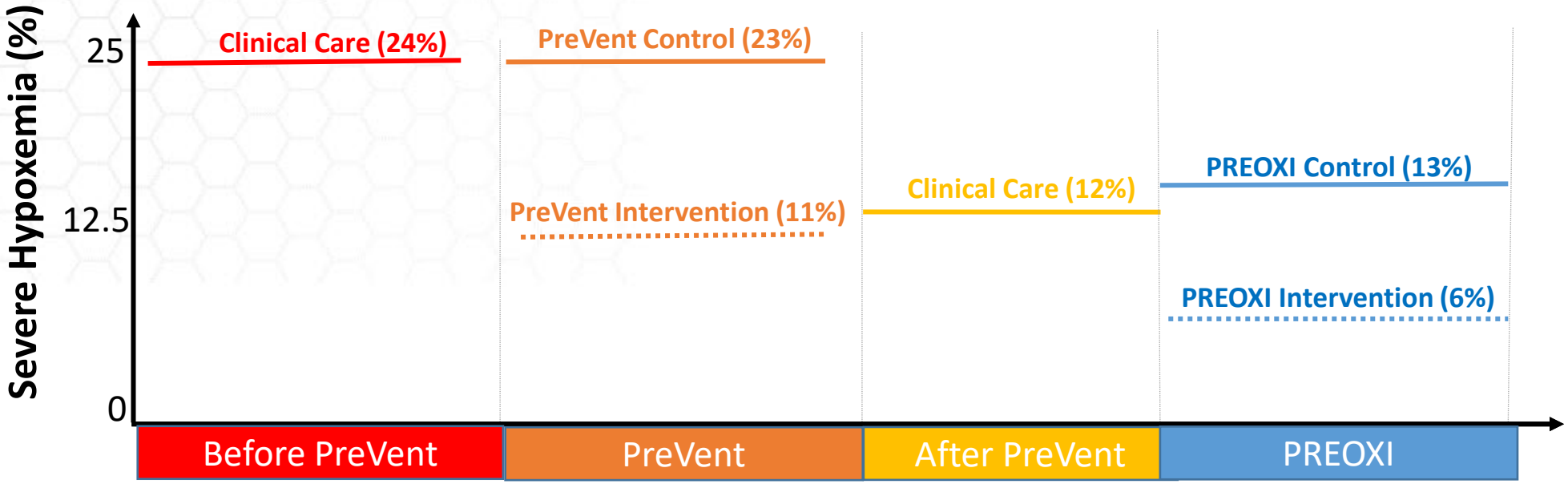
Data given as no. (%) or median [IQR]

Hypoxemia and Cardiac Arrest in Clinical Care



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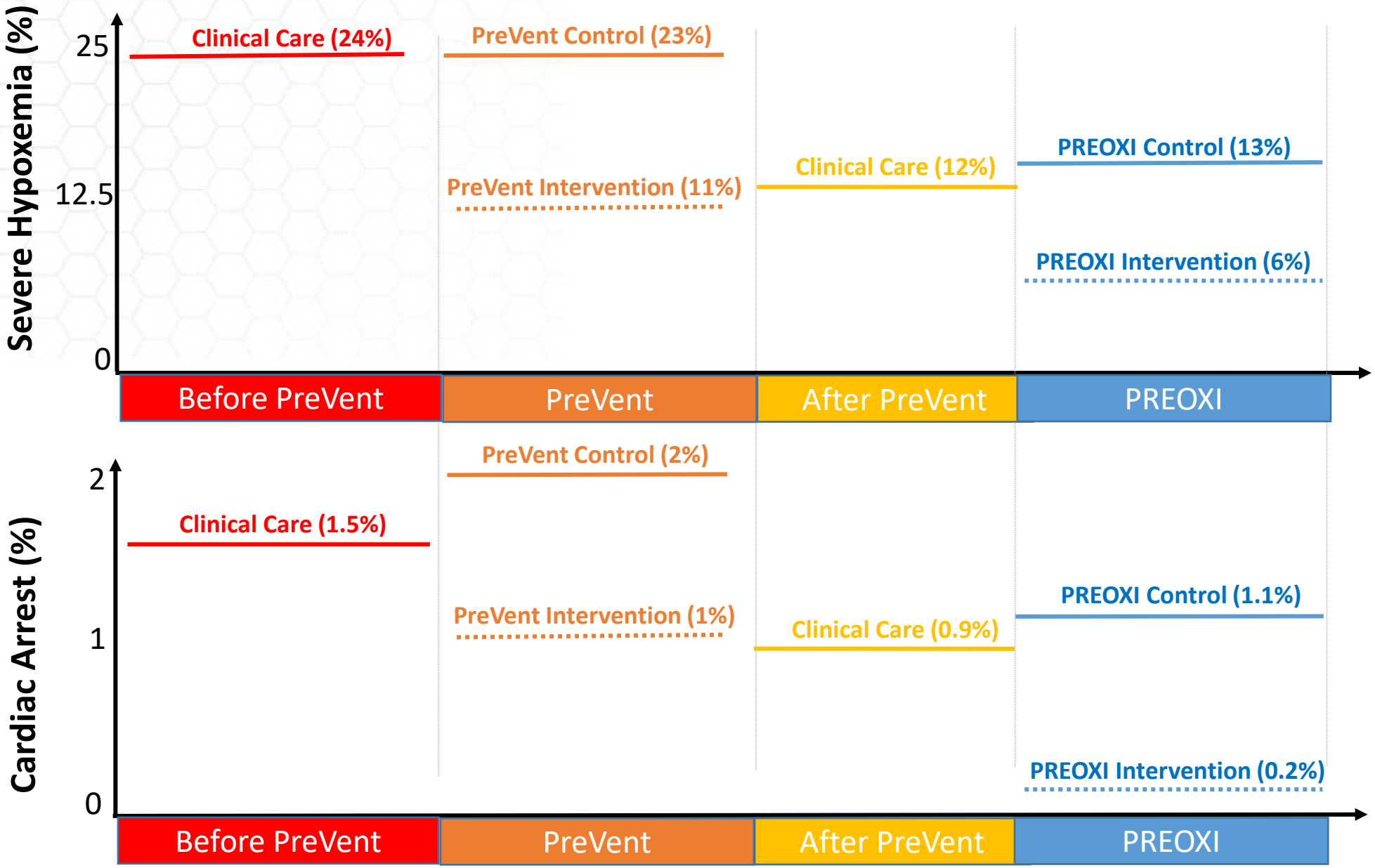
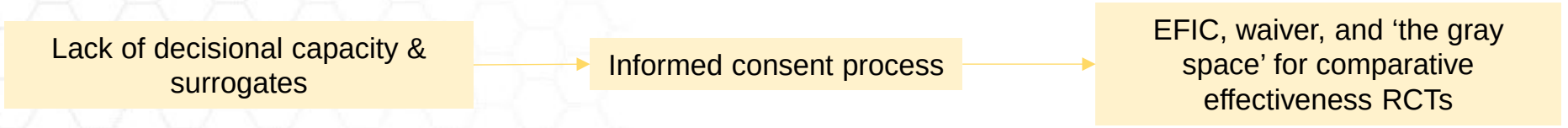
Hypoxemia and Cardiac Arrest in Clinical Care





EFIC, alteration, and waiver of informed consent in pragmatic trials in emergency medicine and critical care

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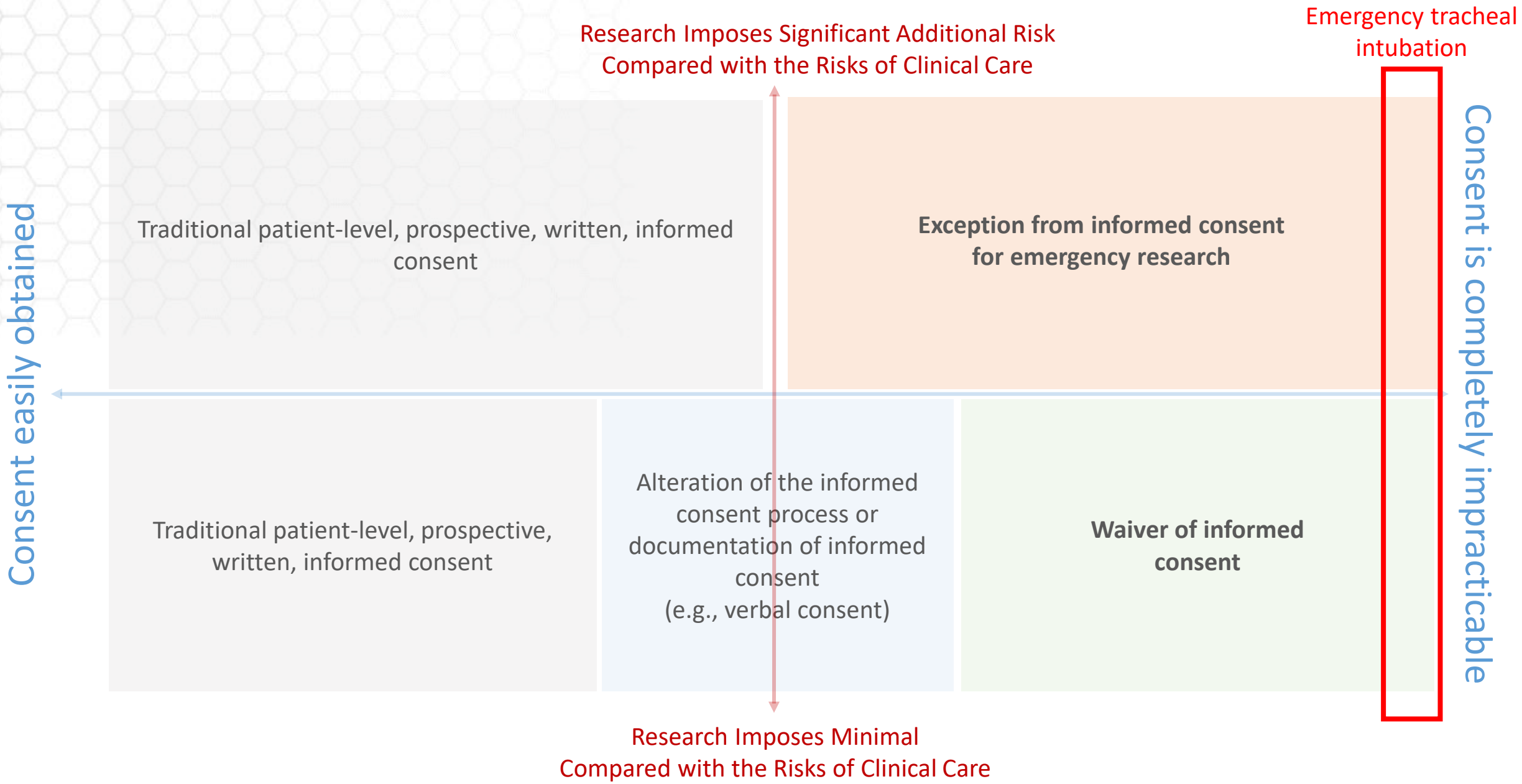
Current Regulations for Informed Consent



Waiver of Informed Consent

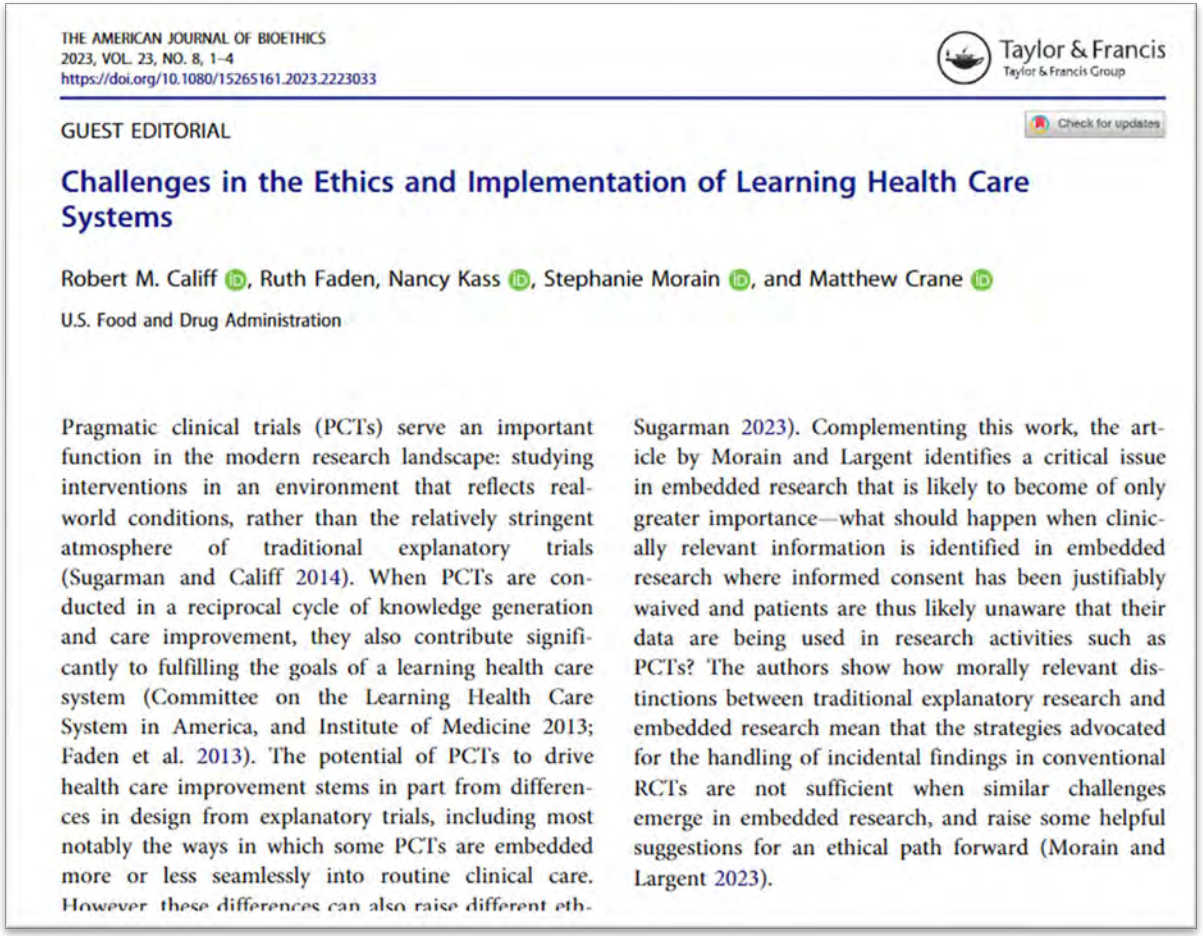
Criteria for waiver of informed consent (45 CFR 46.116(f))

1. **No more than minimal risk to patients**
2. Could not be carried out without the waiver;
3. Only uses identifiable private health information if such information is required to conduct the study
4. Does not adversely affect patients' rights or welfare
5. Whenever appropriate, additional pertinent information is provided after participation.

Why is there controversy on the role of EFIC and waiver in comparative effectiveness research?

FDA Commissioner:

"***Neither HHS nor FDA regulations currently have guidance on whether or when [pragmatic trials] might be categorized as minimal risk . . . These issues need the joint attention of federal agencies, the research community, the health care delivery ecosystem, and patient advocates***"



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GUEST EDITORIAL

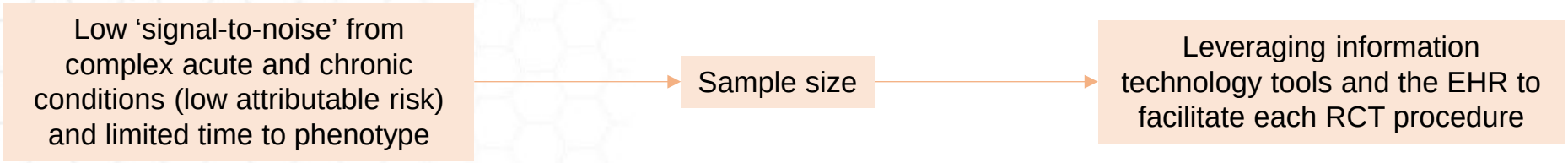
Challenges in the Ethics and Implementation of Learning Health Care Systems

Robert M. Califf, Ruth Faden, Nancy Kass, Stephanie Morain, and Matthew Crane

U.S. Food and Drug Administration

Pragmatic clinical trials (PCTs) serve an important function in the modern research landscape: studying interventions in an environment that reflects real-world conditions, rather than the relatively stringent atmosphere of traditional explanatory trials (Sugarman and Califf 2014). When PCTs are conducted in a reciprocal cycle of knowledge generation and care improvement, they also contribute significantly to fulfilling the goals of a learning health care system (Committee on the Learning Health Care System in America, and Institute of Medicine 2013; Faden et al. 2013). The potential of PCTs to drive health care improvement stems in part from differences in design from explanatory trials, including most notably the ways in which some PCTs are embedded more or less seamlessly into routine clinical care. However, these differences can also raise different eth-

Sugarman 2023). Complementing this work, the article by Morain and Largent identifies a critical issue in embedded research that is likely to become of only greater importance—what should happen when clinically relevant information is identified in embedded research where informed consent has been justifiably waived and patients are thus likely unaware that their data are being used in research activities such as PCTs? The authors show how morally relevant distinctions between traditional explanatory research and embedded research mean that the strategies advocated for the handling of incidental findings in conventional RCTs are not sufficient when similar challenges emerge in embedded research, and raise some helpful suggestions for an ethical path forward (Morain and Largent 2023).



Leveraging the EHR to facilitate trial procedures

Using EHR to efficiently conduct trials large enough to detect small differences in patient-centered outcomes between existing treatments

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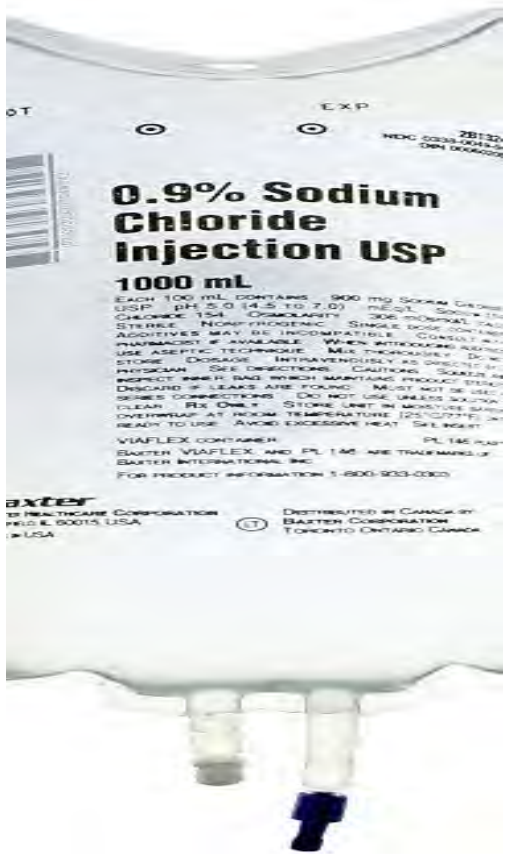
Balanced Crystalloids

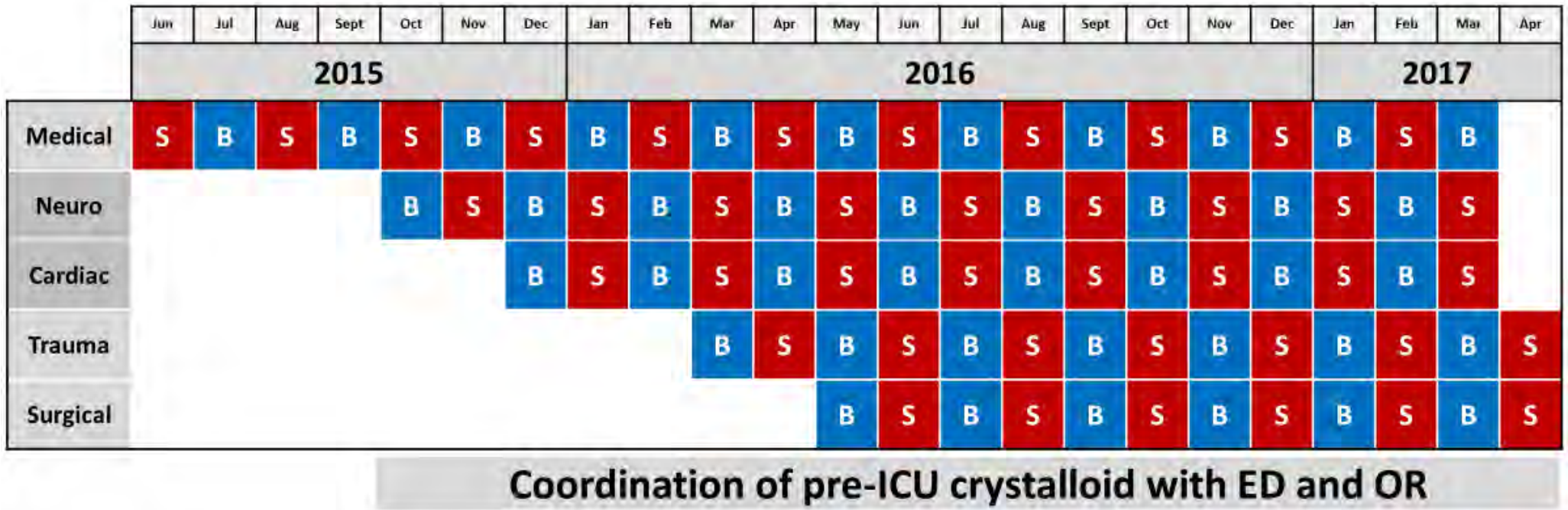
Saline



	Na^+	Cl^-	K^+	Ca^{2+}	Mg^{2+}	Organic anion
0.9% saline	154	**154**				
Lactated Ringer's	130	**109**	4.0	2.7		+
Plasma-Lyte A®	140	**98**	5.0		3.0	+

Pragmatic trial of fluid management

- Isotonic Solutions and Major Adverse Renal Events Trial (SMART)
- Cluster-randomized, multiple-crossover trial
- Adults admitted to five ICUs at Vanderbilt



Step 1

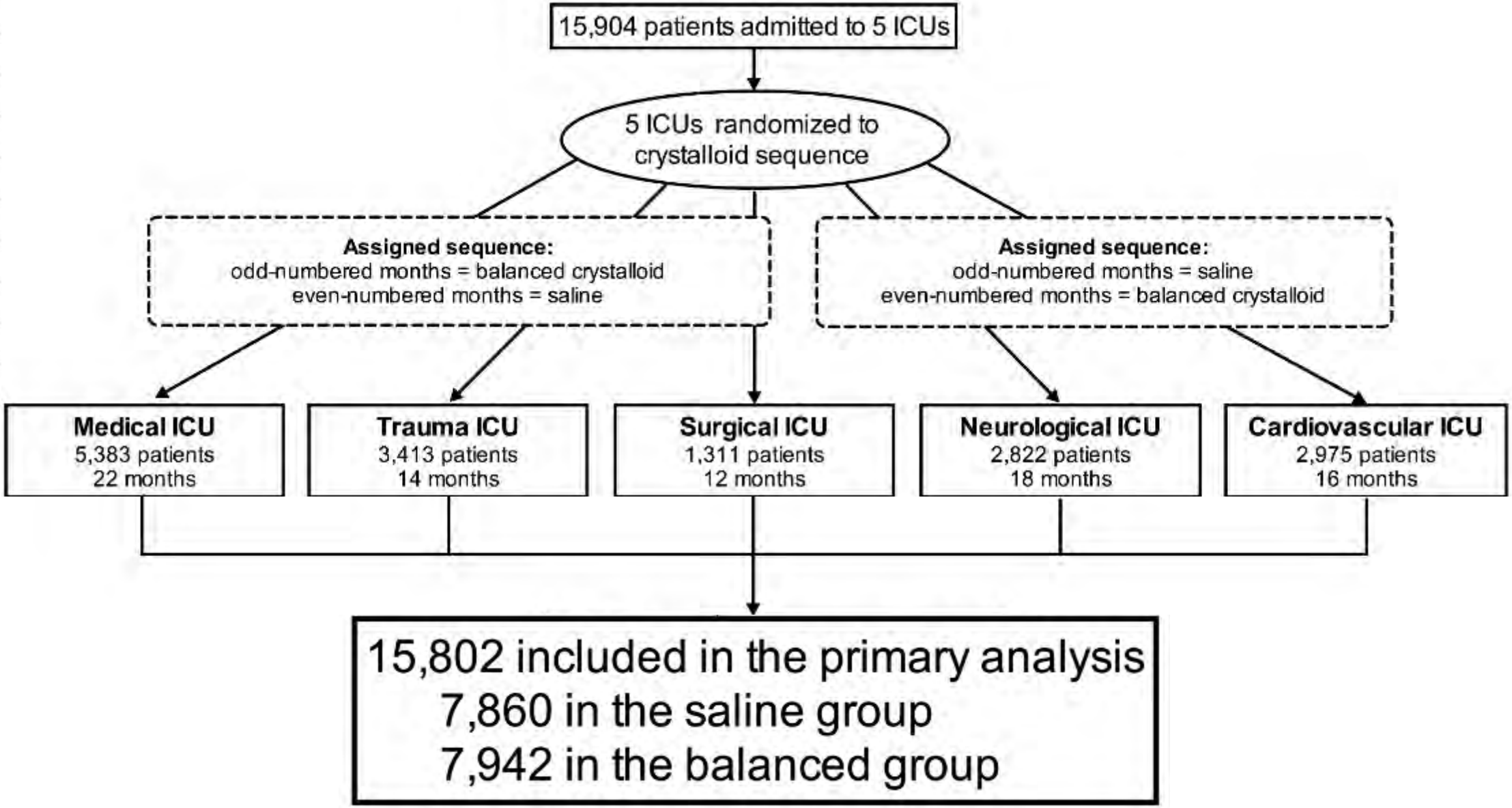
Step 2

This patient has been assigned to receive LR or PLA for all isotonic fluid orders, unless a contraindication is present.

If a contraindication to LR and PLA is present, please select from the list below to order off-study IV fluid. Otherwise, please select option 1 to order LR or 2 to order PLA.

Select an option:

1 Order Lactated Ringer's bolus
2 Order Plasma-lyte bolus
3 Hyperkalemia
4 Brain injury
5 Specific attending request



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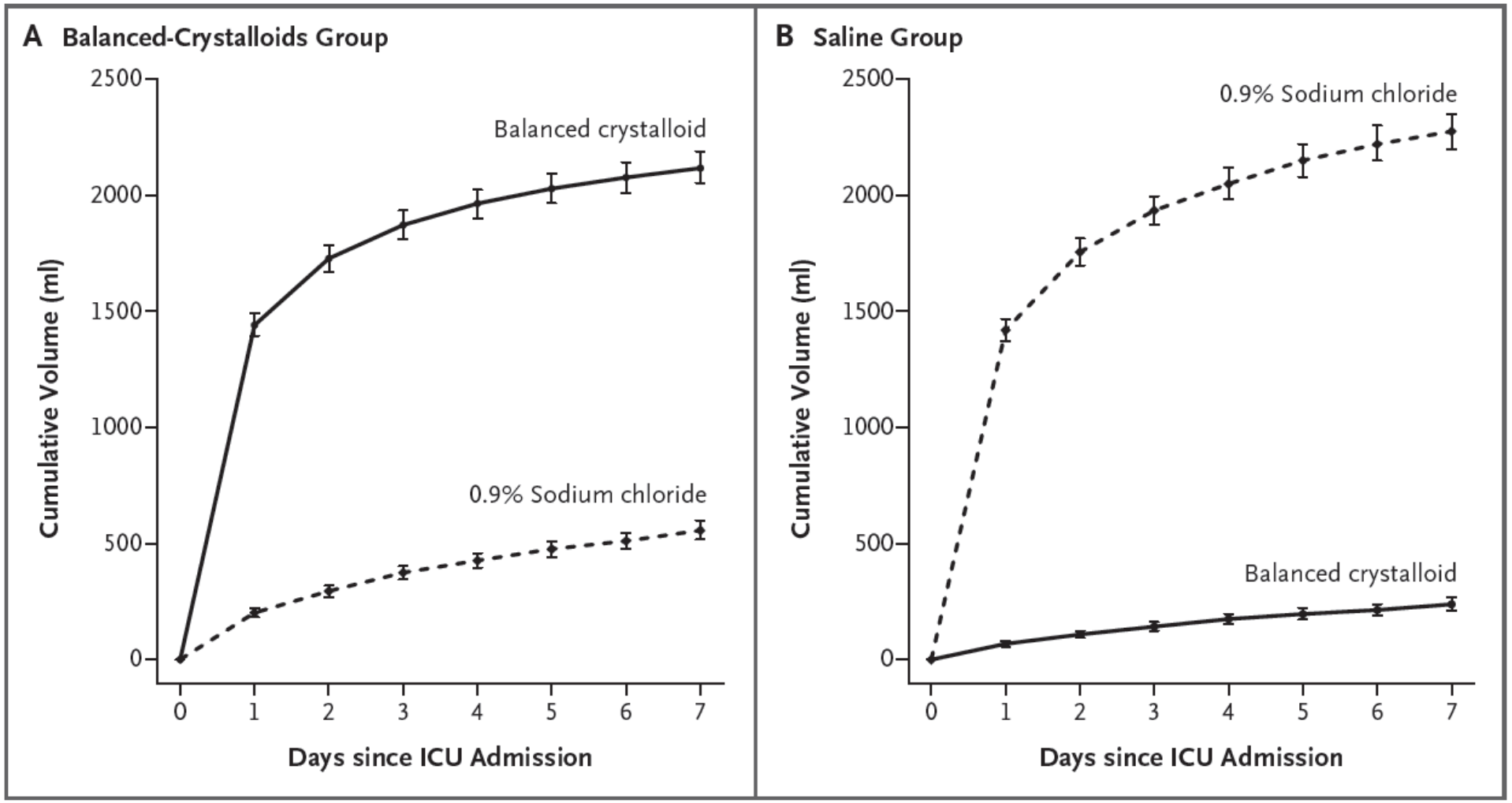
Patient Characteristics	Balanced (n = 7942)	Saline (n = 7860)
Age – years	58 [44 – 69]	58 [44 – 69]
Men	4540 (57.2)	4557 (58.0)
Admitted from ED	3975 (50.1)	3997 (50.9)
Study ICU		
Medical	2735 (34.4)	2646 (33.7)
Trauma	1640 (20.6)	1688 (21.5)
Cardiac	1470 (18.5)	1501 (19.1)
Neurological	1440 (18.1)	1377 (17.5)
Surgical	657 (8.3)	648 (8.2)
Sepsis or septic shock	1167 (14.7)	1169 (14.9)
Vasopressors	2094 (26.4)	2058 (26.2)
Mechanical ventilation	2723 (34.3)	2731 (34.7)
Baseline creatinine – mg/dL	0.89 [0.74 – 1.10]	0.89 [0.74 – 1.10]
Acute kidney injury	681 (8.6)	643 (8.2)

Separation between trial groups



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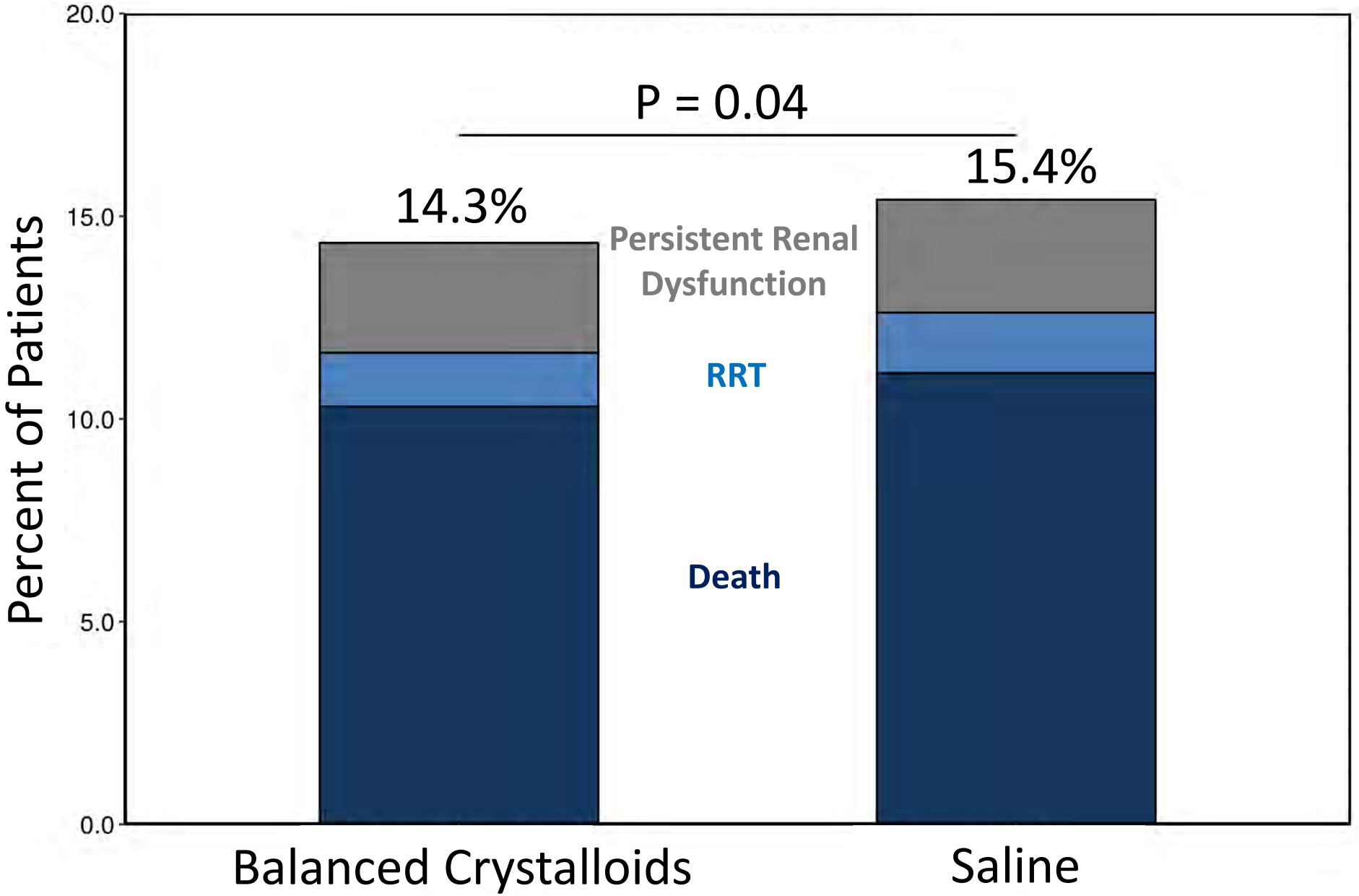
Balanced crystalloids prevented Major Adverse Kidney Events

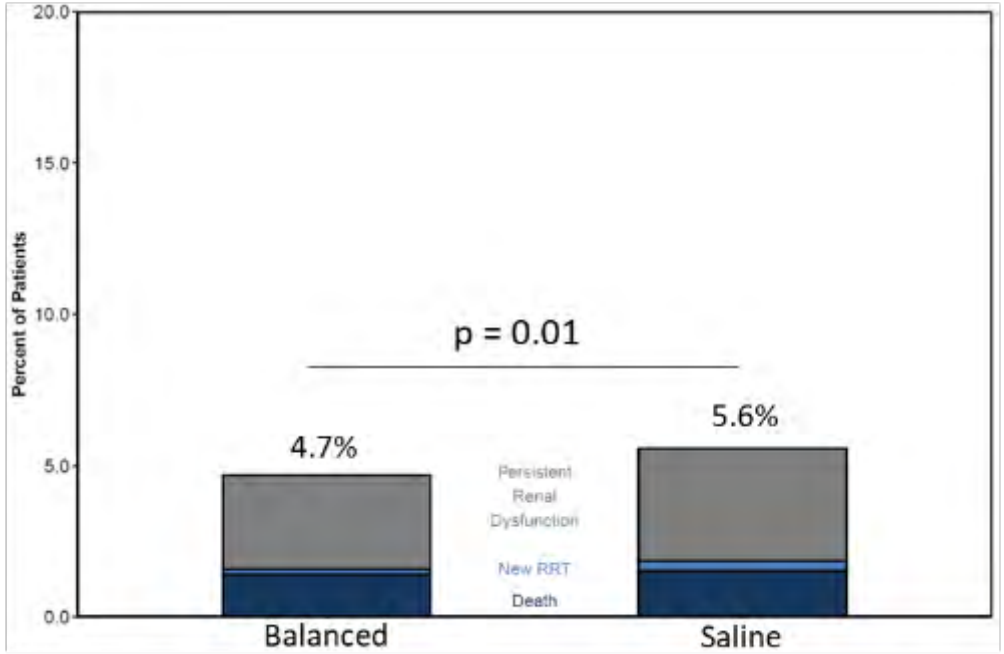


Results similar in second trial

The NEW ENGLAND JOURNAL of MEDICINE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

Wesley H. Self, M.D., M.P.H., Matthew W. Semler, M.D., Jonathan P. Wanderer, M.D., Li Wang, M.S., Daniel W. Byrne, M.S., Sean P. Collins, M.D., Corey M. Slovis, M.D., Christopher J. Lindsell, Ph.D., Jesse M. Ehrenfeld, M.D., M.P.H., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SALT-ED Investigators*



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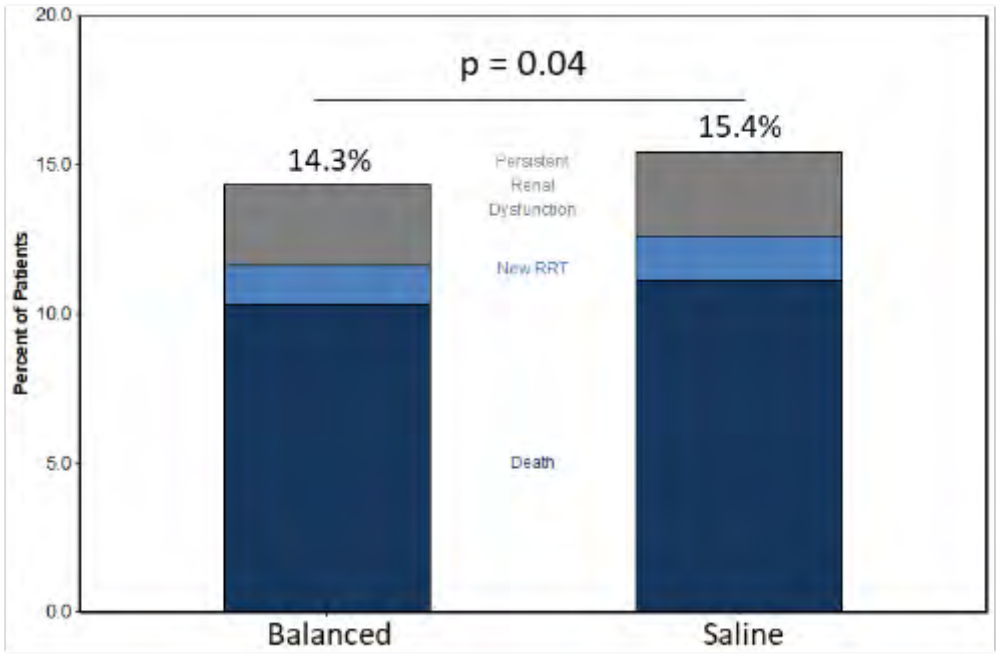

What do trial personnel do in pragmatic trial?

PREOXI Trial

- Train clinicians in trial procedures
- Monitor exclusion vs enrollment
- Verify eligibility after enrollment
- Monitor receipt of intervention
- Provide feedback to clinicians
- Collect data on baseline characteristics and hospital outcomes
- Monitor for AEs
- Communicate with patients and families after enrollment
- Address queries

#3 How to deal with grant reviewer #2

- The scientific and regulatory infrastructure for randomized trials in the US was built for the development of new drugs and devices
- For decades, the NIH and the scientific community have largely conceived of “randomized trials” as explanatory, mechanistic trials
- Peer reviewers may not understand or like trials with pragmatic features

- Our approach:
  - Early on, invest in executing pragmatic trials even without much funding
  - Develop a track record of execution and demonstrate value
  - Seek funders and RFAs that have shown openness to pragmatic trials
  - Jon NIH Collaboratory and other organizations advancing message
  - In grants, describe rigorous trial features without saying “pragmatic”
  - Await turnover in prior generation of scientists and peer reviewers

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Summary

- In every RCT, investigators determine the level of pragmatism for each trial procedure
- Trials with more pragmatic features can sometimes be “better” (more representative) or “more efficient” (shorter enrollment, lower cost)
- The efficiency of pragmatic trials may allow us to answer comparative effectiveness questions that are currently ignored (a moral imperative)
- Pragmatic trials are better suited to comparative effectiveness questions than to the development of new drugs and devices
- Key tools for pragmatic trials are:
  - Embedding trial procedures within clinical care
  - Leveraging the electronic health record to facilitate trial procedures
  - Understanding and appropriately applying EFIC, alteration, and waiver for informed consent
- Barriers to pragmatic trials today are as much cultural or dogmatic as they are scientific or logistical