Anticoagulation in Intracerebral Hemorrhage Survivors for Stroke PreventIon and REcovery

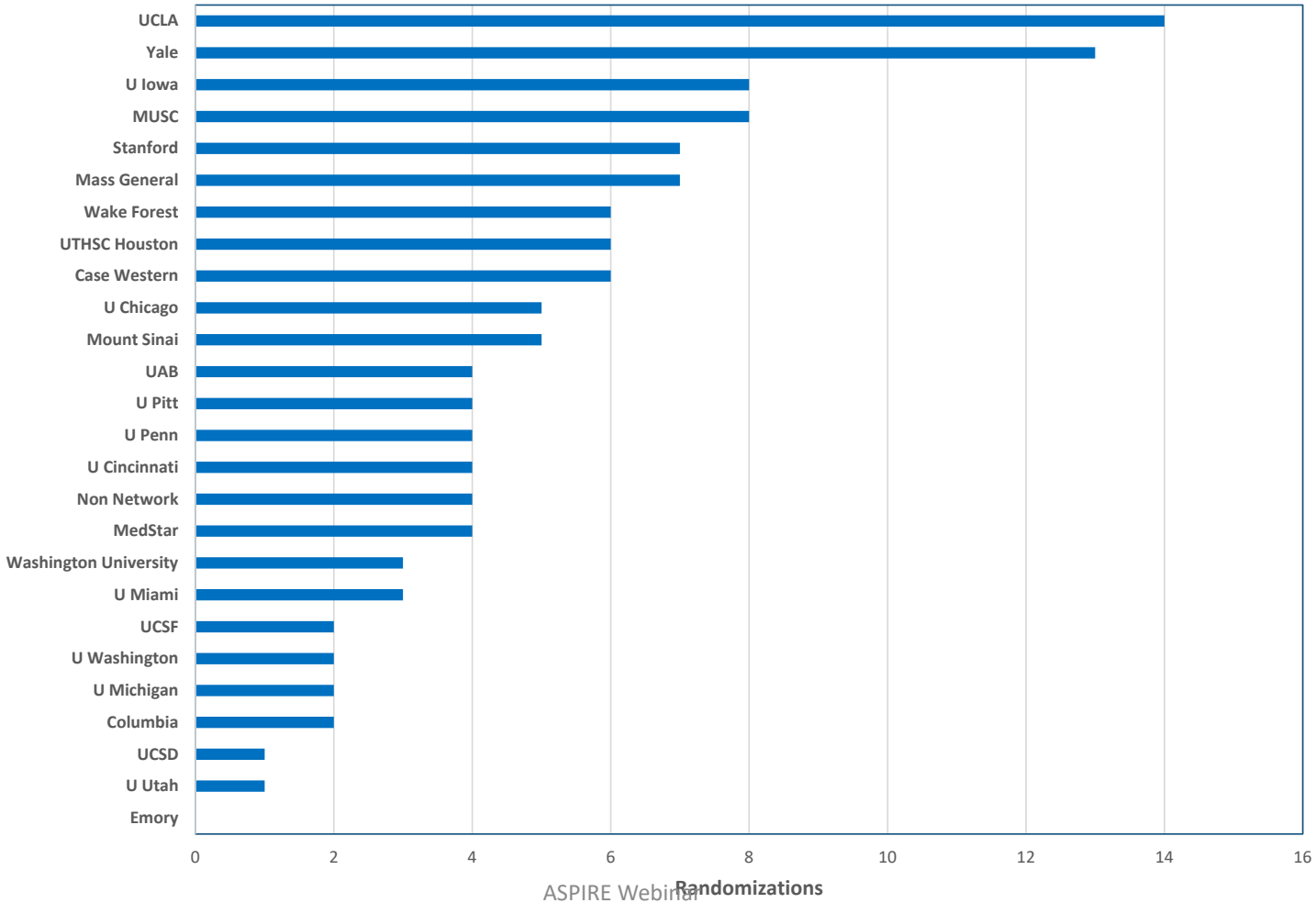
September 28, 2022

NINDS U01 NS106513
NCT03907046

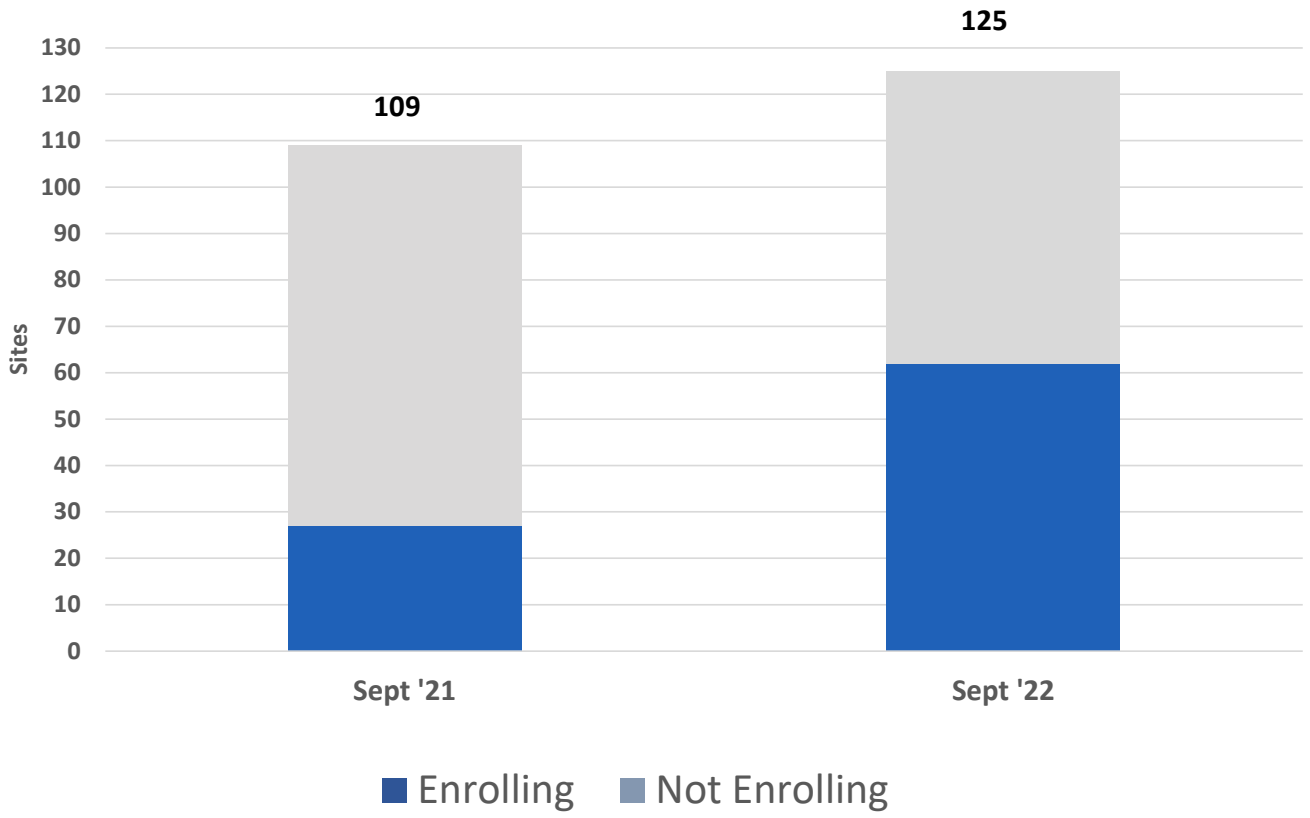
OUTLINE

- ASPIRE Update
- Change in ASPIRE Prohibited Medications
- Updated Guidance for Partnering with Outside Facilities
- LAA Closure Data
- ASPIRE-World Cup Challenge

ASPIRE Randomizations by RCC



Enrolling Sites

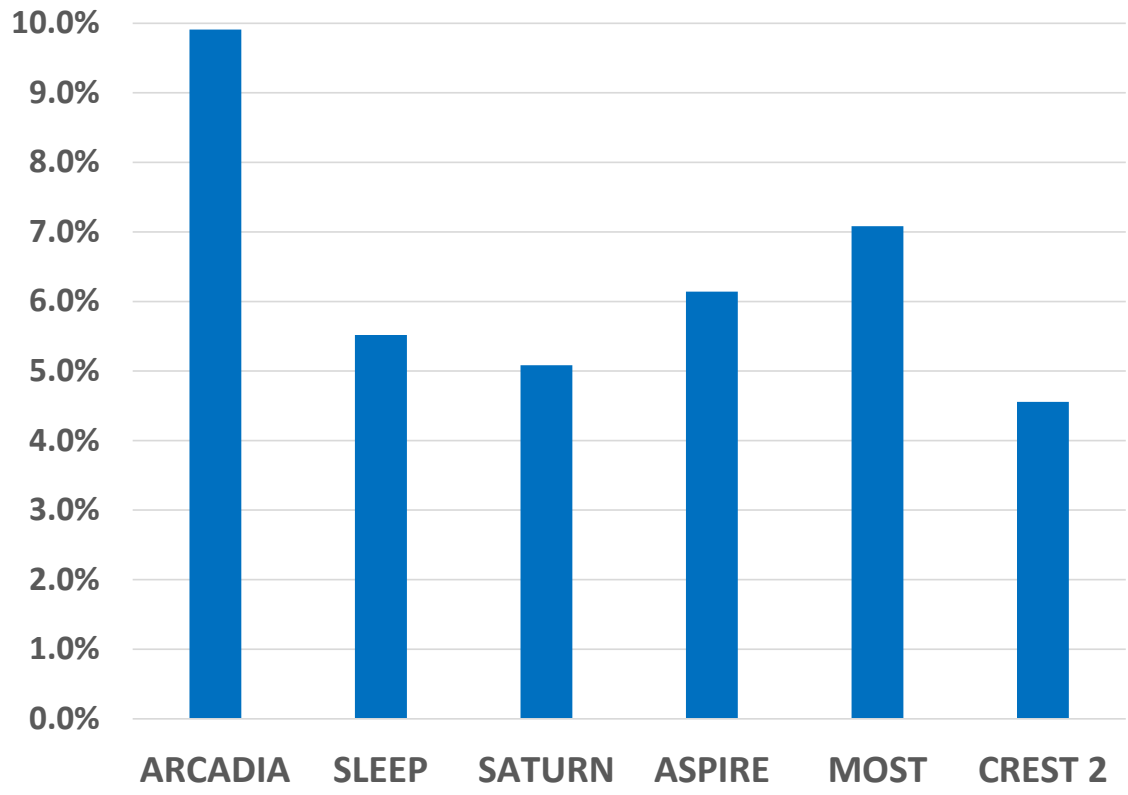


58 Sites Pending 1st Randomization

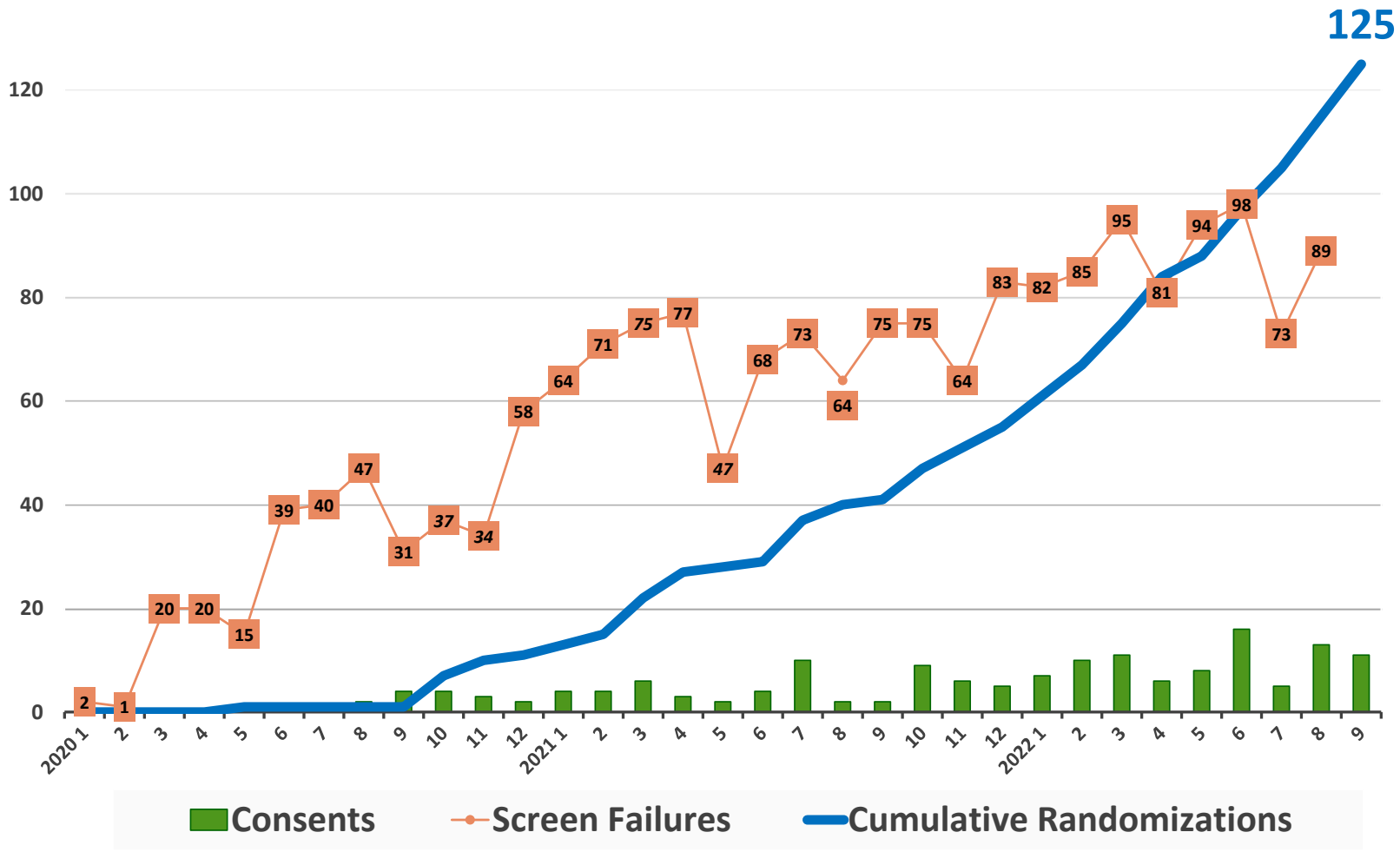
In Study >4 Months

Abbott Northwestern Hospital	Huntington Memorial Hospital	Ronald Reagan UCLA
Abington Memorial Hospital	Javon Bea Hospital - Riverside	SUNY Upstate
Arrowhead Regional Medical Center	Kaiser Permanente Fontana	San Francisco General
Banner University - Tucson Campus	Kaiser Permanente Redwood City	St. Cloud Hospital
Boston Medical Center	Lahey Hospital & Medical Center	St. David's Medical Center
Buffalo General Medical Center	Lehigh Valley Hospital - Cedar Crest	St. John's Hospital
Carolinas Medical Center	Long Beach Memorial Medical Center	St. Mary's Medical Center
Chandler Regional Medical Center	Loyola University Medical Center	Stony Brook University Hospital
Cox Medical Center South	MedStar Washington Hospital Center	Strong Memorial Hospital
Danbury Hospital	Mercy Health Saint Mary's	Thomas Jefferson
Desert Regional Medical Center	Mercy San Juan Medical Center	Tufts Medical Center
Doctors Medical Center Modesto	Methodist University Hospital	UAMS Medical Center
Froedtert Hospital	Montefiore Medical Center	University of Illinois
Geisinger Medical Center	NYP Weill Cornell Medical Center	University of Kentucky
Hartford Hospital	NewYork-Presbyterian Brooklyn	University of Louisville
HealthPartners Methodist Hospital	PeaceHealth Sacred Heart - RiverBend	University of Michigan
Henry Ford Hospital	Rancho Los Amigos	University of Minnesota
Hoag Hospital Newport Beach	Regions Hospital	University of Mississippi
Houston Methodist Hospital	Riverside Methodist Hospital	Vanderbilt University
		Virginia Mason

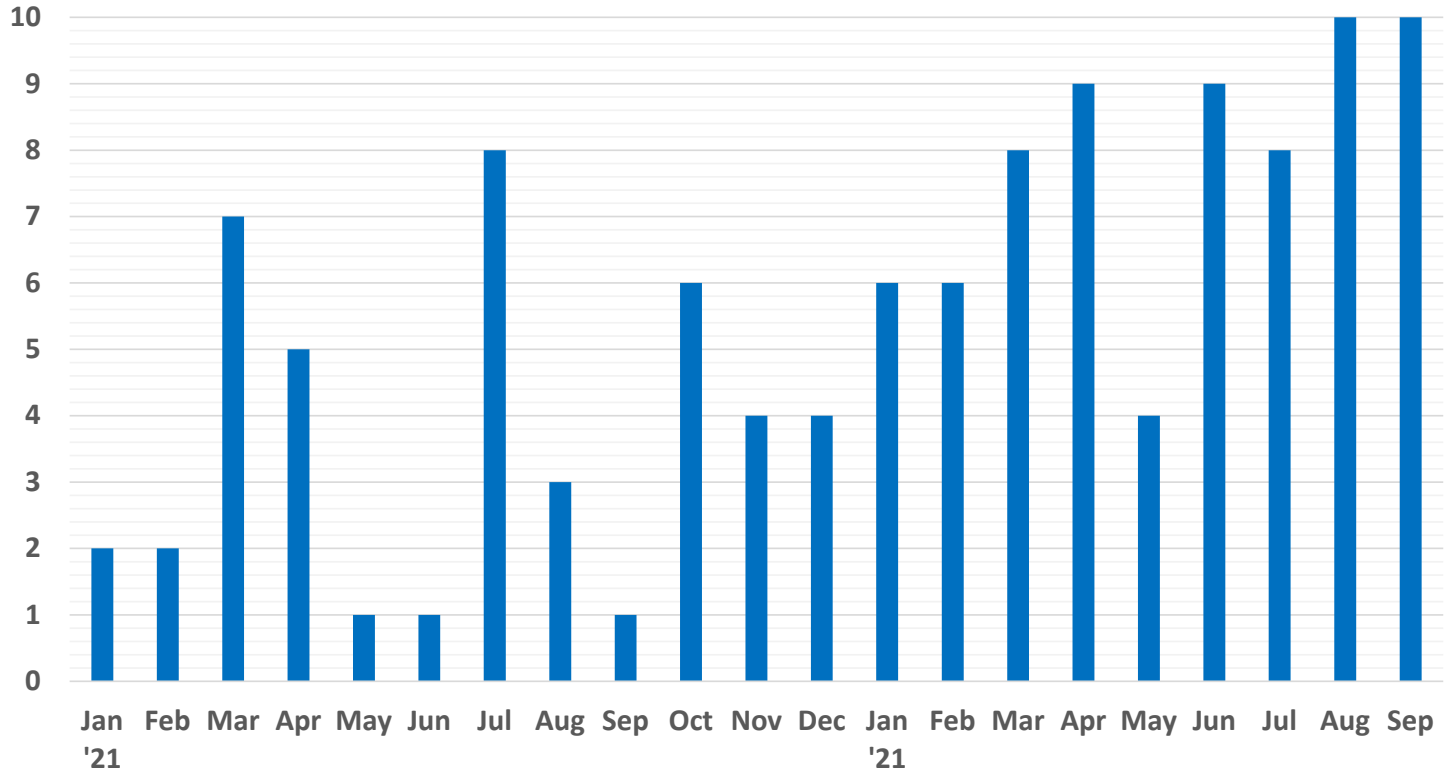
Change in % Enrollment in Last 6 months



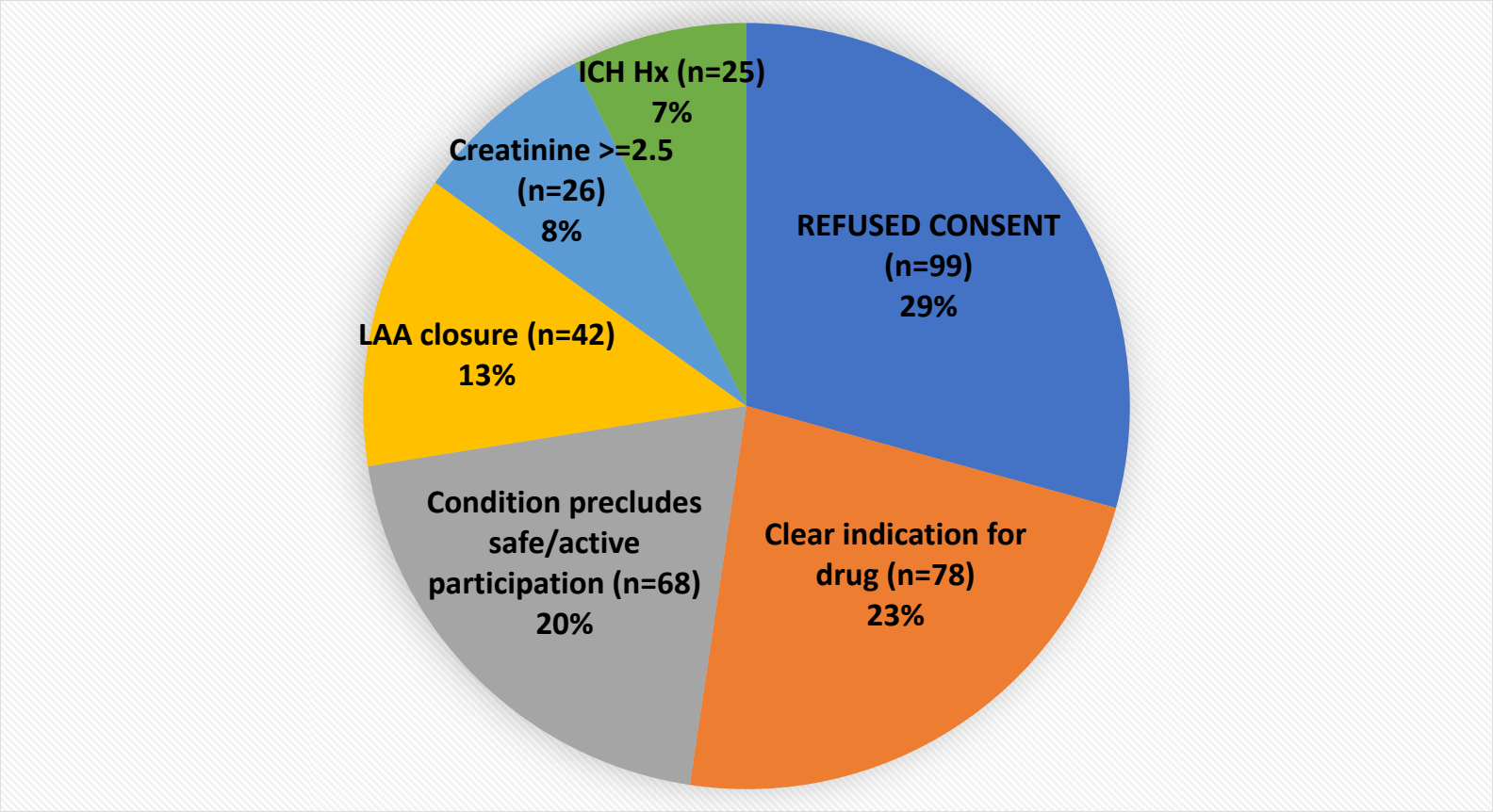
Enrollment Activity



Randomizations by Month
Since 2021



Major Reasons for Screen Failures
In 2022



*Among subjects not excluded as 'unable to enroll in window'.

Diversity in ASPIRE

- GWTG Cohort: 12.2% African Americans, 5.1% Asian, 6.0% Hispanic
- ASPIRE Consented: 11.5% African American, 4.1% Asian, 8.1% Hispanic
- Consent Rates: 42.9% for African American pts; 17.2% for Asian pts; 34.9% for White pts, 42.3% for Hispanic pts
- We offer translation in any language
- Innovative use of unbiased data resources (AHA GWTG)

Drugs
https://doi.org/10.1007/s40265-022-01729-9

REVIEW ARTICLE

In Search of the Optimal Antithrombotic Regimen for Intracerebral Hemorrhage Survivors with Atrial Fibrillation

Teng J. Peng[1] · Catherine Viscoli[1] · Pooja Khatri[2] · Stacey Q. Wolfe[3] · Nirav R. Bhatt[4] · Tarun Girotra[5] · Hooman Kamel[6] · Kevin N. Sheth[1]

Stroke

FOCUSED UPDATES

Focused Update on Vascular Risk and Secondary Prevention in Survivors of Intracerebral Hemorrhage

Kevin N. Sheth, MD; Magdy Selim, MD, PhD

Stroke

FOCUSED UPDATES

Protecting the Brain, From the Heart: Safely Mitigating the Consequences of Thrombosis in Intracerebral Hemorrhage Survivors With Atrial Fibrillation

Laurent Puy, MD, PhD; Rachel Forman, MD; Charlotte Cordonnier, MD, PhD; Kevin N. Sheth MD, PhD

2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

Endorsed by the Society of Vascular and Interventional Neurology

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the Neurocritical Care Society

Steven M. Greenberg, MD, PhD, FAHA, Chair; Wendy C. Ziai, MD, MPH, FAHA, Vice Chair; Charlotte Cordonnier, MD, PhD; Dar Dowlatshahi, MD, PhD, FAHA; Brandon Francis, MD, MPH; Joshua N. Goldstein, MD, PhD, FAHA; J. Claude Hemphill III, MD, MAS, FAHA; Ronda Johnson, MBA; Kiffon M. Keigher, MSN, ACNP-BC, RN, SCRN; William J. Mack, MD, MS, FAHA*; J. Mocco, MD, MS, FAHA†; Eileena J. Newton, MD; Ilana M. Ruff, MD‡; Lauren H. Sansing, MD, MS, FAHA; Sam Schulman, MD, PhD; Magdy H. Selim, MD, PhD, FAHA; Kevin N. Sheth, MD, FAHA*§; Nikola Sprigg, MD; Katharina S. Sunnerhagen, MD, PhD; on behalf of the American Heart Association/American Stroke Association

Secondary Prevention

Management of Antithrombotic Agents and Other Medications

HIGH RISK of thrombotic events
ex. Patient with mechanical valve, LVAD

↓

Early resumption of anticoagulation is reasonable (2a)

Nonvalvular AF
WEIGH RISKS vs BENEFITS of restarting anticoagulation

↓

risk>benefit

Resumption of anticoagulation may be reasonable (2b)

Consider initiation of anticoagulation 7-8 weeks after ICH (2b)

Resumption of antiplatelet therapy may be reasonable based on consideration of benefit and risk (2b)

benefit<risk

LAA closure may be considered (2b)

Statins

Risks and benefits of statins on ICH outcomes and recurrence are uncertain (2b)

NSAIDs

Regular long-term use of NSAIDs is potentially harmful because of the increased risk of ICH (3: Harm)

American Heart Association.

Greenberg, S. M. 2022 AHA/ASA . Guideline for the Management of Patients with Spontaneous Intracerebral Hemorrhage. *Circulation.*

2022 AHA ICH Guidelines

- In patients with AF, the resumption of anticoagulation to prevent thromboembolic events and reduce all-cause mortality may be considered (2B)

- Initiation at 7-8 weeks after ICH may be considered (2B)

- In patients with AF who are otherwise deemed ineligible for anticoagulation, left atrial appendage closure may be considered to reduce the risk of thromboembolic events (2B)

2022 AHA ICH Guidelines

- “Clinical decision making remains challenge given the paucity of prospective RCT’s addressing specific patient populations”

- “Ongoing trials with stratification based on ICH location, mechanism and risk factors for recurrence may lead to more informative decisions”

- “Prospective data are lacking on the safety and efficacy of left atrial appendage closure in patients with ICH”

Site and Participant Engagement

- Interactive forums with PI/coordinator
  - To date, we have had 192 calls; 149 since 9/2021
  - Initiated coordinator office hours
  - Created a WhatsApp account for real time communication

- AHA GWTG Collaboration
  - To date, we have initiated regular reports for 25 sites

- Participant level support
  - Amendment to reimburse participants for follow up visits
  - Amendment to provide home blood pressure cuffs

Change in ASPIRE Prohibited Medications

- **Combined P-gp and strong CYP3A34 inhibitors or inducers** are now classified as prohibited (*rather than discouraged*) for ASPIRE participants.

- Patients unable to stop such medications are ineligible (‘*Condition precludes safe participation*’).

- Enrolled subjects must temporarily hold SD while taking them.

ASPIRE Prohibited and Discouraged Medications List v4.0

PROHIBITED - Combined P-gp and strong CYP3A4 Inhibitors		
ALUVIA	Nirmatrelvir/Ritonavir	Ritonavir
Cobicistat	NORVIR	SPORANOX, SPORANOX PulsePak
EVOTAZ	NOXAFIL	STRIBILD
GENVOYA	ONMEL	SYMTUZA
Itraconazole	PAXLOVID	TOLSURA
KALTERA	Posaconazole	TYBOST
Ketoconazole (oral)	POSANOL	
Lopinavir/Ritonavir Tablet	PREZCOBIX	
PROHIBITED - Combined P-gp and strong CYP3A4 Inducers		
Apalutamide	Fosphenytoin	RIFATER
Carbamazepine	ISONARIF	RIMACTANE
CARBATROL	PHENYTEK	ROFACT
CEREBXY	Phenytoin	St. John's Wort
DILANTIN	RIFADIN	TEGRETOL
EPITOL	RIFAMATE	TEGRETOL XR
EQUETRO	RIFAMPICIN	TREMYTOINE
ERLEADA	Rifampin	

Paxlovid Treatment

- Advise subject to stop taking ASPIRE study drugs (*both bottles*) at start of Paxlovid course and resume taking SD 4 days after last dose of Paxlovid.

- During time off study drugs, you may instruct subject to take aspirin 81 mg daily.

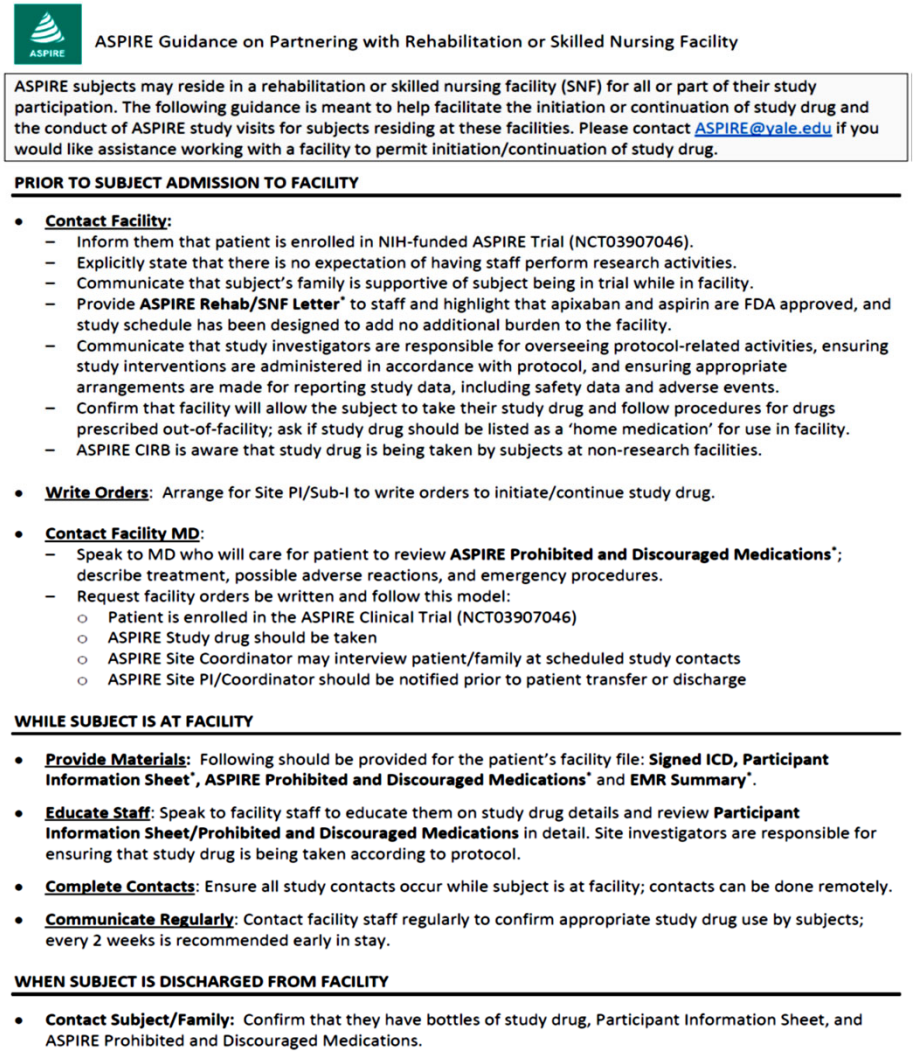
- **Paxlovid Letter to Participants** should be provided to/reviewed with each ASPIRE subject at their next scheduled study contact.

ASPIRE Concomitant Medications

- Medications CRF revisions in process.
- If new prohibited med is being used before revised CRF is posted, make note in General Comments section of F303 and follow MOP for prohibited meds.
- Remind ASPIRE subjects to notify you when a new medication is prescribed.

Revised Guidance for Partnering with Outside Facilities

- Reviewed and approved by ASPIRE cIRB
- Posted in WebDCU>Toolbox



ASPIRE Guidance on Partnering with Rehabilitation or Skilled Nursing Facility

ASPIRE subjects may reside in a rehabilitation or skilled nursing facility (SNF) for all or part of their study participation. The following guidance is meant to help facilitate the initiation or continuation of study drug and the conduct of ASPIRE study visits for subjects residing at these facilities. Please contact ASPIRE@yale.edu if you would like assistance working with a facility to permit initiation/continuation of study drug.

PRIOR TO SUBJECT ADMISSION TO FACILITY

- **Contact Facility:**
  - Inform them that patient is enrolled in NIH-funded ASPIRE Trial (NCT03907046).
  - Explicitly state that there is no expectation of having staff perform research activities.
  - Communicate that subject's family is supportive of subject being in trial while in facility.
  - Provide **ASPIRE Rehab/SNF Letter*** to staff and highlight that apixaban and aspirin are FDA approved, and study schedule has been designed to add no additional burden to the facility.
  - Communicate that study investigators are responsible for overseeing protocol-related activities, ensuring study interventions are administered in accordance with protocol, and ensuring appropriate arrangements are made for reporting study data, including safety data and adverse events.
  - Confirm that facility will allow the subject to take their study drug and follow procedures for drugs prescribed out-of-facility; ask if study drug should be listed as a 'home medication' for use in facility.
  - ASPIRE CIRB is aware that study drug is being taken by subjects at non-research facilities.
- **Write Orders**: Arrange for Site PI/Sub-I to write orders to initiate/continue study drug.
- **Contact Facility MD**:
  - Speak to MD who will care for patient to review **ASPIRE Prohibited and Discouraged Medications***; describe treatment, possible adverse reactions, and emergency procedures.
  - Request facility orders be written and follow this model:
    - Patient is enrolled in the ASPIRE Clinical Trial (NCT03907046)
    - ASPIRE Study drug should be taken
    - ASPIRE Site Coordinator may interview patient/family at scheduled study contacts
    - ASPIRE Site PI/Coordinator should be notified prior to patient transfer or discharge

WHILE SUBJECT IS AT FACILITY

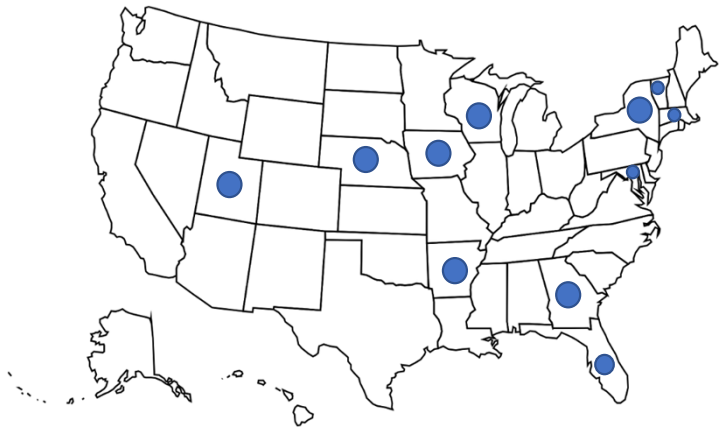
- **Provide Materials:** Following should be provided for the patient's facility file: **Signed ICD, Participant Information Sheet***, **ASPIRE Prohibited and Discouraged Medications*** and **EMR Summary***.
- **Educate Staff**: Speak to facility staff to educate them on study drug details and review **Participant Information Sheet/Prohibited and Discouraged Medications** in detail. Site investigators are responsible for ensuring that study drug is being taken according to protocol.
- **Complete Contacts**: Ensure all study contacts occur while subject is at facility; contacts can be done remotely.
- **Communicate Regularly**: Contact facility staff regularly to confirm appropriate study drug use by subjects; every 2 weeks is recommended early in stay.

WHEN SUBJECT IS DISCHARGED FROM FACILITY

- **Contact Subject/Family:** Confirm that they have bottles of study drug, Participant Information Sheet, and ASPIRE Prohibited and Discouraged Medications.

LAA closure after ICH in US

- All-payer claims data from all hospitalizations across 11 US states
- 18,371 AF patients with ICH in 2016-2020



How many underwent LAA closure after ICH?

1.5% During average follow-up of ~2 years

2016	2017	2018	2019	2020
1.3%	1.3%	2.3%	1.7%	1.4%

No clear trend over time

3.1% Among patients discharged home after ICH

Suggested LAAc Talking Points

- LAA closure never tested in this population & not being widely used
- Remains unclear if LAA closure is equivalent to anticoagulation for ischemic stroke prevention
- No data on risk of ICH with LAA closure versus NOAC or aspirin therapy
- LAA closure is promising but untested and not necessarily the “safest” option given concerns about ischemic stroke prevention

ASPIRE-World Cup Challenge 2022!

Group Stage Started

September 1

ASPIRE-World Cup Challenge
Group Stage Rules

- Sites active on 9/1 randomly assigned to groups A-L
- Sites earn points from study activities from 9/1 through 10/31
- 32 sites will advance to Bracket Stage
  - —Top 2 from each group
  - —Plus 8 sites across all groups with most points

Challenge Points

Study Activity	Points Earned
CONSENTING	
Sent eligible event for review to ASPIRE@yale.edu	2
Consent obtained	5
Translated consent used	2
Day post ICH consent obtained	2 for day 0-7; 1 for day 8-14
Blood sample submitted to Biobank	2
RANDOMIZING	
Randomization	10
Day post ICH patient randomized	2 for day 14-21; 1 for day 22-30
Subject resided in rehab/other outside facility at randomization	3
Screening/Baseline CRFs submitted on time (*w/in 5 days of randomization*)*	2
Brain images uploaded to Biobank on time (*w/in 14 days of randomization*)*	1
SCREENING	
Screen Failure forms submitted	0.5 * Number SF forms
Highest number of Screen Failure forms submitted in stage	1
WEBINAR ATTENDANCE	1 for Coor (*max*); 1 for PI

**For subjects randomized during Challenge stage.*

Scoreboard Updates

- Weekly scoreboard emailed on Friday
- Last scoreboard (from 9/23) shown on next 2 slides

A	University of Alabama Hospital	13	B	Boston Medical Center	8.5	C	Kaiser Permanente LA Medical Center	2.5
	UC Davis Medical Center	2		Inova Fairfax Hospital	1		Javon Bea Hospital - Riverside	1
	UAMS Medical Center	1		Abington Memorial Hospital	0.5		Arrowhead Regional Medical Center	0
	UH Cleveland Medical Center	1		Harborview Medical Center	0		Augusta University Medical Center	0
	Cedars-Sinai Medical Center	0		Jackson Memorial Hospital	0		Baystate Medical Center	0
	Geisinger Medical Center	0		Kaiser Permanente Redwood City	0		Huntington Memorial Hospital	0
	Henry Ford Hospital	0		Kaiser Permanente Sacramento	0		Mayo Clinic	0
	Rancho Los Amigos National Rehabilitation Center	0		Lahey Hospital & Medical Center	0		PeaceHealth Sacred Heart - RiverBend	0
	Regions Hospital	0		Loyola University Medical Center	0		St. David's Medical Center	0
	Thomas Jefferson University Hospital	0		Ochsner Medical Center - Main Campus	0		The University of Vermont	0
				Prisma Health Greenville Memorial Hospital	0			
D	Maimonides Medical Center	12	E	Massachusetts General Hospital	19	F	Riverside Methodist Hospital	3.5
	St. Cloud Hospital	2.5		University of South Alabama Hospital	17		The Mount Sinai Hospital	1
	Beth Israel Deaconess Medical Center	0		Oregon Health & Science U Hospital	12		Rhode Island Hospital	0.5
	Hoag Hospital Newport Beach	0		Stanford University Medical Center	1		St. Mary's Medical Center	0.5
	Medical University of South Carolina University Hospital	0		Mount Sinai West	0.5		Carolinas Medical Center	0
	Memorial Hermann Texas Medical Center	0		San Francisco General Hospital	0.5		Desert Regional Medical Center	0
	Moses H. Cone Memorial Hospital	0		Cleveland Clinic Akron General	0		Montefiore Medical Center	0
	NYU Langone Hospital - Brooklyn	0		MedStar Georgetown University Hospital	0		Morton Plant Hospital	0
	St. John's Hospital	0		NewYork-Presbyterian Brooklyn Methodist	0		North Shore University Hospital	0
	UMass Memorial Medical Center	0		OSF St. Francis Medical Center	0		OSU Wexner Medical Center	0
	University of Michigan University Hospital	0					University of Cincinnati Medical Center	0

G	University of North Carolina Medical Center	23	H	Barnes Jewish Hospital	32	I	University of Illinois Hospital	1
	University of Iowa Hospitals & Clinics	18		UPMC Presbyterian Hospital	6.5		Lehigh Valley Hospital - Cedar Crest	0.5
	Abbott Northwestern Hospital	0		University of Utah Healthcare	1.5		Vanderbilt University Hospital	0.5
	Banner University Medical Center - Tucson Campus	0		MedStar Washington Hospital Center	1		Central DuPage Hospital	0
	Cleveland Clinic	0		MetroHealth Medical Center	1		McLaren Flint	0
	Danbury Hospital	0		Chandler Regional Medical Center	0.5		McLaren Macomb	0
	Kaiser Permanente Fontana Medical Center	0		Froedtert Hospital	0.5		UC Irvine Medical Center	0
	Methodist University Hospital	0		HealthPartners Methodist Hospital	0		University of Chicago Medical Center	0
	Tampa General Hospital	0		Long Beach Memorial Medical Center	0		University of Louisville Hospital	0
	University of Nebraska Medical Center	0		Rush University Medical Center	0		University of Mississippi Medical Center	0
				Vassar Brothers Medical Center	0			
J	Yale New Haven Hospital	21	K	The Queen's Medical Center	1	L	University of Minnesota Medical Center Hospital	2
	Hospital of the University of Pennsylvania	15		Wake Forest Baptist Medical Center	1		OU Medical Center	0.5
	NYP Columbia University Medical Center	1.5		Cox Medical Center South	0		UVA Medical Center	0.5
	Houston Methodist Hospital	0.5		Hartford Hospital	0		Buffalo General Medical Center	0
	Grady Memorial Hospital	0		PIH Health Hospital - Whittier	0		Doctors Medical Center Modesto	0
	Kings County Hospital Center	0		Providence St. Vincent Medical Center	0		Mercy San Juan Medical Center	0
	Mercy Health Saint Mary's	0		Ronald Reagan UCLA Medical Center	0		St. John Medical Center	0
	NYP Weill Cornell Medical Center	0		St. Joseph's Hospital	0		Stony Brook University Hospital	0
	SUNY Upstate Medical University	0		Strong Memorial Hospital	0		University of Kentucky Hospital	0
	Temple University Hospital	0		University of New Mexico Hospital	0		University of Texas Health Science Center San Antonio	0
	Tufts Medical Center	0					WVU Healthcare Ruby Memorial Hospital	0

Thank You!