NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NIH StrokeNet Network Meeting
Los Angeles, CA
15-Feb- 2016

Joseph P. Broderick, MD

Department of Neurology and Rehabilitation Medicine

University of Cincinnati Neuroscience Institute, Comprehensive Stroke Center

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PI Interactions with NINDS and Proposal Process

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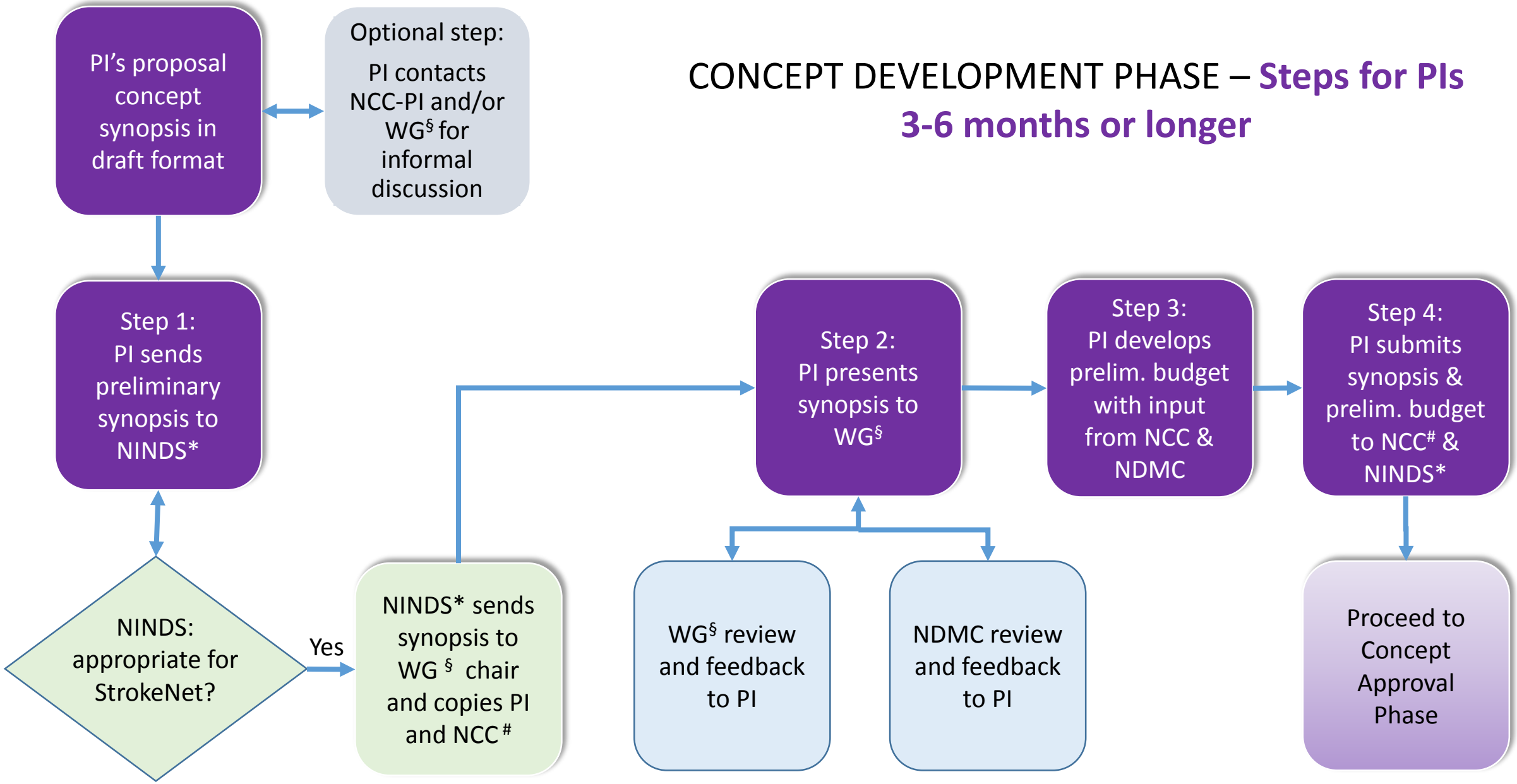
NINDS Consideration and Approval of Concept (ESC)

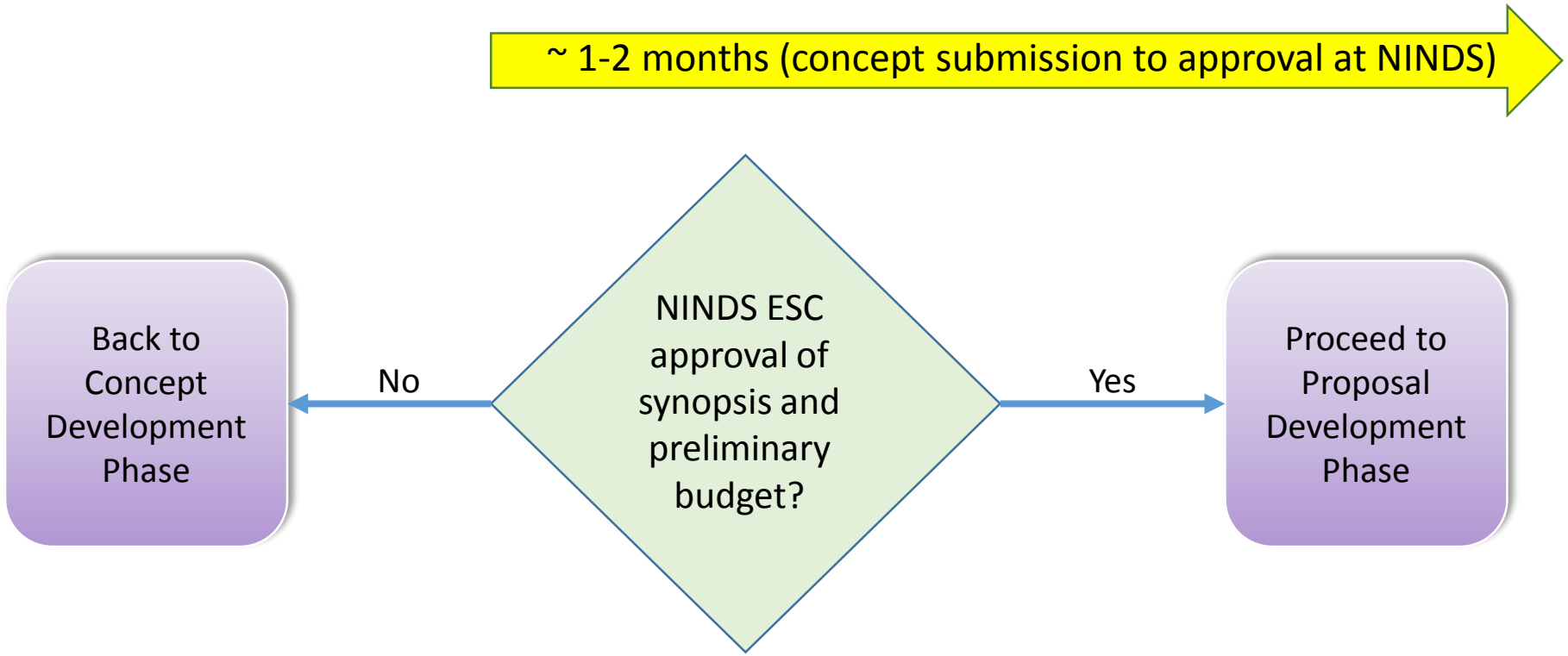
- ESC – Extramural Science Committee
  - Approves all NINDs initiatives and large proposals for submission, including all StrokeNet proposals
- Concepts are considered for NINDS priority and ability to pay
  - Budget estimate is important
  - Not a scientific review
- Factors considered in discussion:
  - Relevance to NINDS
  - Priority within portfolio/gaps in science
  - Overall cost

CONCEPT DEVELOPMENT PHASE – **Steps for PIs**
3-6 months or longer

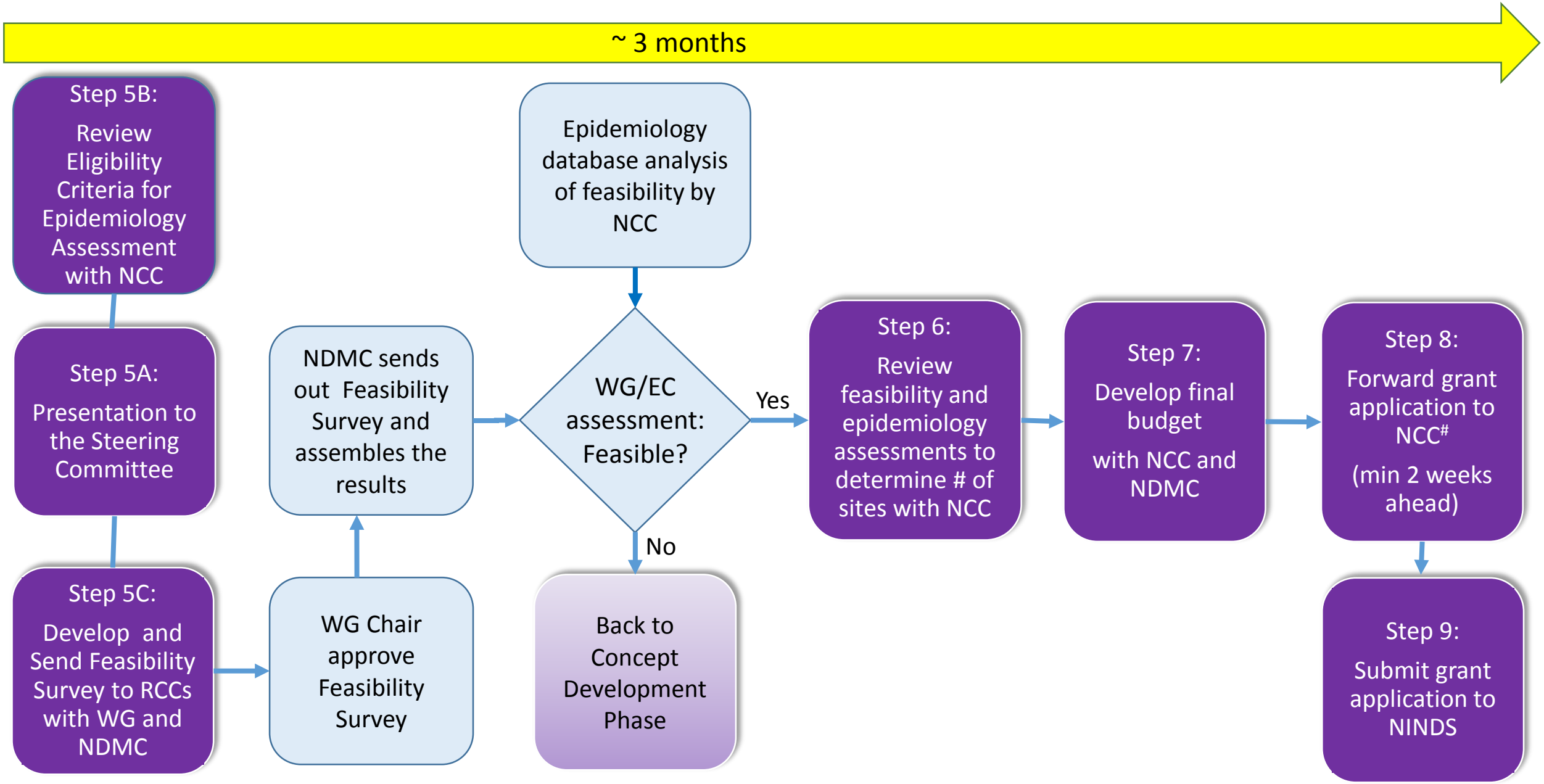


* Contact at NINDS: Lupe Aquino (lupe.aquino@nih.gov); # Contact at NCC: Rose Beckmann (BECKMARE@ucmail.uc.edu); § See WG composition (last slide)

CONCEPT APPROVAL PHASE



STROKENET: PROPOSAL DEVELOPMENT PHASE – **Steps for the PI**



STROKENET: Working Groups

Acute Stroke	Primary and Secondary Prevention	Recovery and Rehabilitation
• Chair: Pooja Khatri University of Cincinnati • Co-chair: Jeff Saver UCLA • Renee' Martin NDMC • Greg Albers Imaging Core • David Liebeskind Imaging Core • TBD Minority Recruitment and Retention • Bill Barsan University of Michigan (ad hoc NETT member) • Lee Schwamm Massachusetts General Hospital • Ed Jauch Medical University of South Carolina • Brett Meyer UC San Diego • Phil Scott University of Michigan • Jay Mocco Mt. Sinai School of Medicine – (#2) • Cathy Sila Case Western Reserve University School of Medicine • Wade Smith UC San Francisco • Azam Ahmed University of Wisconsin • Michel Torbey The Ohio State University • Coordinator: Kiva Schindler Emory University	• Chair: Tom Brott Mayo Clinic Jacksonville • Co-Chair: Ralph Sacco University of Miami School of Medicine • Sharon Yeatts NDMC • Colin Derdeyn Imaging Core • Steve Warach Imaging Core • Bernadette Boden-Albala PhD. Mt. Sinai School of Medicine/New York City Collaborative Minority Recruitment and Retention • Amy Towfighi USC/UCLA • Scott Kasner University of Pennsylvania • Kamakshi Lakshminarayan University of Minnesota • David Tirschwell University of Washington • Shyam Prabhakaran Northwestern University • Enrique Leira University of Iowa • Marc Chimowitz Medical University of South Carolina • Natalia Rost Massachusetts General Hospital • Coordinator: Glenn Schubert University of Washington	• Chair: Steve Cramer UC Irvine • Co-chair: Steve Wolf PhD Emory University • NINDS representative: Daofen Chen, PhD • Caitlyn Ellerbe NDMC • Max Wintermark Imaging Core • TBD Minority Recruitment and Retention • Ron Lazar Columbia University • Alex Dromerick The Medstar Research Institute • Larry Wechsler University of Pittsburgh • Sean Savitz University of Texas at Houston • Lorie Gage Richards University of Utah • Maarten Lansberg Stanford University • Andrew Grande University of Minnesota • Elliot Roth Northwestern University • Harold Adams University of Iowa • Kari Dunning University of Cincinnati (ad hoc) • Coordinator: Mary Pautler University of Utah

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WebDCU StrokeNet Dashboard - Demo

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https://webdcu.musc.edu/nett/ProjectSelection2.asp

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WebDCU™
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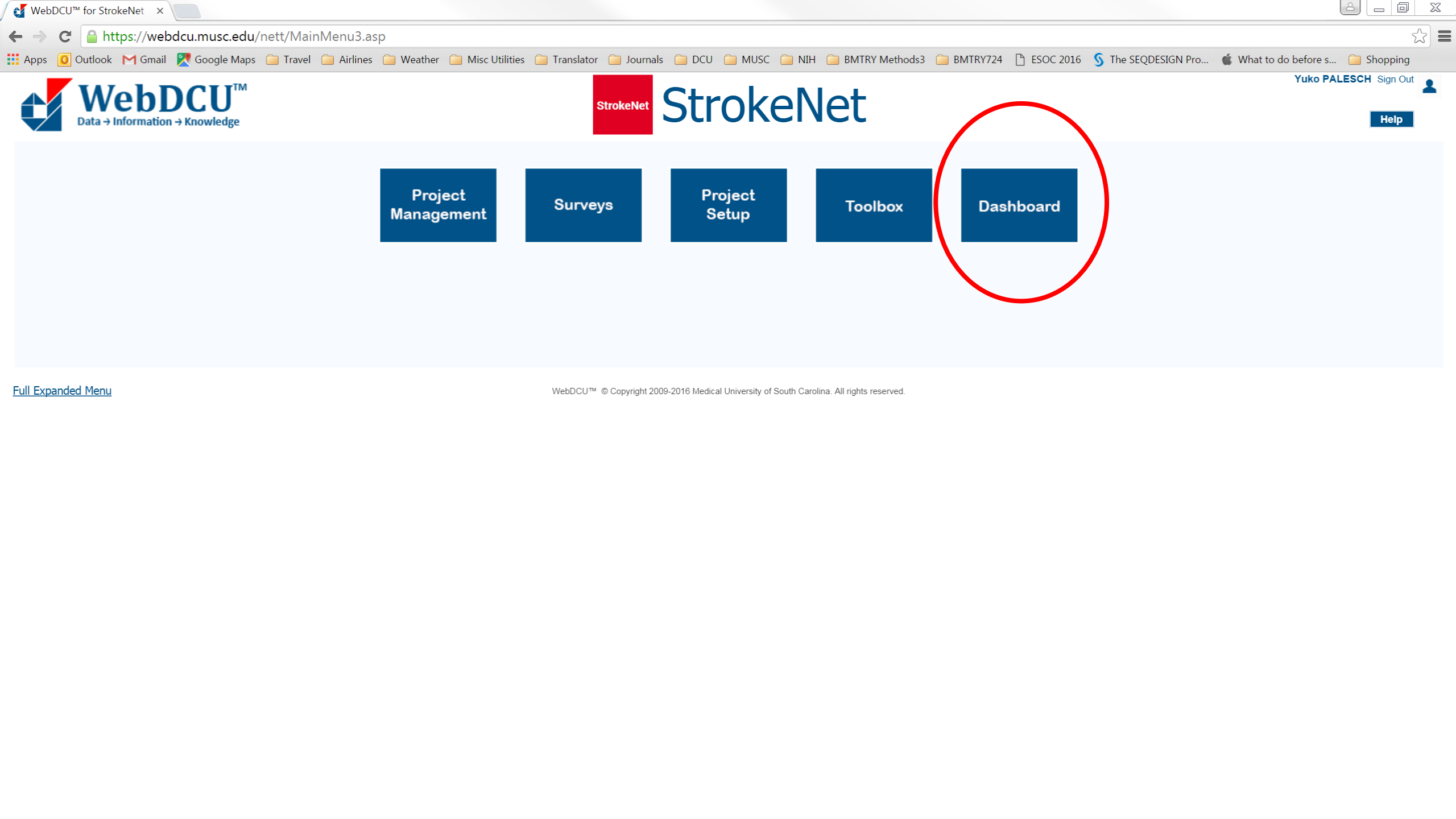
Yuko PALESCH Sign Out

NETT RAMPART ProTECT point StrokeNet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WebDCU™ for StrokeNet

https://webdcu.musc.edu/nett/StrokeNet/CustomCode/StrokeNetPerformanceReport.asp?theFormID=1605

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WebDCU StrokeNet

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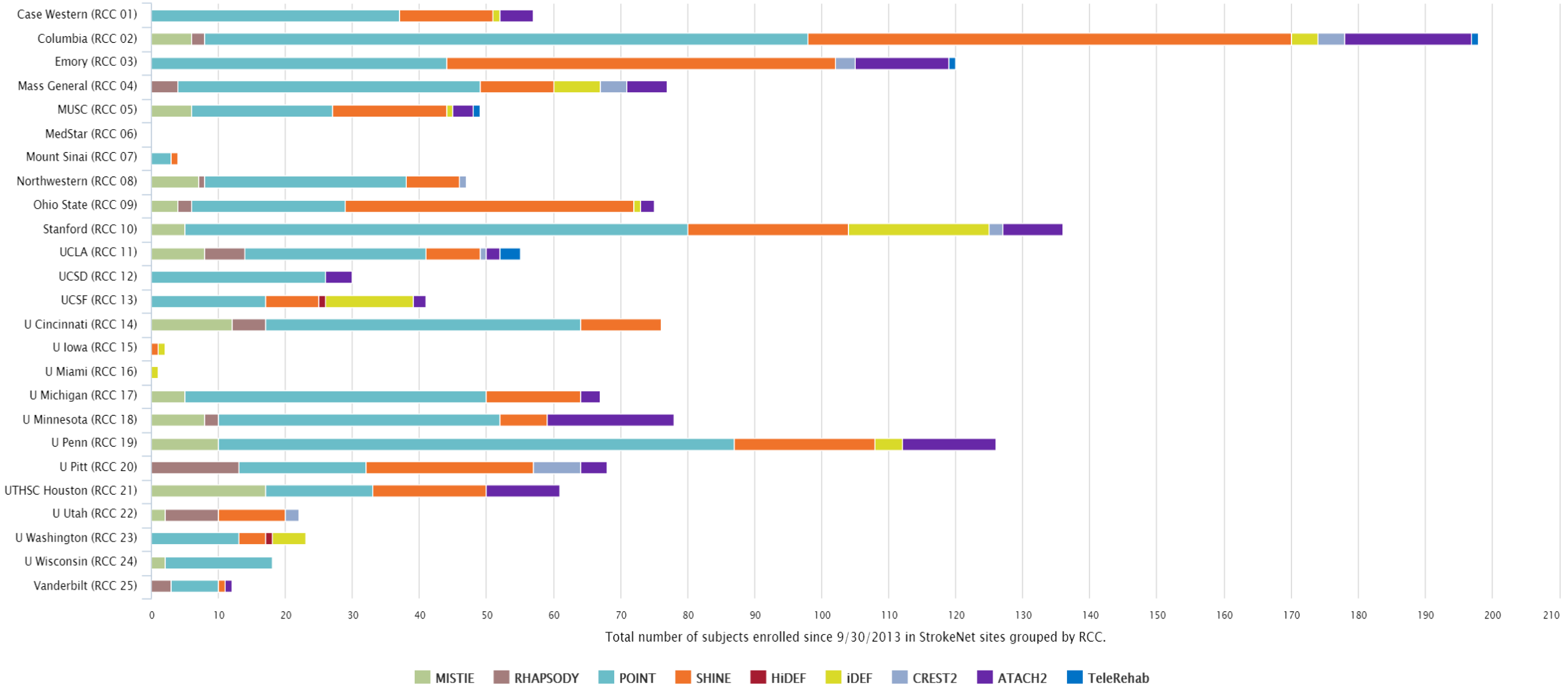
NIH StrokeNet Operation Progress Dashboard

Help

A. Subject Enrollment by RCC

StrokeNet Trials | Non StrokeNet Trials | All Trials



NIH StrokeNet Operation Progress Dashboard

Help

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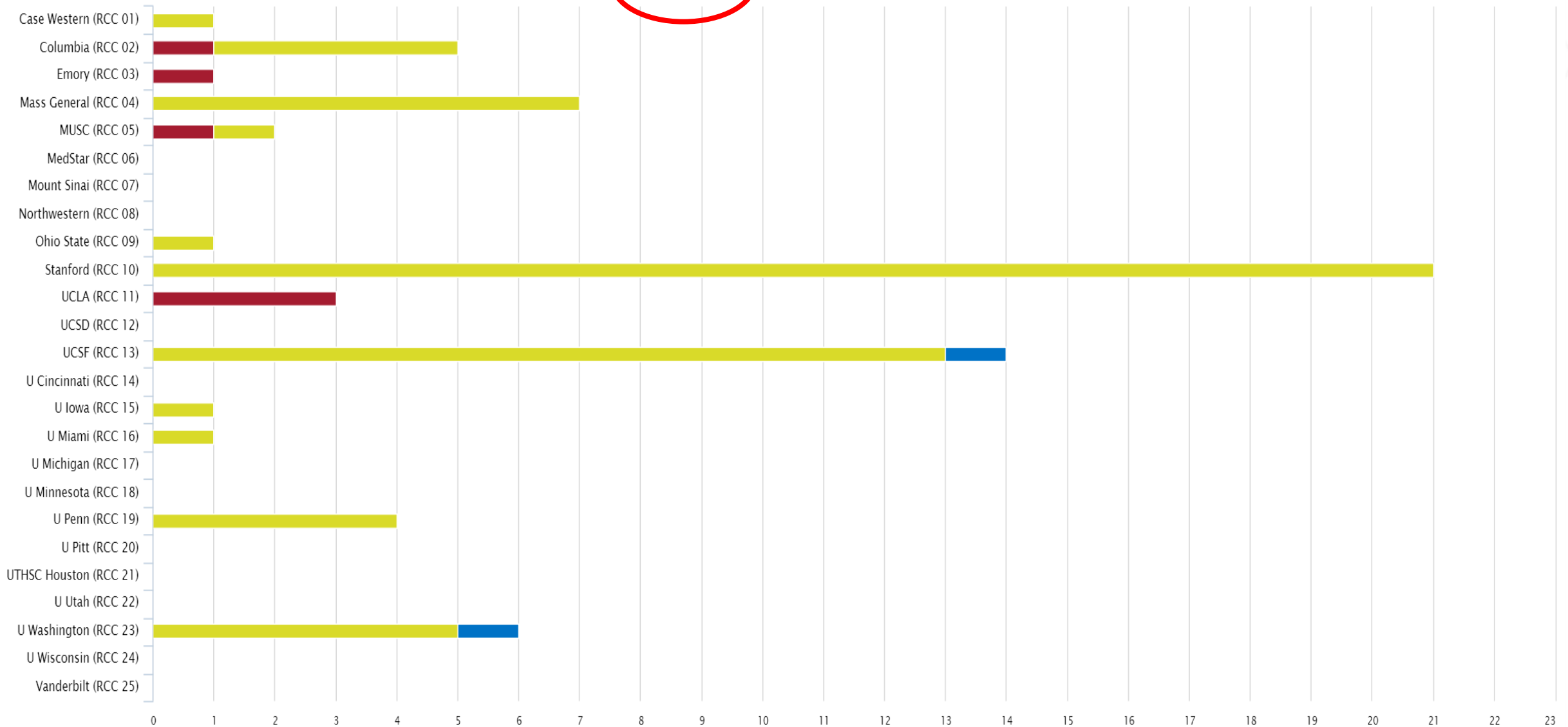
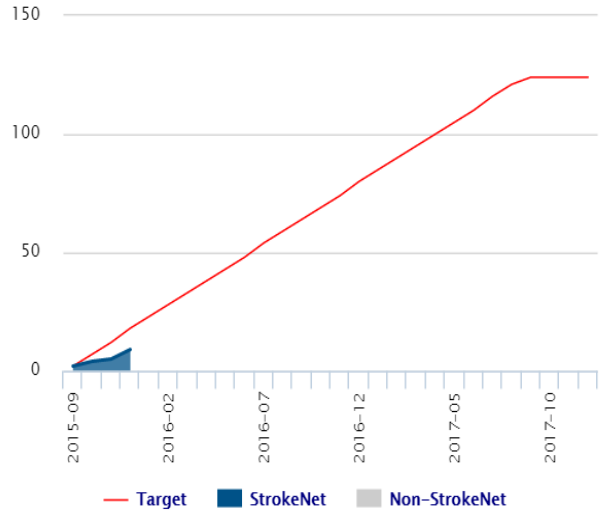


B. Subject Enrollment by Project

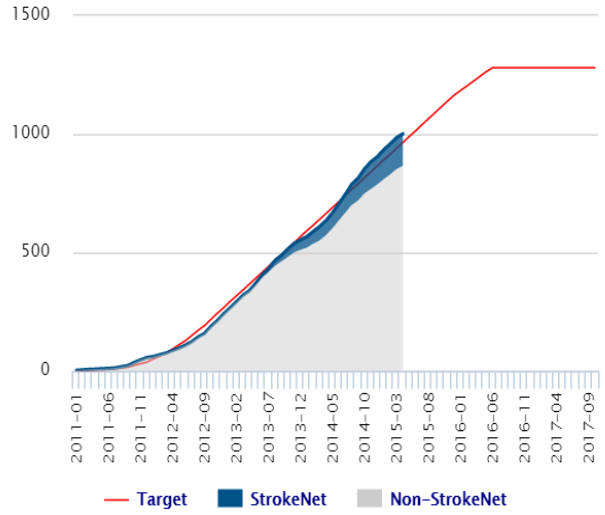
TeleRehab

Current = 9, Sample Size =124
Completed =7.3%
StrokeNet =9 (100.00%)



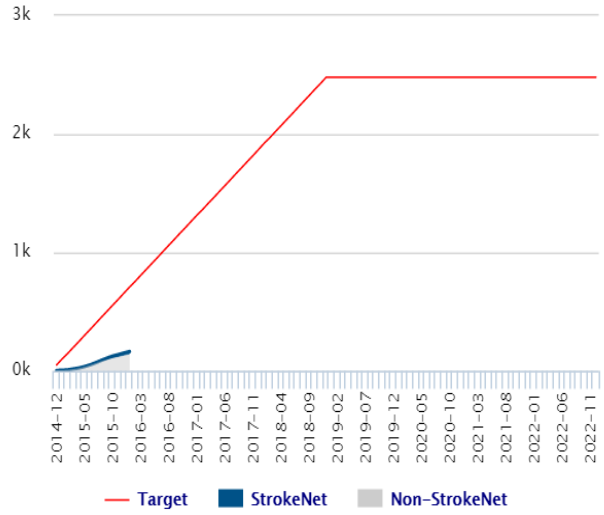
ATACH2 (Terminated)

Current = 1,001, Sample Size =1,280
Completed =78.2%
StrokeNet =135 (13.49%)



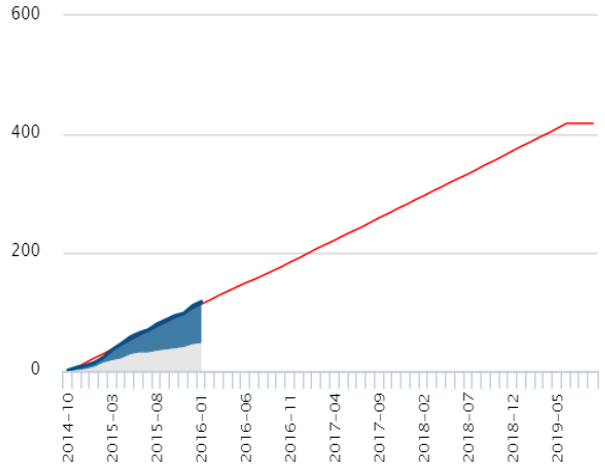
CREST2

Current = 163, Sample Size =2,480
Completed =6.6%
StrokeNet =24 (14.72%)



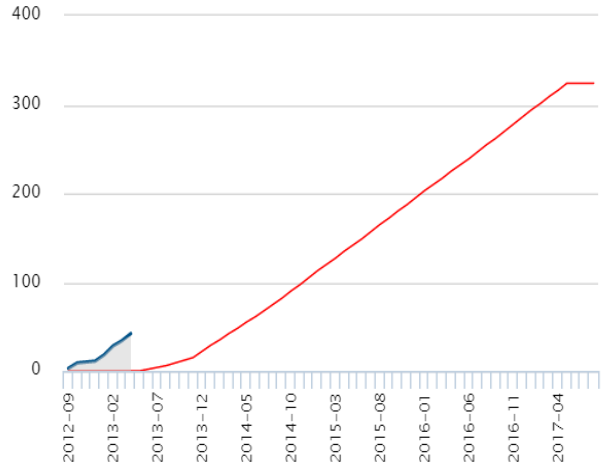
iDEF

Current = 117, Sample Size =418
Completed =28.0%
StrokeNet =70 (59.83%)



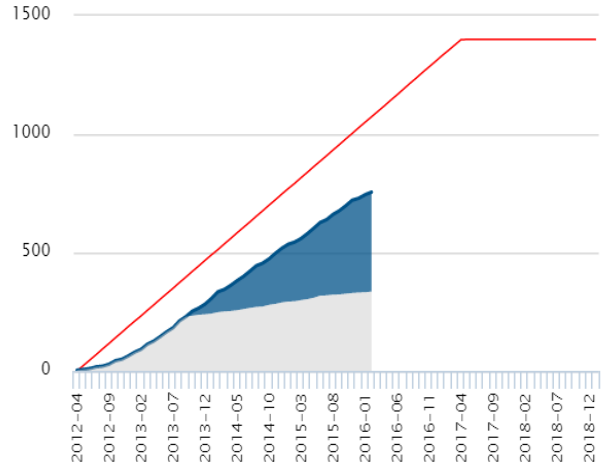
HiDEF (Terminated)

Current = 42, Sample Size =324
Completed =13.0%
StrokeNet =2 (4.76%)



SHINE

Current = 755, Sample Size =1,400
Completed =53.9%
StrokeNet =420 (55.63%)



C. RCC Project Operation Summary

Enrollment Retention

RCC	Enrolled	Not Retained	%
1 Ohio State	69	0	100
2 Case Western	57	0	100
3 UTHSC Houston	44	0	100
4 MUSC	43	0	100
5 UCSD	30	0	100
6 Vanderbilt	9	0	100
7 Mount Sinai	4	0	100
8 U Miami	1	0	100
9 Stanford	129	2	98.4
10 U Michigan	62	1	98.4
11 Emory	117	2	98.3
12 UCLA	40	1	97.5
13 Columbia	186	5	97.3
14 Mass General	69	3	95.7
15 U Washington	23	1	95.7
16 U Minnesota	68	3	95.6
17 UCSF	41	2	95.1
18 U Penn	116	6	94.8
19 U Wisconsin	16	1	93.8
20 U Cincinnati	59	5	91.5
21 U Pitt	48	5	89.6
22 Northwestern	38	4	89.5
23 U Utah	10	2	80
24 U Iowa	2	1	50

Regulatory Document Collection

RCC	Collected	Required	Outstanding	%
1 U Utah	229	116	0	100
2 U Cincinnati	4388	3211	18	99.6
3 U Michigan	4002	2244	26	99.4
4 U Minnesota	3913	1410	28	99.3
5 U Penn	4093	1368	47	98.9
6 Emory	2737	974	30	98.9
7 MUSC	1304	430	15	98.9
8 UCLA	1935	882	24	98.8
9 U Miami	165	119	2	98.8
10 Columbia	4037	1544	77	98.1
11 Vanderbilt	511	155	13	97.5
12 U Iowa	470	309	12	97.5
13 UCSF	1767	764	51	97.2
14 Mass General	4999	1865	148	97.1
15 Northwestern	879	428	28	96.9
16 Ohio State	2951	1110	98	96.8
17 U Wisconsin	537	223	18	96.8
18 Stanford	2686	1216	98	96.5
19 UCSD	918	349	49	94.9
20 U Washington	529	325	29	94.8
21 Case Western	1508	694	89	94.4
22 U Pitt	2281	1232	155	93.6
23 UTHSC Houston	1116	425	76	93.6
24 Mount Sinai	729	439	76	90.6

Case Report Form Collection

RCC	Submitted	Outstanding	%
1 U Wisconsin	429	0	100
2 Mount Sinai	108	0	100
3 U Miami	47	0	100
4 U Minnesota	1983	8	99.6
5 UCSF	1688	8	99.5
6 UCLA	1084	5	99.5
7 Northwestern	964	6	99.4
8 U Cincinnati	1518	12	99.2
9 Stanford	4284	43	99
10 U Michigan	1686	18	98.9
11 Case Western	1638	18	98.9
12 U Iowa	93	1	98.9
13 UCSD	791	13	98.4
14 UTHSC Houston	1317	24	98.2
15 U Pitt	1356	26	98.1
16 U Penn	3232	71	97.9
17 Ohio State	2100	45	97.9
18 Columbia	5407	122	97.8
19 Emory	3389	75	97.8
20 Mass General	2084	49	97.7
21 U Washington	838	25	97.1
22 U Utah	301	10	96.8
23 MUSC	1216	51	96
24 Vanderbilt	222	14	94.1

D. New Project Development Progress (Partial Test Data)

Type	Project	NINDS Grant Submission					Project Initiation			
		Concept Synopsis Approved by NINDS ESC	Feasibility Assessment	Grant Submit to NINDS	Scientific Peer Review	Awarded	Protocol Submit to CIRB	CIRB Approval	First Site Released	First Subject Enrolled
	Summary		Min=-6 Max=89 Med=22	Min=30 Max=106 Med=54	Min=92 Max=162 Med=147	Med=97	Med=1	Med=15		
Acute	DEFUSE 3	5/7/2014	-6 1/26/2015	31 58	162 11/10/2014 92	97	1	15 10/16/2015		
Acute	ICTUS 3	6/4/2014	89	30	155 3/5/2015					
Acute	MOST	8/13/2014	-1	50 7/5/2015	155 3/5/2015 131 11/13/2015					
Acute	IMPACT	6/2/2015	20	106	147 3/1/2016					
Acute	PreLIMBS	7/23/2015	21	54	147 3/1/2016					
Prevention	PICASSO	10/16/2014	55	53	144 6/25/2015					
Prevention	ARCADIA	3/6/2015	21 1/27/2016	80	150 11/12/2015					
Prevention	ARREST	11/3/2015	22 11/25/2015							
Prevention	SleepSMART	11/3/2015	22 11/25/2015							
Prevention	SATURN	2/3/2016								
Recovery	RISiS	12/15/2015	45 1/29/2016							

Active Inactive Awarded

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CREST-2 and StrokeNet Site Enrollment

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CREST-2 and StrokeNet Enrollment

- Total Enrollment = 181
- StrokeNet enrollment = 28

CREST-2 and StrokeNet Enrollment

- With 120 centers, CREST-2 needs to enroll only 6 patients per site per year to exceed target enrollment target.

- Current StrokeNet enrollment rate = 1.2

StrokeNet Enrollment

- 35 CREST-2 StrokeNet Sites have been approved to move forward with IRB
- 25/35 have received green-light letters and are enrolling
- 16/25 have not enrolled a patient (the average number of months these sites have been enrolling = 4 months)

10 StrokeNet Sites have enrolled

Site	Principal Investigator	# of Patients Enrolled
UPMC Presbyterian, Pittsburgh, PA	Lawrence Wechsler, MD	7
Columbia University Medical Center, New York, NY	Randolph Marshall, MD	5
Massachusetts General Hospital, Boston, MA	Scott Silverman, MD	4
Emory University Hospital, Atlanta, GA	Ravi Veeraswamy, MD	3
Kaiser Permanente, San Diego, CA	Robert J. Hye, MD	2
University of Utah Hospitals & Clinics, Salt Lake City, UT	Jennifer Majersik, MD	2
Tulane University, New Orleans, LA	Albert Sam II, MD	2
University of California, Los Angeles, CA	Wesley S. Moore, MD	1
Keck Medical Center of the University of Southern California, Los Angeles, CA	Fred Weaver, MD	1
University Hospitals Case Western Medical Center, Cleveland, OH	Vikram Kashyap, MD.	1

Action Items from YOU

Selected Ideas

1. Find a method for your StrokeNet site to determine carotid volumes:
   - patients with asymptomatic stenosis
   - treating MDs
   - referring MDs (e.g. Illuminate in place at Mayo)
2. C2 PI calls RCC PI monthly for 2 months, then quarterly.
3. C2 Director for Recruitment calls the StrokeNet RCC operations lead monthly for 2 months and then quarterly.
3. C2 notifies StrokeNet RCC PI and RCC operations lead coordinator for every CREST-2 enrollment by site.
4. Provide RCCs an additional $500 per CREST-2 patient enrolled for extra work involved.

CREST-2 Registry

- CMS reimburses and will go through 2022 at least
- Symptomatic patients
  - conventional risk and high risk
- Asymptomatic patients
  - Includes CREST-2 eligible ≤ 1:1
    per institution, not per interventionist
- 76 sites enrolling
- 75 interventionists approved, 65 pending
- 545 patients
  - 57% through Society of Vascular Surgery registry
  - 43% through American College of Cardiology registry

Lessons Learned

Donald Heck, MD
CREST-2 Site PI
Novant Health
Winston-Salem, NC

"…CREST-2 is an easy trial for me to recommend to our patients. I emphasize the fact that there is no "placebo" arm of the trial. All patients in the trial receive state of the art medical care, and that is likely to make patients in the trial healthier than they might otherwise be."

Enrollment Tools in Progress

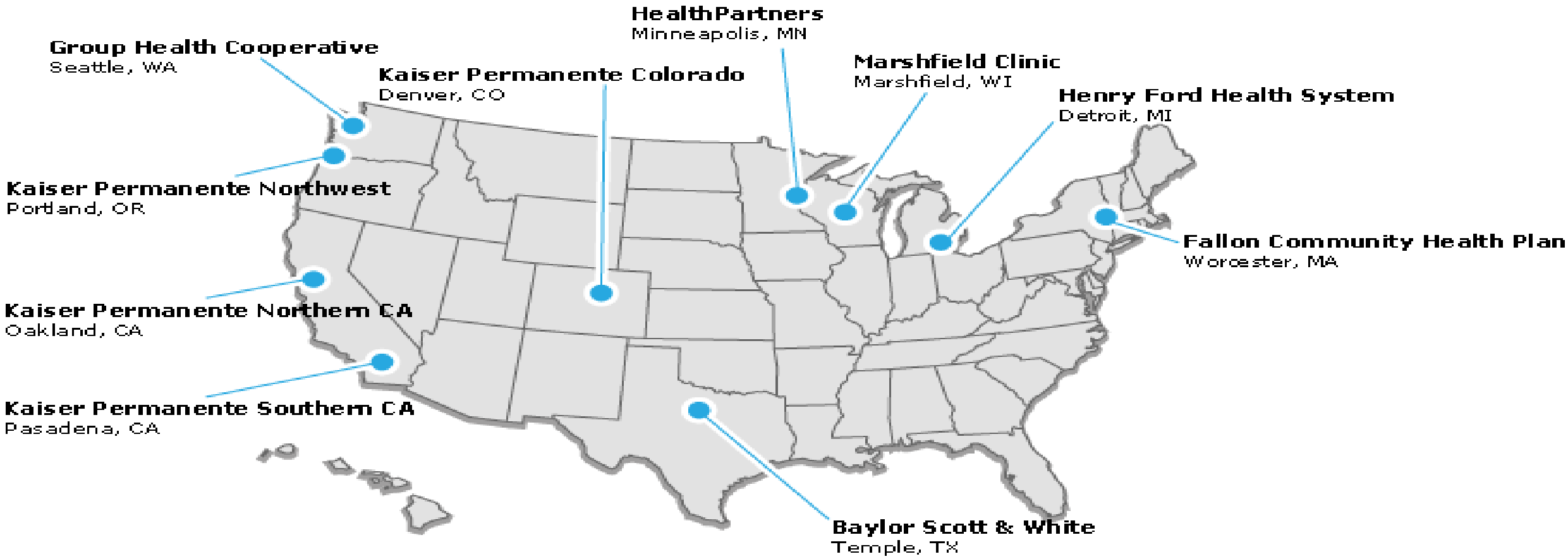
- Social Media
  - CREST-2 Website
  - Twitter Account
- Illuminate
- ResearchMatch Volunteer Database
- NCATS

Ideas to Enhance Enrollment

David C. Goff, Jr, MD, PhD
Dean and Professor

Colorado School of Public Health
Aurora, Colorado

Cardiovascular Research Network Centers



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Clinical Trial Recruitment

National Center for Advancing Translational Sciences

NCATS hubs are forming a national network to overcome barriers to participant recruitment for clinical trials.

Michael V. Homer, M.D., examines clinical trial participant

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Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke

Steven C. Cramer, MD

Professor, Depts. Neurology, Anatomy & Neurobiology, and PM&R
Clinical Director, Sue & Bill Gross Stem Cell Research Center
Associate Director, Institute for Clinical & Translational Science

University of California, Irvine

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Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke

- Greater rehabilitation therapy = better outcomes
- Most patients do not receive higher doses, due to
  - Low compliance
  - Low access
  - High cost
- Advances in telemedicine suggest capacity to provide larger therapy doses, individualized, cost-efficient
- Telehealth is a tool that enables therapists, RNs, and MDs—does not replace them.

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Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke

- 124 subjects with arm motor deficits 4-20 weeks after ischemic stroke, randomized to intensive arm motor therapy (a) traditional in-clinic vs.

  (b) in-home telerehabilitation

- 36 sessions (18 supervised + 18 unsupervised), 80 min each, over 6 weeks; intensity, duration, and frequency matched across groups

- Assessor-blind, randomized, non-inferiority design

clinicaltrials.gov NCT02360488

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Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke

- Primary endpoint: change in arm motor status (Fugl-Meyer scale) to 30 days post-therapy

- Arm movement the focus here because it is
  - central to human function

clinicaltrials.gov NCT02360488

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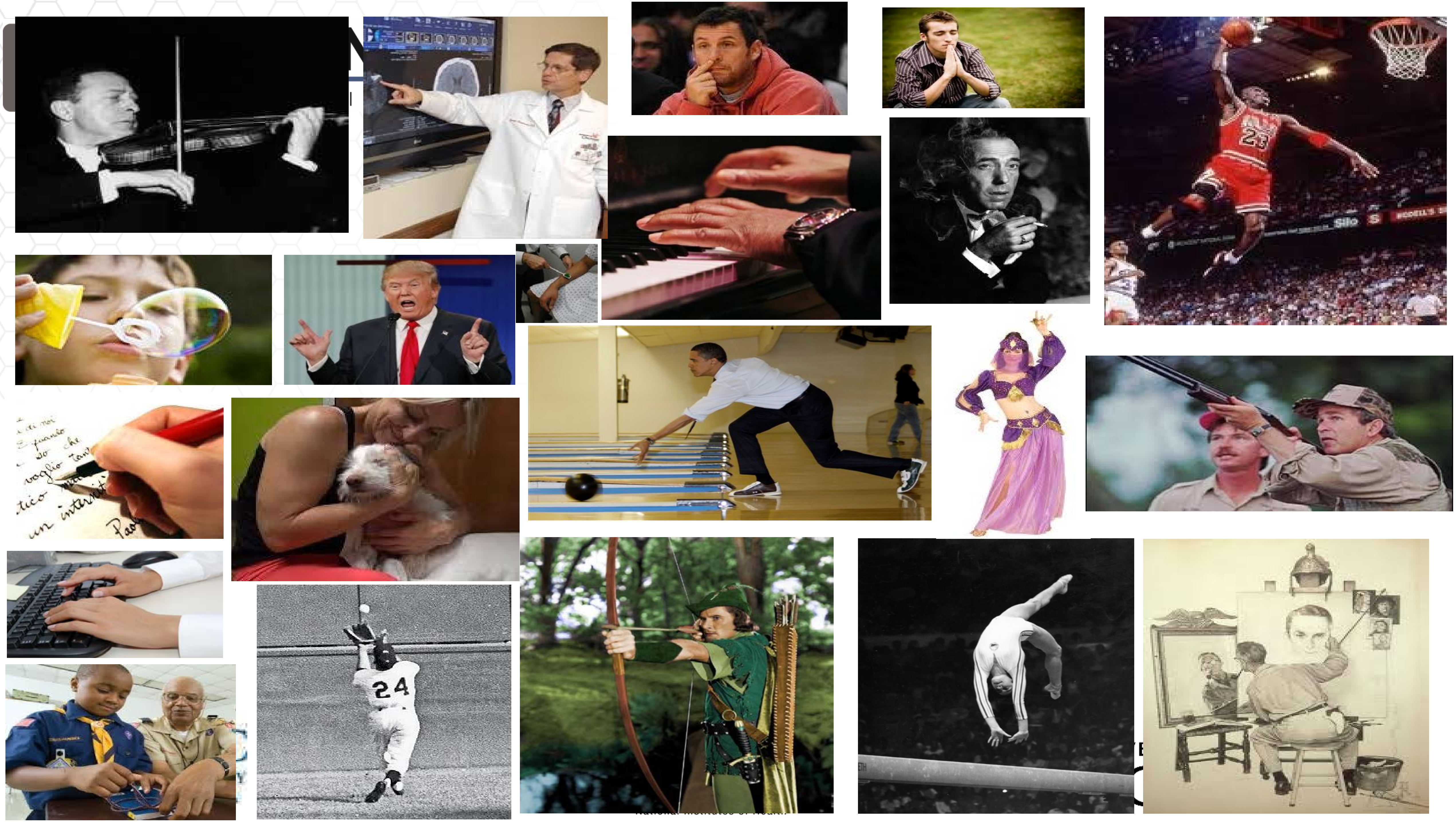
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Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke

- Primary endpoint: change in arm motor status (Fugl-Meyer scale) to 30 days post-therapy

- Arm movement the focus here because it is
  - central to human function
  - commonly affected after stroke
  - strongly linked to disability level and to well-being after stroke

clinicaltrials.gov NCT02360488

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Main Study Aims

- **Aim 1**. Subjects randomized to receive telerehabilitation will show arm motor gains that are not inferior to subjects treated in-clinic.

- **Aim 2**. Targeted education for 6 weeks will significantly increase patient knowledge related to stroke prevention and stroke risk factor control.

- **Aim 3**. Subjects in the telerehabilitation arm will show comparable or better
  - compliance with therapy and
  - activity-inherent motivation, which reflects how much a patient enjoys a therapy.

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Telerehabilitation: assess, treat, monitor

Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke

Parent RCC	Study Site
Los Angeles Southern California	University of California, Irvine
Northwest Stroke Trials Network	Harborview Medical Center
Chicago Stroke Trials Consortium	Rehabilitation Institute of Chicago
Cleveland Regional Coordinating Center	MetroHealth Rehabilitation Institute of Ohio
Georgia StrokeNet	Emory Rehabilitation Hospital
South Carolina Collaborative Alliance for Stroke Trials	MUSC Center for Rehabilitation Research in Neurological Conditions
Stroke Trials Network of Columbia and Cornell	Burke Rehabilitation Hospital
New England Regional Coordinating Center	Spaulding Rehabilitation Hospital

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Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke

- **Start Date**: Sept 2015
- **Estimated Complete Date**: April 2017
- **# enrollment sites**: 8
- **# patients screened and rejected**: 7
- **# patients enrolled**: 9 (across 6 of the sites)

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Why the slow start to enrollment?

- Startup issues common with any new technology.
- December recruitment tough given demands protocol makes on enrollees: 4 assessment + 18 supervised treatment sessions over 6 weeks.
- Variability in stroke research across cultures

  (acute vs. subacute vs. chronic)
- Variability in stroke research practice across sites

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Telerehabilitation in the Home versus Therapy In-Clinic for Patients with Stroke:
An assessor-blind, randomized, non-inferiority trial

Survey to understand each site's recruitment practices

1) *From where does your site identify potential enrollees?*

	ER	ICU	Acute Stroke Unit	Acute Rehab Unit	Stroke Outpatient	Outpatient Rehab	Other Outpatient	Other
Burke				X	X			
Emory				X	X	X		
Harborview	X	X	X	X	X	X	X: OT	
Metrohealth[1]				X	X			X
MUSC[2]		X	X	X	X			X
RIC	X	X	X	X	X	X		
Spaulding				X	X	X		
UCI[3]	X	X	X	X	X	X		

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Burke				X	X			
Emory				X	X	X		
Harborview	X	X	X	X	X	X	X: OT	
Metrohealth[1]				X	X			X
MUSC[2]		X	X	X	X			X
RIC	X	X	X	X	X	X		
Spaulding				X	X	X		
UCI[3]	X	X	X	X	X	X		

Potential for consistent and in some cases increased RCC role for subject recruitment into the Telerehab trial

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Burke				X	X			
Emory				X	X	X		
Harborview	X	X	X	X	X	X	X: OT	
Metrohealth[1]				X	X			X
MUSC[2]		X	X	X	X			X
RIC	X	X	X	X	X	X		
Spaulding				X	X	X		
UCI[3]	X	X	X	X	X	X		

Potential for consistent and in some cases increased RCC role for subject recruitment into the Telerehab trial and
into forthcoming StrokeNet Recovery & Rehabilitation trials

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DEFUSE 3

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DEFUSE 3: Hypothesis

Stroke patients with MCA or ICA occlusion and *salvageable tissue* identified by CT/MR benefit from endovascular therapy in the 6-16 hour time-window

DEFUSE 3: Study Design

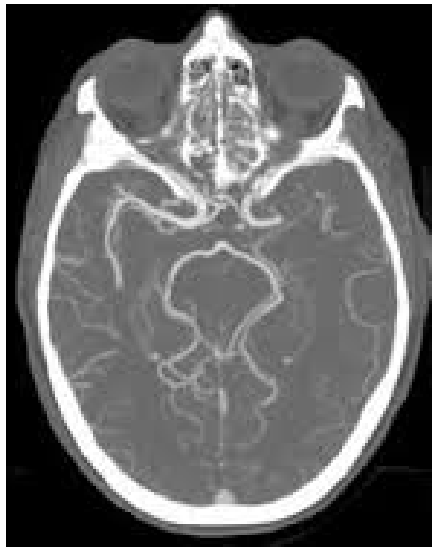
- Prospective, Randomized, Open-treatment, Blinded Endpoint, Adaptive trial
- Maximum sample 476 patients at 45 sites *(Each site expected to enroll at least 10 patients)*
- 1:1 randomization: endovascular vs. medical therapy

Clinical Inclusion Criteria

- Signs and symptoms consistent with an acute anterior circulation stroke
- Age 18-90 years
- Baseline NIHSSS ≥ 6 immediately prior to randomization
- Endovascular treatment (femoral puncture) between 6-16 hours of stroke onset (onset is defined as time last known well)
- Pre-stroke mRS score 0-2 (= functionally fully independent for all ADLs)
- Patient or Legally Authorized Representative has signed Informed Consent

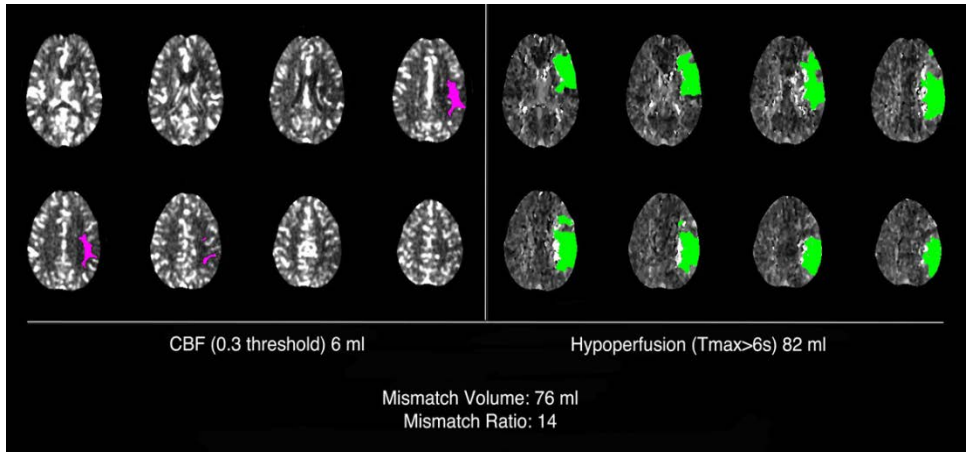
Neuroimaging Inclusion Criteria

1) MRA / CTA demonstrates
   - M1 segment MCA occlusion, or
   - ICA occlusion (cervical or intracranial; with or without tandem MCA lesions)



AND

2) Target Mismatch Profile on CT perfusion or MRI (RAPID)
   - Ischemic core < 70 mL
   - Mismatch ratio ≥ 1.8
   - Mismatch ≥ 15 mL



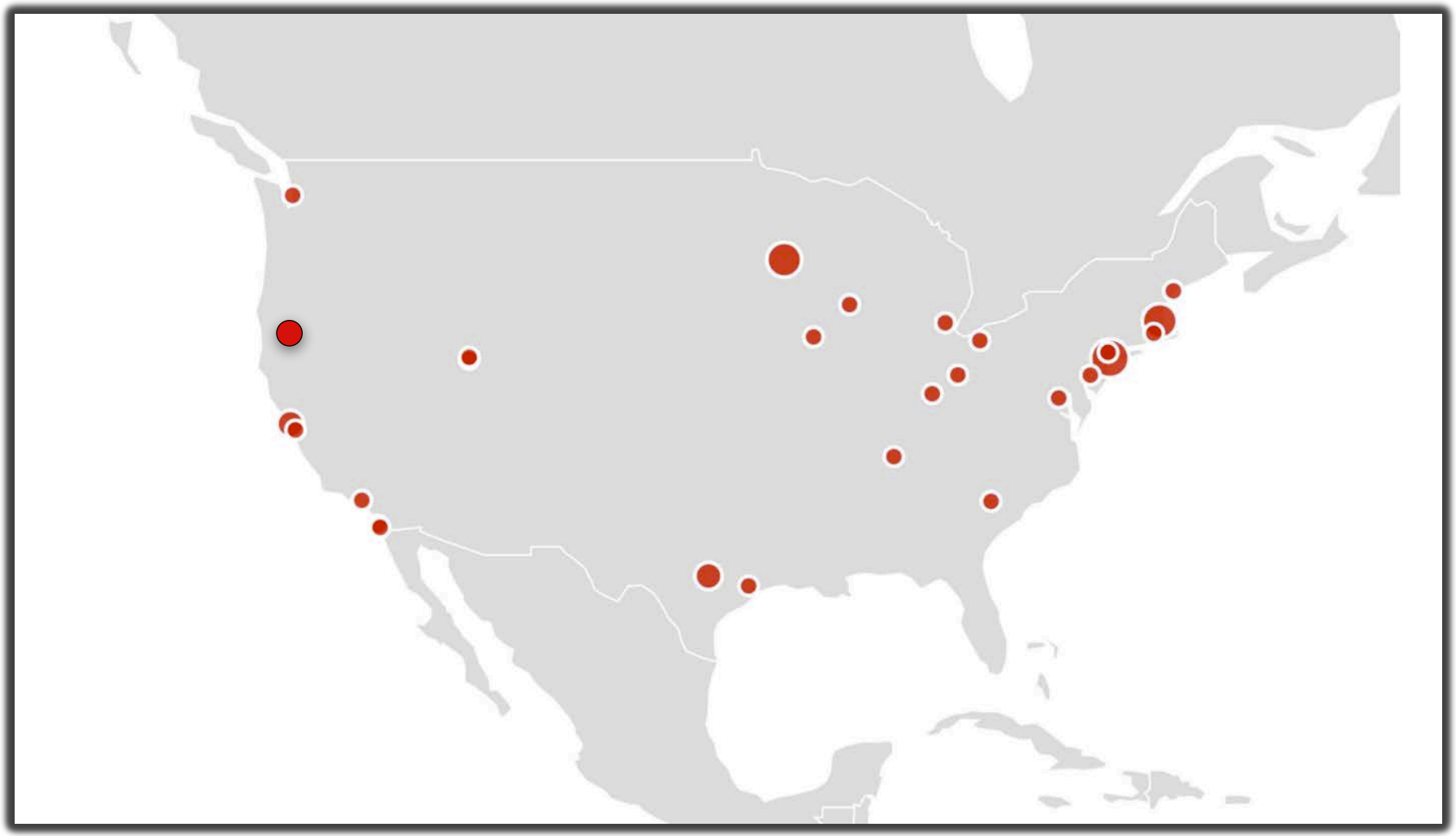
DEFUSE 3 Roadmap

- StrokeNet feasibility and approvals
- FDA IDE approval (required for NIH submission)
- NIH submission / review / council / funding
- StrokeNet working groups provide final input on protocol
- DEFUSE 3 Exec Committee finalize protocol
- Final Protocol approved by FDA
- Central IRB approval
- CMS payment approval
- DSMB review and approval
- CRF development and approval
- Randomization algorithm validated
- WebDCU programed and tested
- Protocol Trial Agreements completed by NCC

DEFUSE 3 Site Activation

- RAPID license agreement
- RAPID IT approval
- RAPID installation
- DEFUSE 3 CT&MRI protocols installed / test cases approved
- Endovascular credentialing
- Site training (protocol / endovascular / imaging / technologists)
- Site local IRB review/modify of consent form
- Site approval of Protocol Trial Agreement
- Regulatory approvals at site
- Randomize 1st patient!!!!!

DEFUSE 3 Sites



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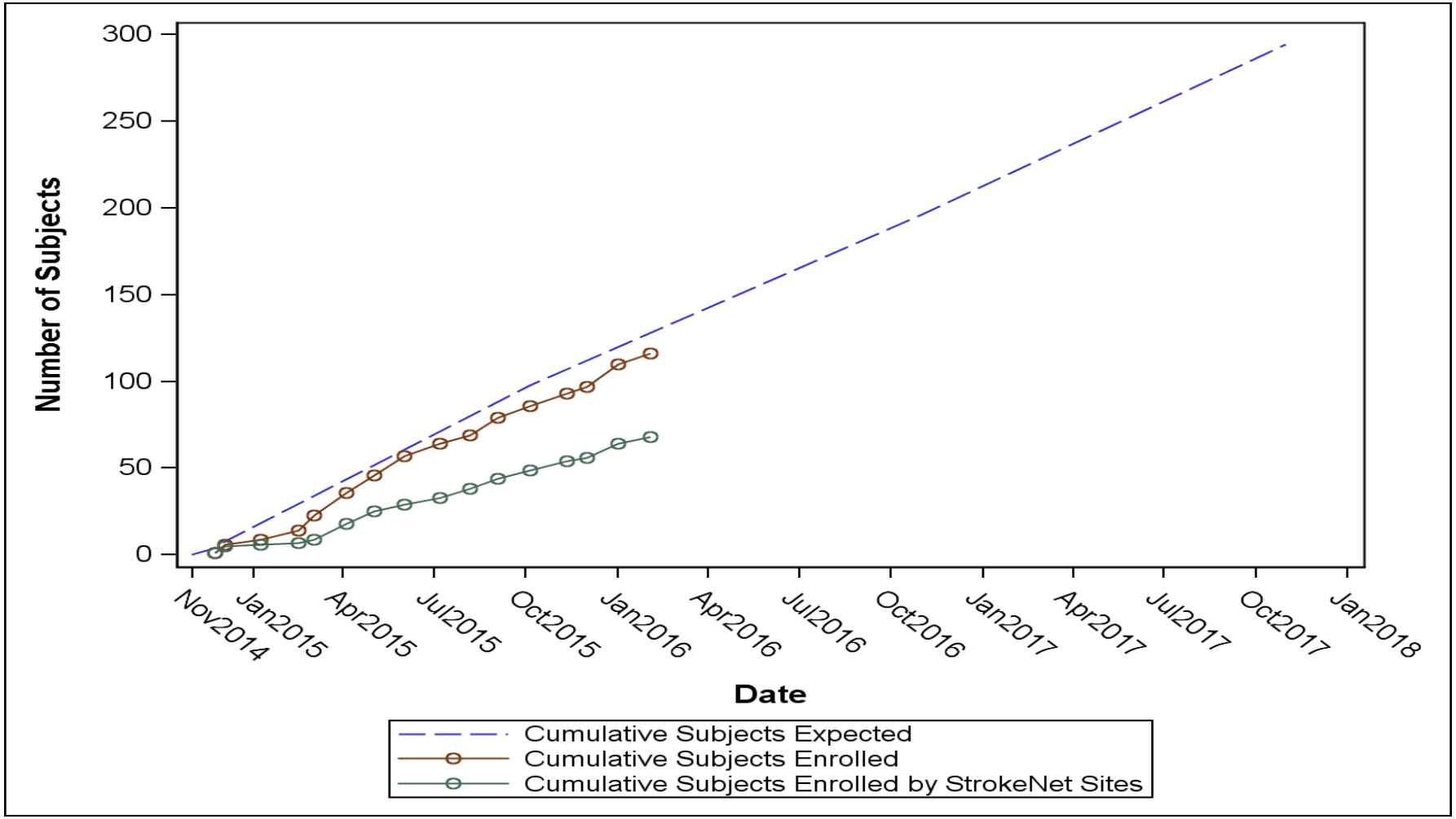
Screening Summary

		Subjects Screened	Subjects Randomized	
	Date Site Released to Enroll	N	N	%
All as of 11FEB2016		3558	116	3.3%
StrokeNet Sites		1573	68	4.3%
Baptist Hosp of Miami	04NOV2015	13	1	7.7%
Beth Israel Deaconess Med Ctr	06OCT2014	107	2	1.9%
Harborview Med Ctr	17NOV2014	224	5	2.2%
Hosp of the Univ of Pennsylvania	18NOV2014	82	6	7.3%
Jackson Memorial Hosp	10NOV2015	12	0	0.0%
MUSC	08SEP2015	5	1	20.0%
Massachusetts General Hosp	15DEC2014	87	0	0.0%
Mount Sinai Med Ctr	09SEP2015	12	0	0.0%
NYP Columbia Univ Med Ctr	06APR2015	50	4	8.0%
NYU Langone Med Ctr	26AUG2015	21	0	0.0%
Ohio State Univ Wexner Med Ctr	04DEC2014	124	1	0.8%
Oregon Health & Science Univ Hosp	04NOV2014	70	21	30.0%
Rush Univ Med Ctr	14JUL2015	156	0	0.0%
San Francisco Gen Hosp	04NOV2014	68	14	20.6%
Stanford Univ Med Ctr	08NOV2014	100	4	4.0%
Tufts Med Ctr	08DEC2014	70	0	0.0%
UH Case Med Ctr	01JUN2015	52	2	3.8%
UMASS Memorial Med Ctr	03DEC2014	164	6	3.7%
Univ of Iowa	04DEC2014	156	1	0.6%

Enrollment Summary



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MISTIE III

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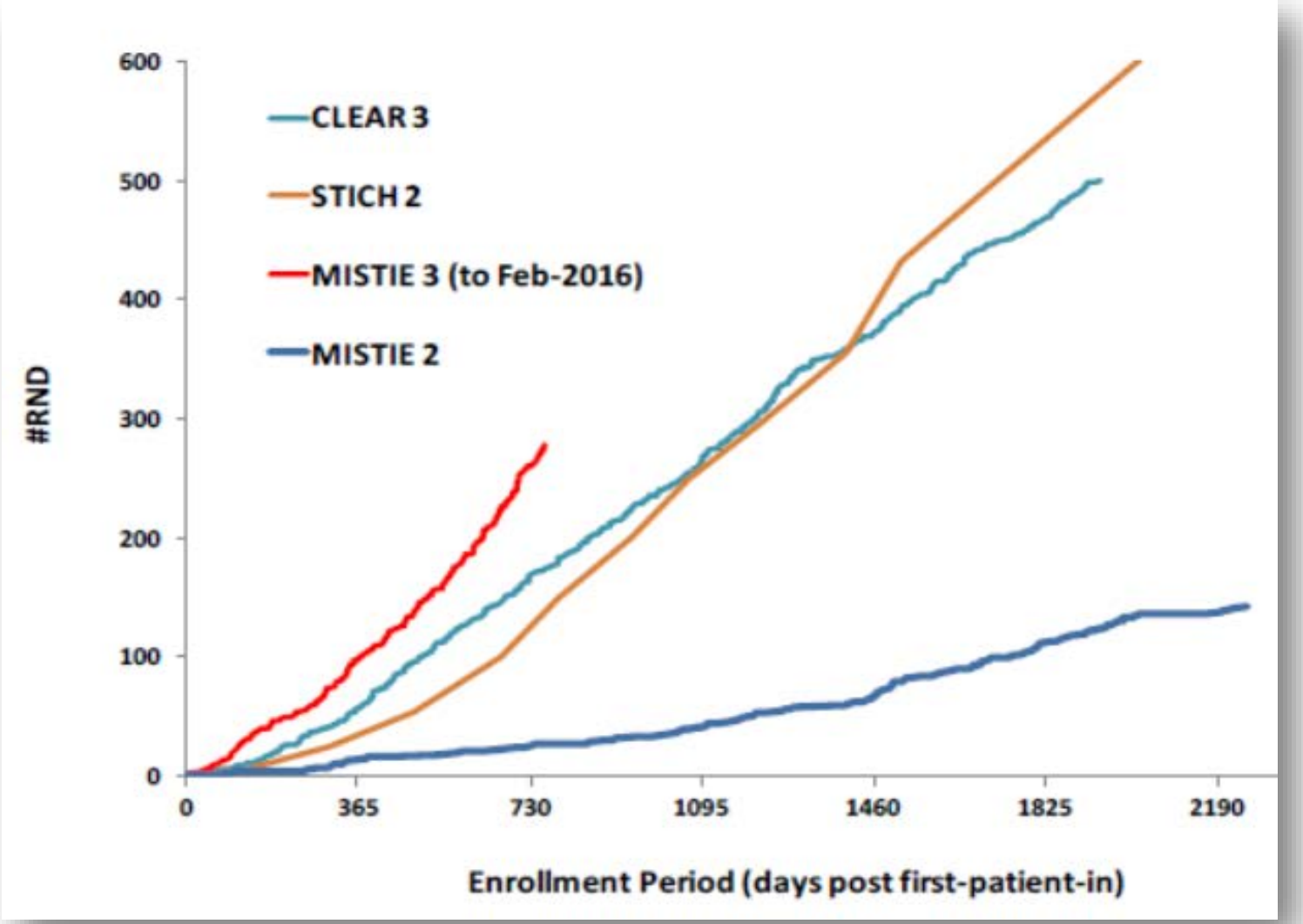
Recruitment

- 281 subjects enrolled
- Across 66 sites
  - 64 currently active
- In 9 countries:
  - US
  - Canada
  - Israel
  - UK
  - Germany
  - Hungary
  - Spain
  - Australia
  - China



Data as of February 9, 2016

Activated StrokeNet vs. All Non StrokeNet Sites

	Total Sites	% of Sites	% of Randomizations (n=281)
StrokeNet Hub	8	9%	12%
StrokeNet Spoke	20	22%	25%
Non StrokeNet	65	70%	63%
Total	93	100%	100%

*Includes sites on administrative hold and closed sites

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Trial Overview

- Enrollment is ongoing
- Monthly educational webinars
- Quarterly Seminars
  - Surgical Center Report
  - Safety Forum
  - Training Refresher
- DSMB: March 2016
- DSMB: Futility Analysis (n=375) Spring 2017

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StrokeNet Training Core Update

Dawn Kleindorfer, MD

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NIH StrokeNet Training Core Members

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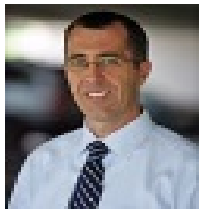
Chair

Dawn Kleindorfer, MD
University of Cincinnati

Co-Chair

Randolph Marshall, MD
Columbia University

NINDS Project Scientist



Scott Janis, PhD
NINDS

Faculty

Barbara Bregman, PT, PhD
Georgetown University

Faculty

David Liebeskind, MD.
University of California, Los Angeles

Faculty

David Tirschwell, MD
University of Washington

Coordinator

Susan Love, MA
University of Minnesota

Coordinator

Heena Olalde, RN, MSN
University of Iowa

Core Coordinator

Jeanne Sester
University of Cincinnati

Trainee 2015-2016

Mara Ayodele, MD
University of Miami

Trainee 2015-2016

Scott Mendelson, MD
Northwestern University

Trainee 2014-2015

Cemal Sozener, MD
University of Michigan

Trainee 2014-2015

Farhaan Vahidy, MD, PhD
University of Texas, Houston

Current 2015-2016 Trainees

- 26 trainees, 42% female (last year 24%)
  - 1 trainee dropped out due to medical illness
- 12% under-represented minority (1 hispanic, 2 black) last year was 0%
- 4/25 are faculty members
- Degrees
  - MD 15
  - MD/PhD 3
  - DO 2
  - PhD 3
  - PharmD 1
  - MD, JD 1
  - DPT 1

Disciplines of Trainees

• Vascular Neurology	13
• Vascular Intervention	1
• Rehabilitation/PM&R	2
• PT/rehab	1
• Neuroradiology	1
• Neurosurgery	2
• NSICU	1
• Neurology	2
• Emergency medicine	0
• Pharmacy	1
• Biomedical engineering	1
• Epidemiology	1

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Activities of the Training Core

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Didactic Webinars

- We have held 6 Stroke Net webinars so far this academic year
  - Always the 4th Thursday of the month at 4pm EST
  - Average attendance = **85 in 2015-16**! 82 in 2014-15, 75 in 2013-14
- 94% average of attendees felt the webinar to be useful to their academic practice
  - All webinars are archived on the StrokeNet website
  - All previous SPOTRIAS webinars are also online
    - Broader audience and inclusion of career development compared to SPOTRIAS

2015-16 Didactic Webinars

Date	Topic	Speaker	Institution	Moderator
July 30	Ethics in Acute Research and Emergency Medicine	Michelle Biros	UMinn	Liebeskind
Aug 27	BP and Cognition - Impact of Blood Pressure and Hypertension on Cognitive Function	Clinton Wright	Miami	Marshall
Sept 24	Consent in Clinical Trials Remote Enrollment by Telemedicine	Jennifer Majersik Teddy Wu	Utah Texas	Liebeskind
Oct 29	Treatment of Carotid Stenosis	Seemant Chaturvedi	Miami	Marshall
Nov 19	Rehab in Acute Stroke/Neuroplasticity	Lorie Richards	Utah	Marshall
Jan 28	Imaging Selection Approaches in Endovascular Trials	David Liebeskind	UCLA	Tirschwell
Feb 25	Brain Computer Interface for Rehab	Elliott Roth	Northwestern	Liebeskind
Mar 24	Gloves Off for Acute Stroke Management; Fellow Case Presentations to two Stroke Experts	Jay P Mohr TBD	Columbia	Kleindorfer
April 28	Neuroprotection – STAIR Criteria and the Future	Louise McCullough	Texas	Marshall
May 26	ICH Secondary Prevention	Magdy Selim	Beth Israel	Tirschwell

Professional Development Webinars

- Process: Topics and speakers suggested by members of the education core and end-of-the-year trainee survey
- Variable times and dates (by request of some RCCs)
- Topics and speakers voted upon during Training Core call

Professional Development Webinars 2015-16

Date	Topic	Speaker	Time	Institution	Moderator
July 27 Monday	Writing your CV & Biosketch (updated with new format)	Dawn Kleindorfer	4:00	Cincinnati	
Aug 20 Thursday	Approval Process for Medical Devices in Stroke	Wade Smith	2:00	UCSF	Tirschwell
Sept 30 Wednesday	How to Present your Data	Enrique Leira	3:00	Iowa	Kleindorfer
Oct 20 Tuesday	Creating a Study Budget	Joe Broderick Judy Spilker	1:30	Cincinnati	Kleindorfer
Nov 12 Thursday	Grant Writing	Steve Greenberg	1:00	MGH	Marshall
Jan 21 Thursday	Training Grants and Tips for Success from NINDS	Steven Korn	1:00	NINDS	Kleindorfer

Trainee Research Presentations

- 21 RCC Trainees submitted summary of their research (only 12 last yr)
  - Assigned 2+ faculty mentors to review their work for feedback
  - Training core members reviewed the applications and scored them
- 3 will present at ISC StrokeNet General Meeting
- 6 presented at a session prior to the StrokeNet meeting, with designated mentors present
  - Very engaged group, lots of great discussions
- 12 will present webinars monthly over the remainder of the year.
- List of trainee research presented at 2016 ISC at registration and via email
  - Includes this year and last year's trainees

Date	Title	Trainee	Time	University	Moderator
Jan 20 Wednesday	A Retrospective Cohort Study of the Relation of Primary Language to Thrombolytic Therapy in Patients with Acute Ischemic Stroke Modulating the Brain with Bihemispheric Transcranial Direct Current Stimulation and Constraint-Induced Movement Therapy to Enhance Stroke Motor Recovery	Natalie Cheng Pratik Chhatbar	4:00	UCSF MUSC	Tirschwell
Feb 29 Monday	Frequency of Microembolic Signals in Symptomatic Carotid Occlusion Compared to Carotid Stenosis Relationship Between Perfusion Imaging-Based Reperfusion and Clinical Variables in Acute Ischemic Stroke Patients Treated with Intraarterial Therapy	Ava Liberman Sun Kim	2:00	UPENN Stanford	Tirschwell
Mar 29 Tuesday	Modulating Cortical Excitability with Direct Electrical Stimulation Outcome Comparisons in Severe Cerebral Vasospasm in Aneurysmal Subarachnoid Hemorrhage Patients with Incomplete Neurological Exam	Jared Olson Joshua Lim	2:00	Washington Minnesota	Marshall
April 13 Wednesday	Race-Ethnic Disparities Among Intracerebral Hemorrhage (ICH) Patients in the Florida-Puerto Rico Collaboration to Reduce Stroke Disparities (FL-PR CReSD) Wallerian Degeneration in Ischemic Versus Hemorrhagic Stroke: A Neuroimaging Study TBA – Trainee Presentations	Maranatha Ayodele Muhammad Haque	1:00	Miami Texas	Vahidy
May 18 Wednesday	Noninvasive Brain Stimulation to Evaluate Neural Plasticity After Stroke Using Fresh Frozen Plasma, Vitamin K, and Platelets to Stop Intracranial Bleeding in Patients Presenting with Spontaneous & Traumatic Intracerebral Hemorrhage	Whitney Gray Peter Morone	2:00	Emory Vanderbilt	
May 23 Monday	Characterization of Mitochondrial Function in Peripheral Blood of Patients with Slow and Rapid Progression of Anterior Circulation Ischemic Strokes Shoulder-Hand Muscle Interactions Post Stroke	Marcelo Rocha Shashwati Geed	2:00	Pittsburgh MedStar	Liebeskind

Activities of the Training Core

- Supervision of the RCC Training Programs
  - Ensure that adequate focus on stroke research
  - Education plans with milestones for progress due prior to trainee arrival
    - All approved last year, with two requiring more information for the core's review
  - Mid-year progress reports- **not doing this year!**
  - Final Progress Report
    - Including information about their next position and success in research so far, contact information
  - Trainee survey regarding their experiences in the program

Activities of the Training Core

- Serve as a resource for trainees and mentors
  - Maintain contact info for current and past trainees- online
  - Post training opportunities, such as NINDS Clinical Trials Workshop
  - Job postings
  - Assist with finding mentors for trainees off-site
    - 3 requests this year: Shyam Prabhakaran and Susan Fagan, 1 request postponed d/t illness
    - Away rotations?

Last Year's Survey:
Suggestions for Improvement-Themes

- More ways for networking amongst trainees
  - Last night: an informal meeting of only trainees at a local hotel bar. XX were able to attend, many were not due to flight times.
    - Why not today? Rooms are tight and expensive, training core does not have a budget
    - (insert picture here)
  - New program for networking: "Slack", led by Cemal Sozener.

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StrokeNet Trainee Networking Platform

Cemal Sozener, MD

Education Core Committee Member

StrokeNet Trainee 2014-15

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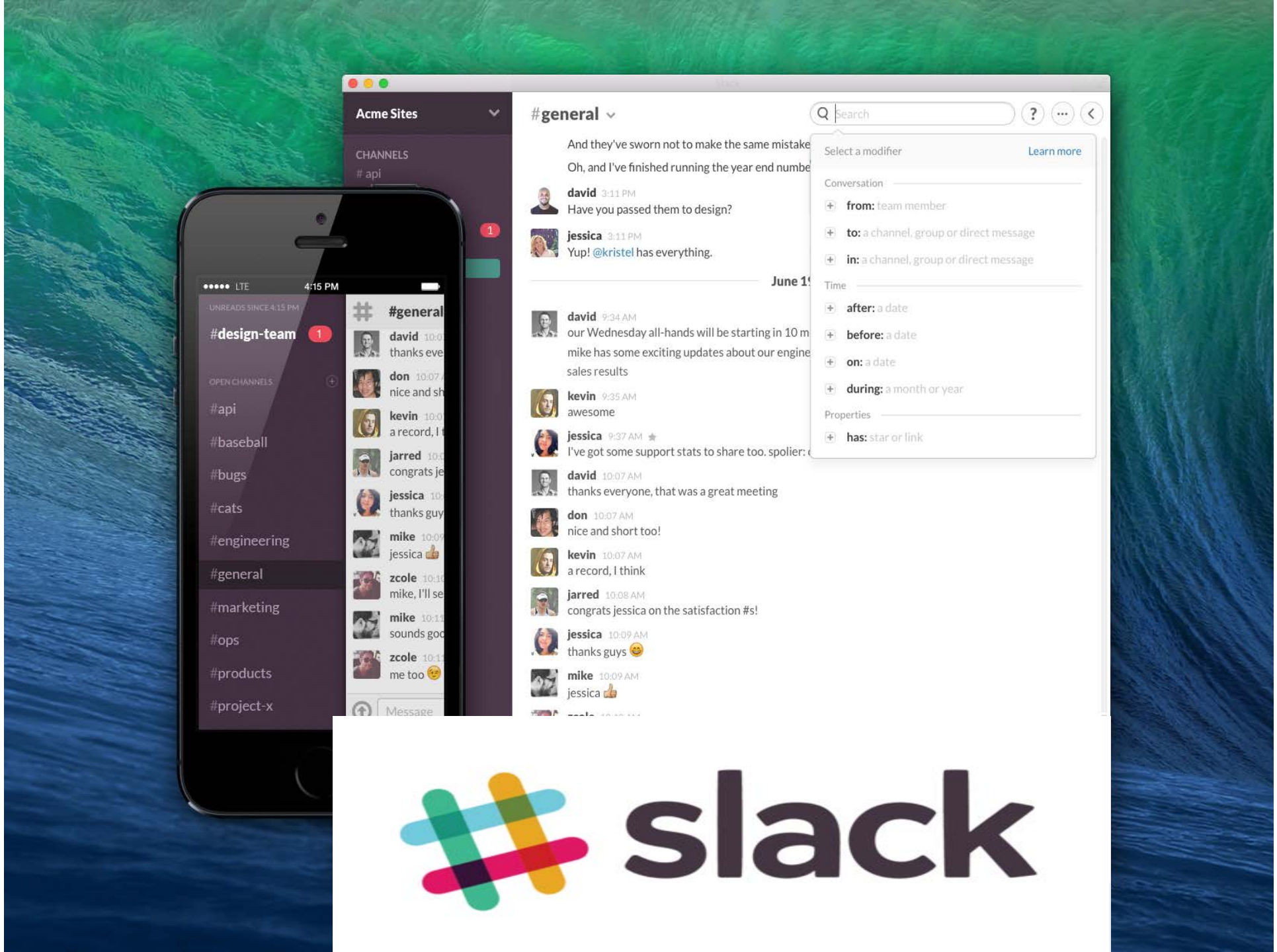
Goals

- Allow trainees to easily communicate and network with one another
- Be able to send messages to one trainee, all trainees or groups of trainees
- Get away from overused platforms such as email, listservs


Acme Sites
CHANNELS
api
#general
Search
Select a modifier
Learn more
Conversation
from: team member
to: a channel, group or direct message
in: a channel, group or direct message
Time
after: a date
before: a date
on: a date
during: a month or year
Properties
has: star or link
And they've sworn not to make the same mistake
Oh, and I've finished running the year end numbe
david 3:11 PM
Have you passed them to design?
jessica 3:11 PM
Yup! @kristel has everything.
david 9:34 AM
our Wednesday all-hands will be starting in 10 m
mike has some exciting updates about our engine
sales results
kevin 9:35 AM
awesome
jessica 9:37 AM
I've got some support stats to share too. spolier:
david 10:07 AM
thanks everyone, that was a great meeting
don 10:07 AM
nice and short too!
kevin 10:07 AM
a record, I think
jarred 10:08 AM
congrats jessica on the satisfaction #s!
jessica 10:09 AM
thanks guys
mike 10:09 AM
jessica
LTE
4:15 PM
UNREADS SINCE 4:15 PM
#design-team
OPEN CHANNELS
#api
#baseball
#bugs
#cats
#engineering
#general
#marketing
#ops
#products
#project-x
Message
slack

- Free team communication platform
- Seamless between laptop, desktop, tablet and smartphone
- Can organize public or private channels or direct message other members
- Drag and drop files for sharing
  - Even from cloud drives (Dropbox, Google Drive or Box)
- All messages and documents are archived and searchable

- Invitations coming out soon
- Fellows can easily network with other trainees from across the country
- Goal to build collaborations and encourage communication

Suggestions for Improvement-cont.

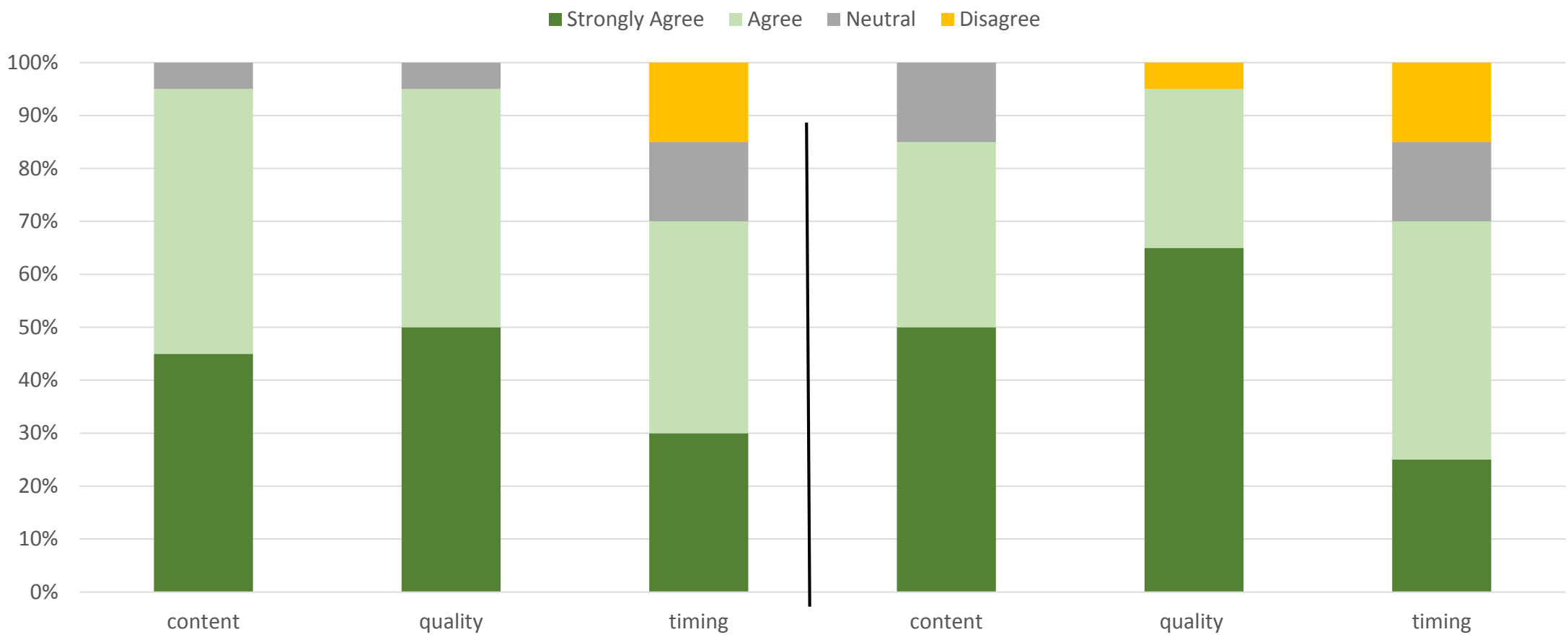
- Requests for more information earlier from the Training Core, more interaction with our members
  - ACTION PLAN: most of the trainees have had a brief time on **Training Core calls** to introduce themselves, meet the core, and describe their program and research interests
    - Positive feedback from trainees so far, feels more connected with the core, a chance to ask questions

Evaluation of The Program

- End of the year survey for 2014-15 Trainees

How satisfied are you?	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
My overall experience was good, and I believe it enhanced my stroke research career.	70%	30%			

Webinar Evaluations



Didactic

Professional

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Evaluation of Communication and Website

How satisfied are you?	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Communication					
The time to network and share ideas with peers was adequate.	30%	40%	20%	10%	
The communication you received from the training core was adequate.	50%	30%	20%		
Website					
Viewing webinars after the fact was easy.	50%	45%	5%		
The information provided online is sufficient.	55%	35%	10%		

Evaluation of Local RCC Mentorship

How satisfied are you?	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Mentorship					
The time you were able to spend with your mentor met your needs.	70%	30%			
The feedback you received from your mentor was adequate & helpful.	70%	25%	5%		
Did the mentor assigned develop into a relationship	80%	15%	5%		

Open-ended comments from trainees

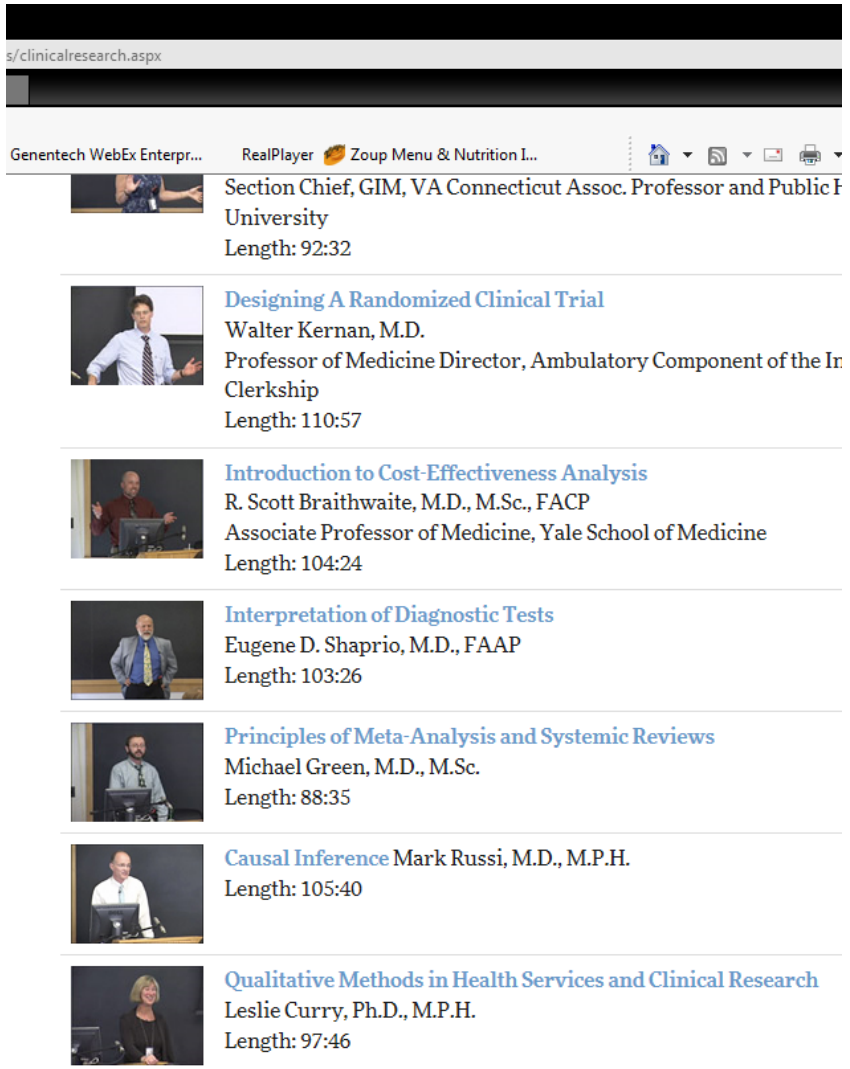
- “This program was outstanding and instrumental in setting up my research career. Without this opportunity, I would never have been able to achieve the progress I made over the last year and would have had marked difficulty guiding my career into one with a heavy emphasis on clinical trial design and execution like I wanted.”

- “Highly qualified and renowned professionals from the highest accredited centers in the U.S. are available to fellows, either in the form of formal mentors or just providing input on your work in the different meetings throughout the year. Wide variety of topics in the webinars. Fellows and mentors with varied backgrounds. Room for research in many different aspects of stroke.”

- “This was an outstanding experience. My sincere thanks to StrokeNet for allowing me to gain content expertise in stroke at the same time as being able to mold my research career in a protected environment.”

Other Future Projects

- Stroke Research Core Curriculum-First approach: online biostatistical core curriculum for stroke researchers



Other Future Projects

- Further encourage cross-center mentorship and interaction

- Improve Trainee Webinar Presentation Interactions
  - Dead silence after the trainee finishes….moderator usually is the only one asking questions

Future of Training Core

- Need volunteers for new Training Core membership

- Under-represented minority trainees: opportunity for an extra year of training at your institution (via UC's T32 program)
  - If interested talk to me offline

Metrics for Measuring Success of Training Core

- Webinar Attendance and Attendee Surveys
- Research Presentations by Trainees
- Final Trainee Survey
- Trainees themselves!
  - Publications (working on this, huge task…)
  - Future participation in research
    - Academic institutions
    - Participation in clinical trials/clinical research
      - 24/25 of 2014-15 trainees reported their next position was in academia and will be “significantly involved” in research
    - Writing/receiving grants

Training Plan for 2016-17: DUE May 2nd!

- Name of the trainee, discipline, and CV. Contact info, if you haven't submitted this already.
- Rotation schedule
  - strongly suggest that the year be 50% dedicated to research or more.
  - Please list in a way that we can understand how much time is protected
- Planned didactic coursework and other research training
- Research interests and mentor, if known.
- Any requests for off-site mentors and/or rotations.
- Email to Jeanne Sester

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Fellow Presentations

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Evaluation of capillary transit time distribution as a biomarker for endothelial dysfunction in acute ischemic stroke

NIH StrokeNet Meeting

February 15th 2016

Arne Lauer, MD
NIH StrokeNet Trainee
Massachusetts General Hospital
New England Regional Coordinating Center (NERCC)

Outline

- Capillary Transit Time Distribution

- Methods

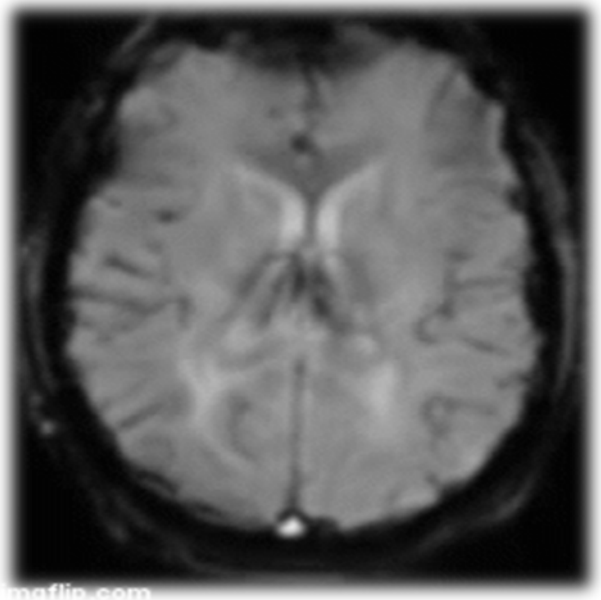
- Imaging cohort

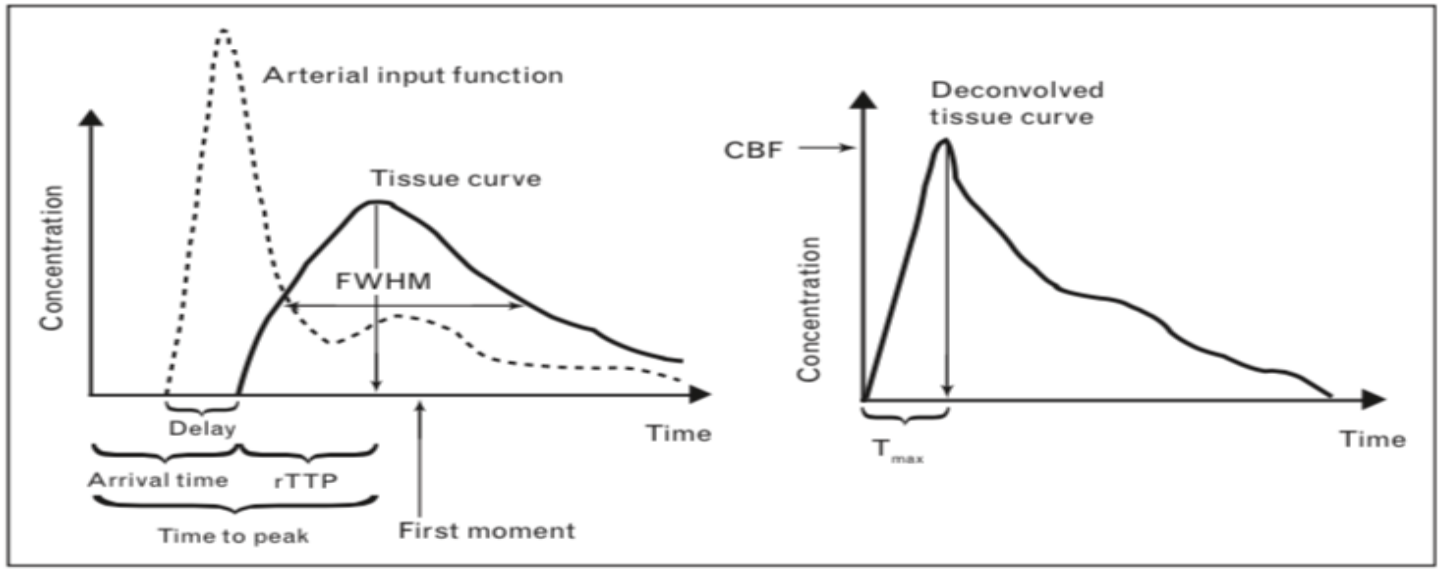
- Preliminary results

- Project aims

- Future directions

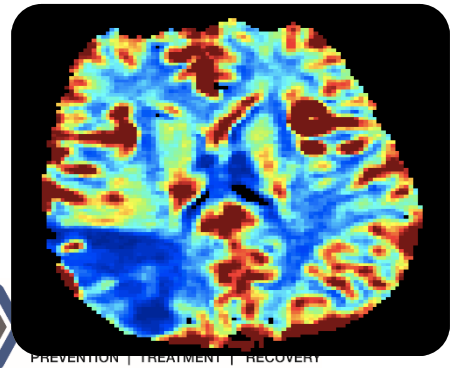
Estimation of Cerebral Perfusion and Perfusion Imaging



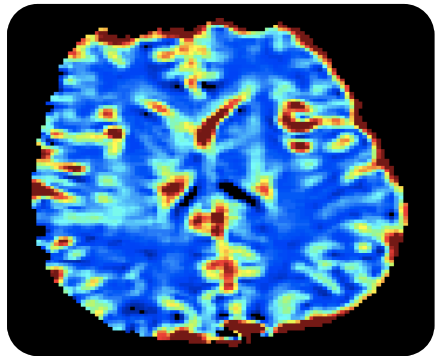


CBF = CBV / MTT

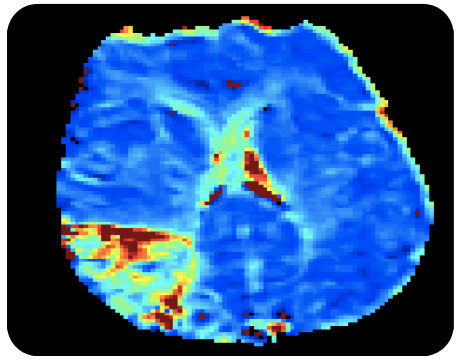
CBF

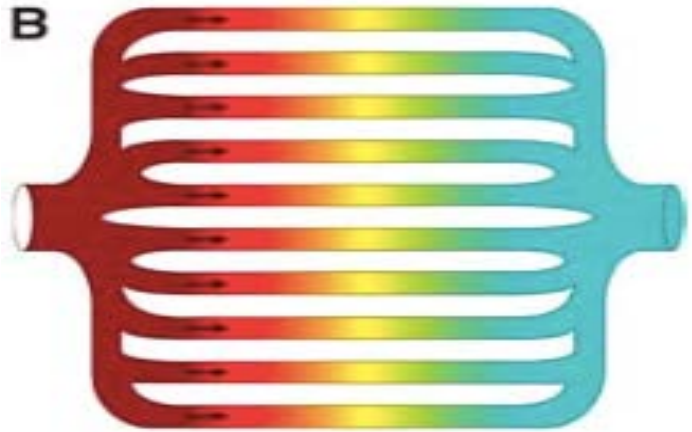


CBV



MTT





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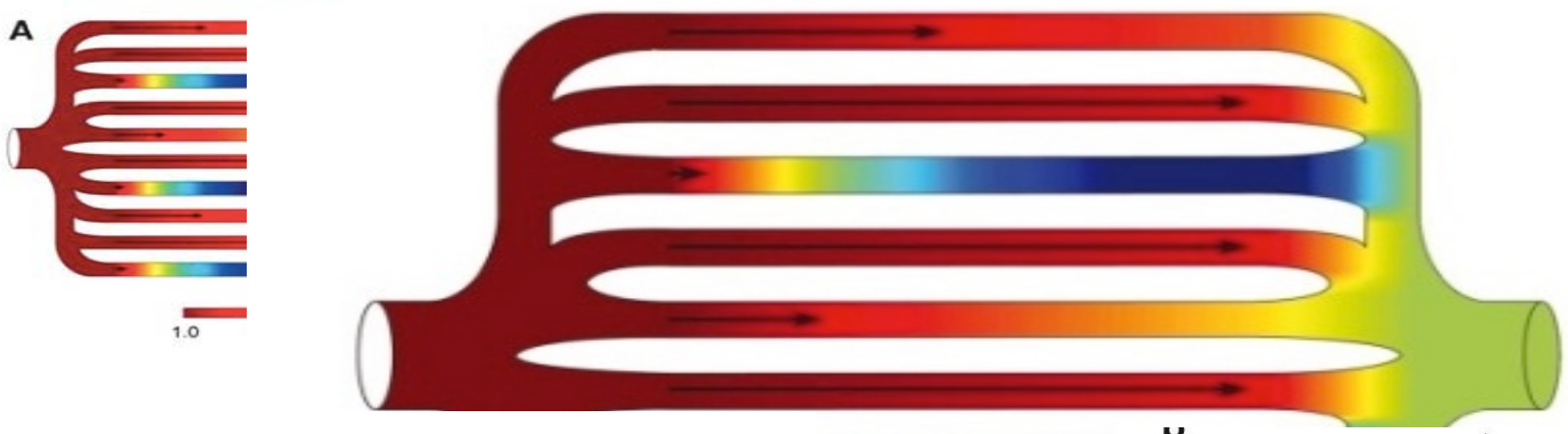
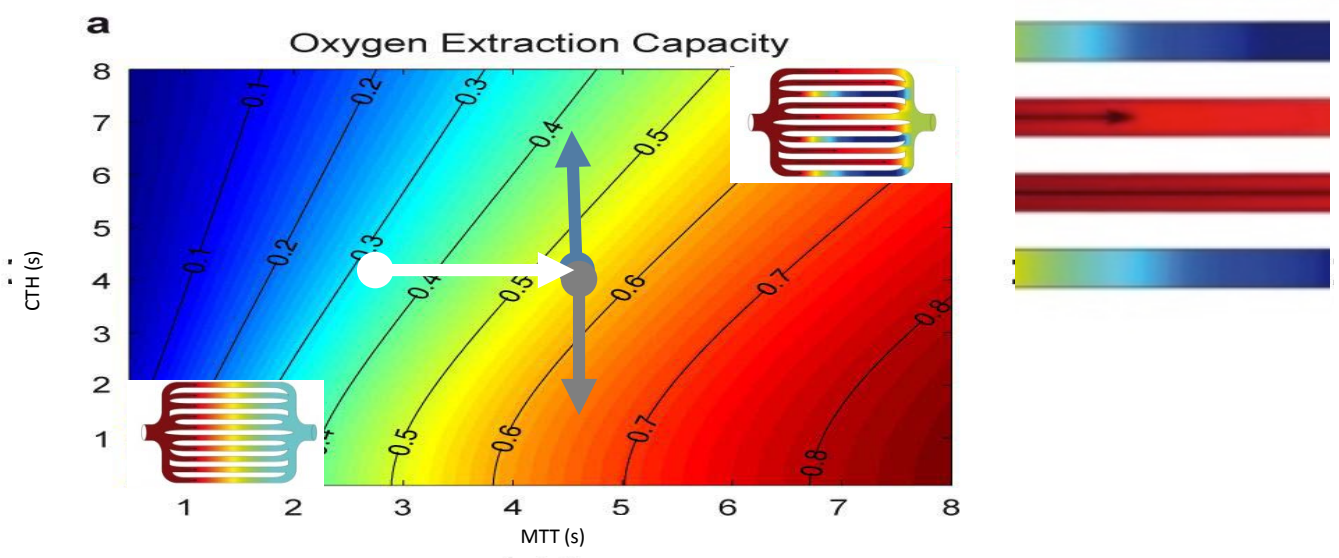
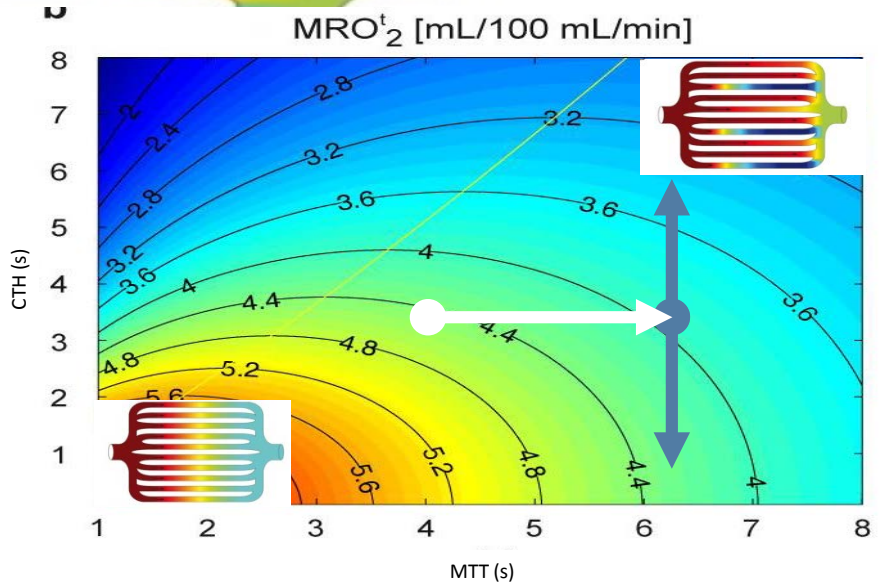
Capillary Flow Pattern determine Oxygen Extraction Capacity

Flow Homogenization:

Increase of flow: CBF ↑

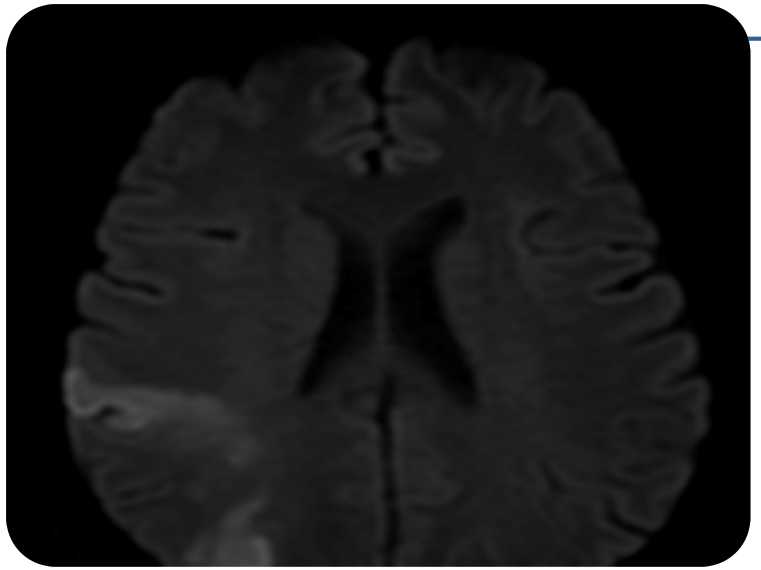


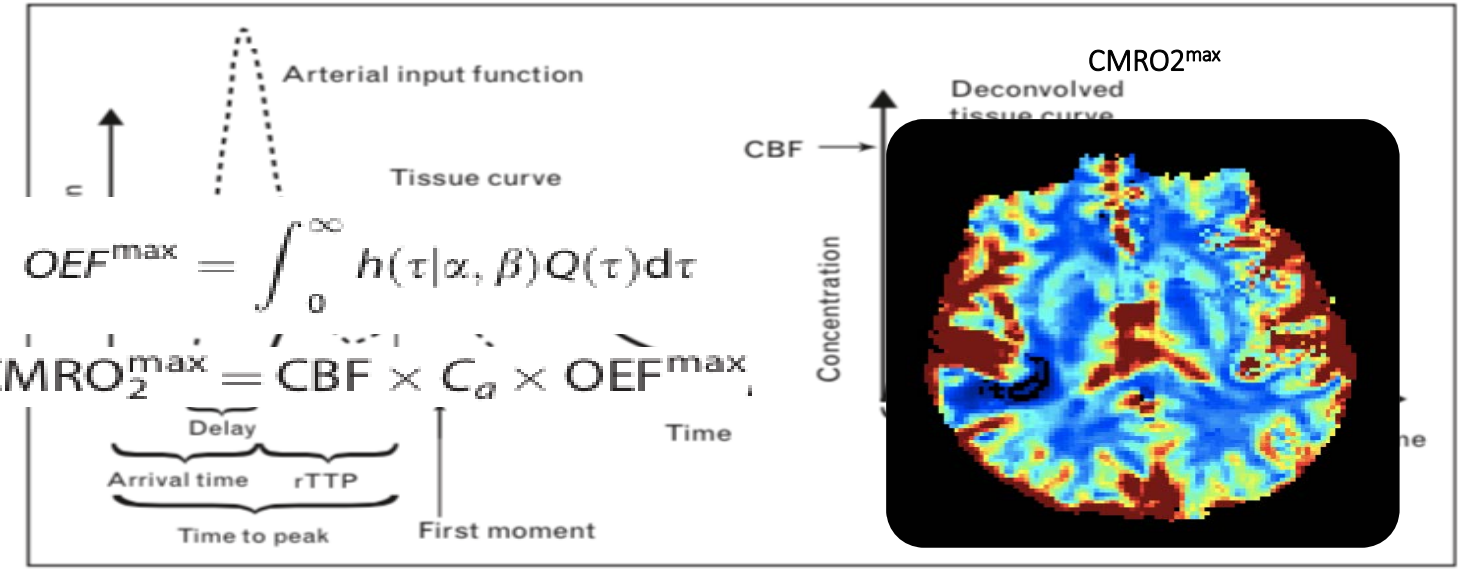




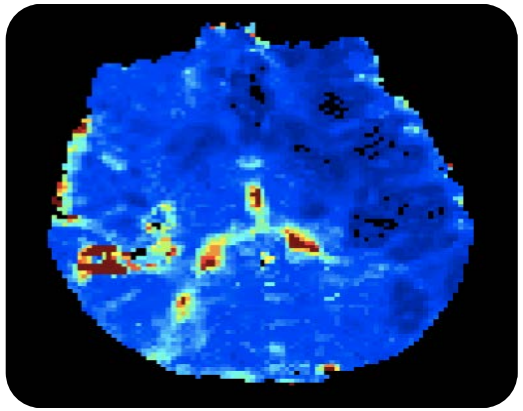
Mouridsen et al. Neuroimage 2006

Estimation of Capillary flow pattern: Capillary Transit Time Heterogeneity

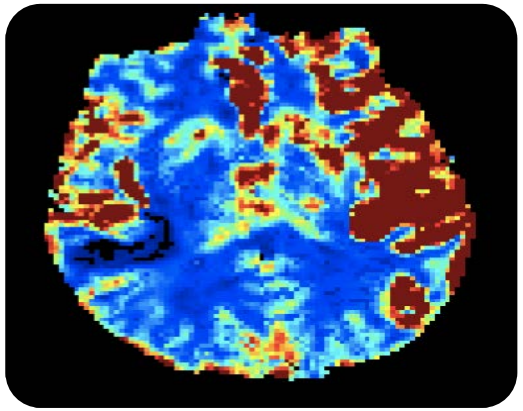




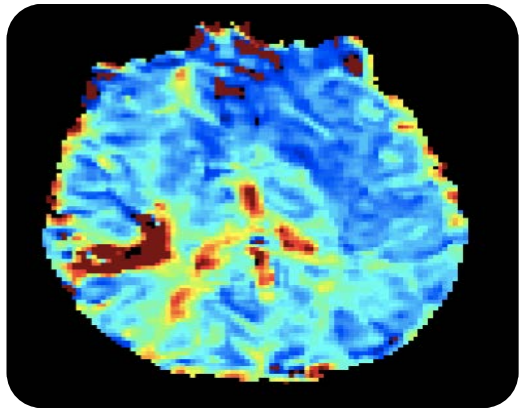
CTH



CBF



MTT



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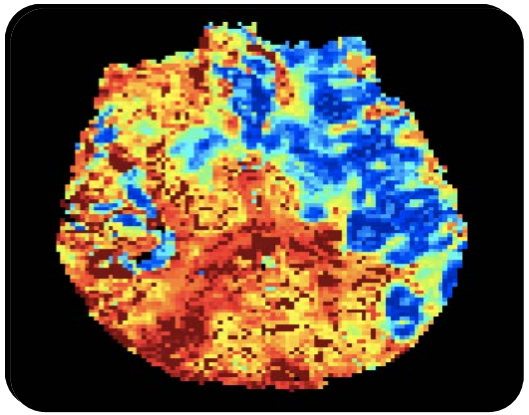

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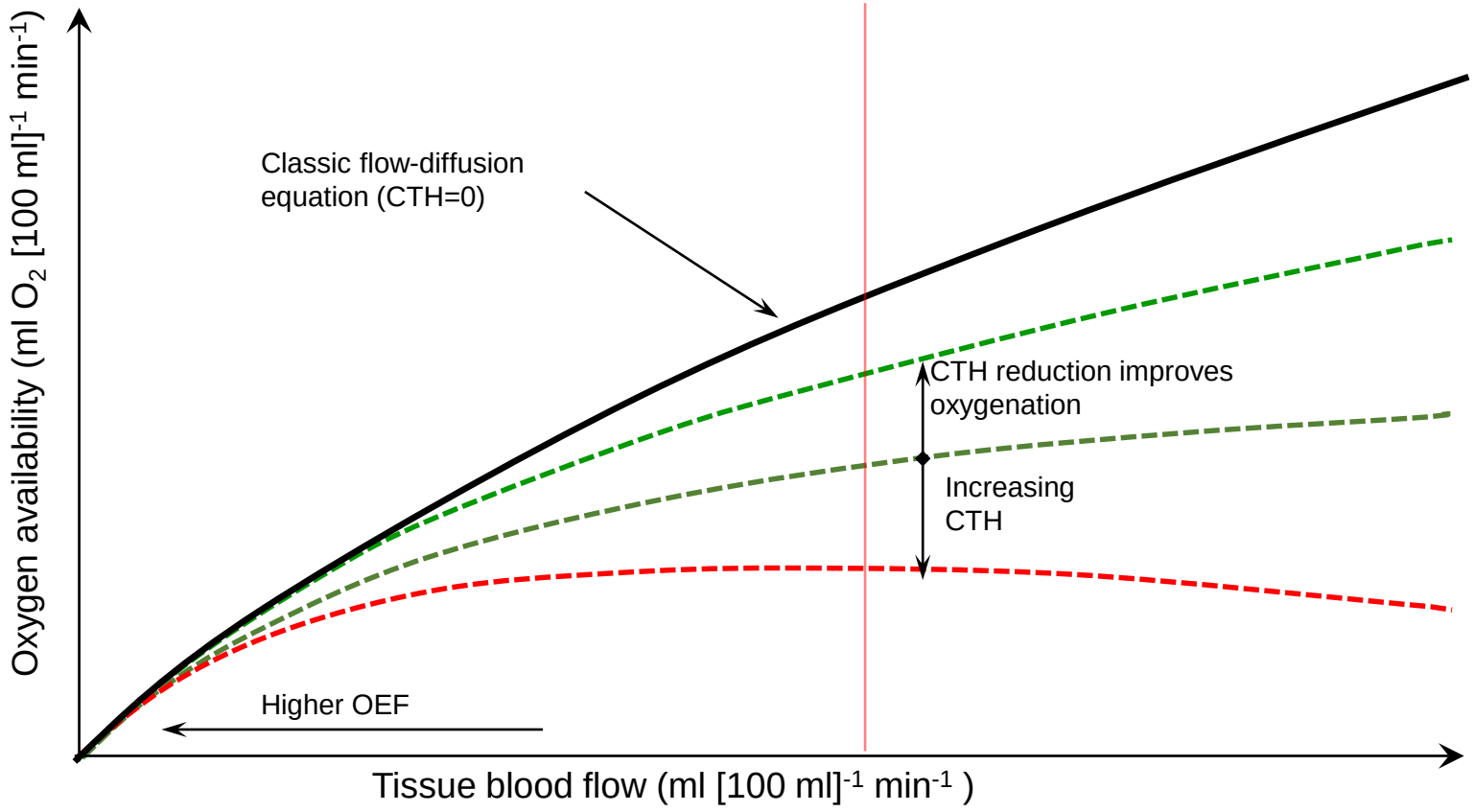
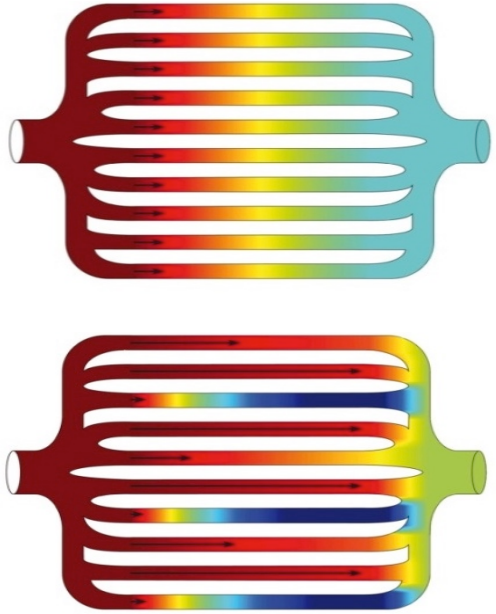
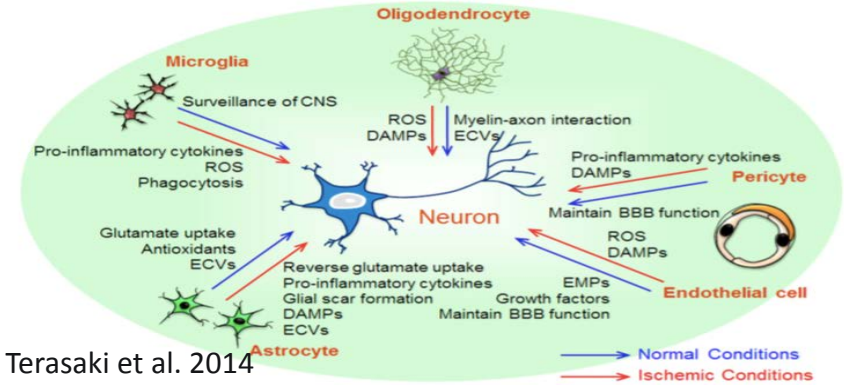
Maximum Supportable Metabolic Rate Depends on CTH







Terasaki et al. 2014

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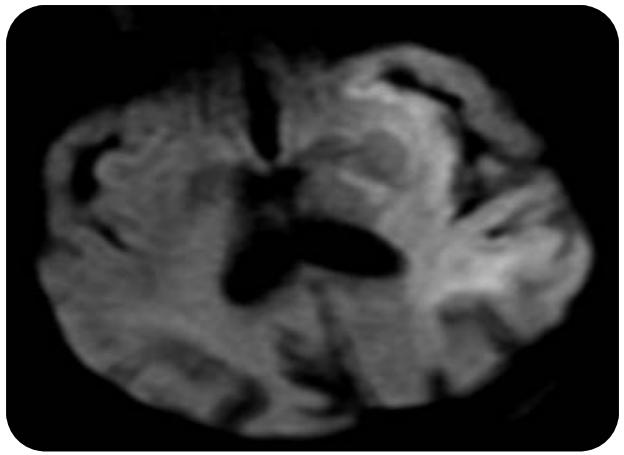
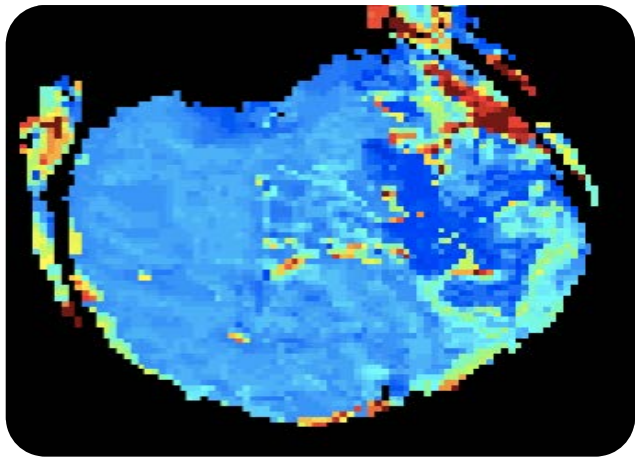
Variation for the Transit Time Distribution (CoV)

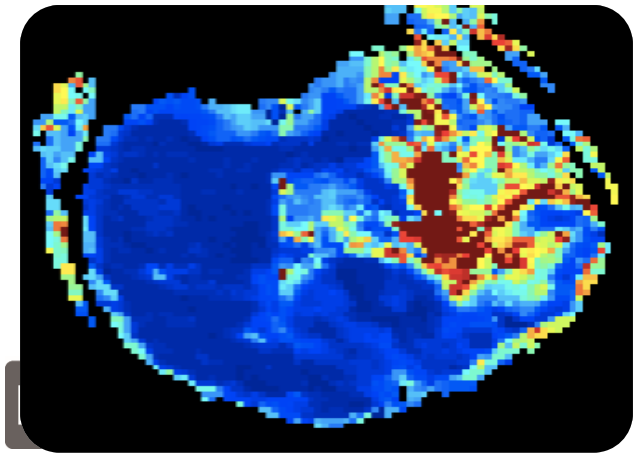
DWI



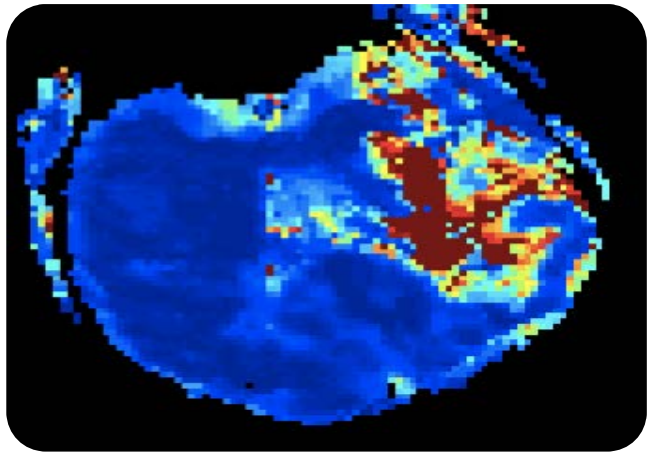
CoV

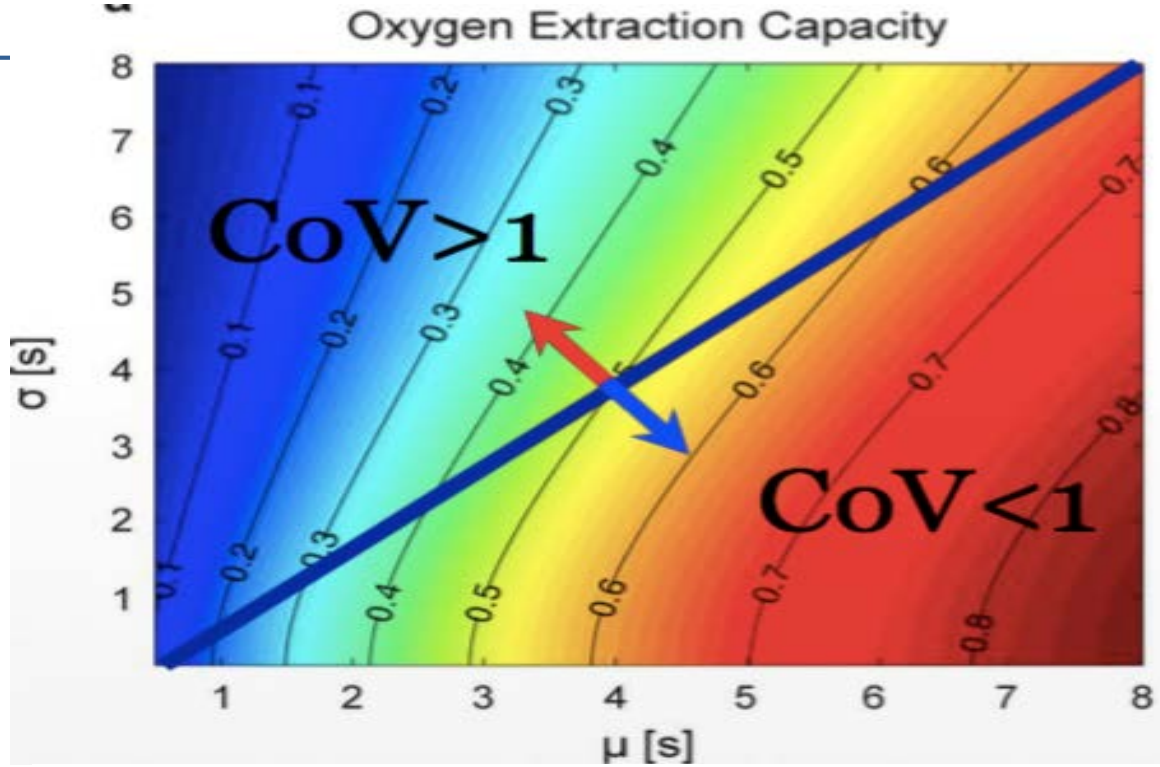


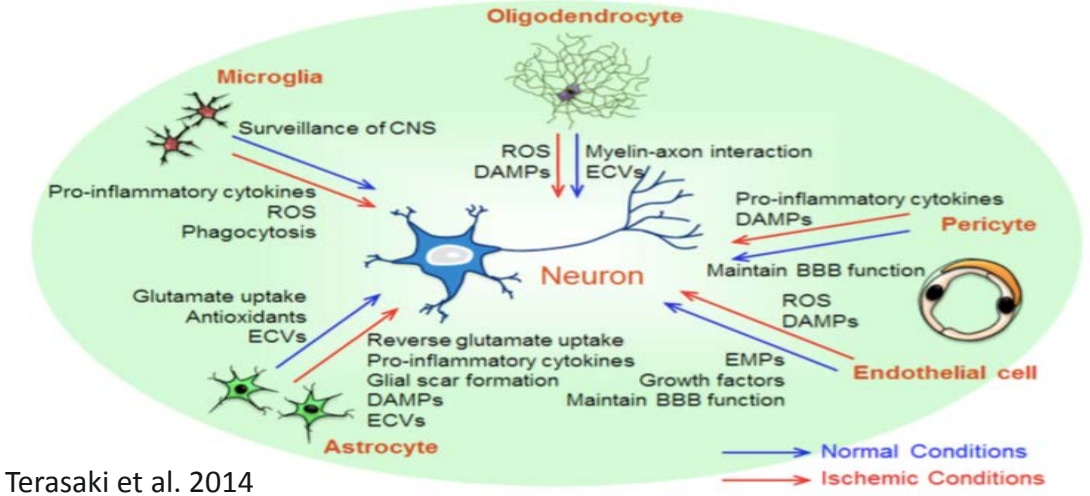
CTH



MTT







Terasaki et al. 2014

Acute Ischemic Stroke Imaging Cohort

- NIH-NINDS SPOTRIAS project (P50-NS051343, Furie – PI)
- 279 AIS patients with baseline MRI (LSW <9h)
- Available baseline perfusion imaging:
  - MRP: n=217
  - CTP: n=98
  - MRP+CTP: n=60 at admission
- 74 subjects with repeated MRP (BL, +6h, +24h) (Singhal – PI)
- Admission blood samples
- 29 HT on follow up (17 PT, 12PH)

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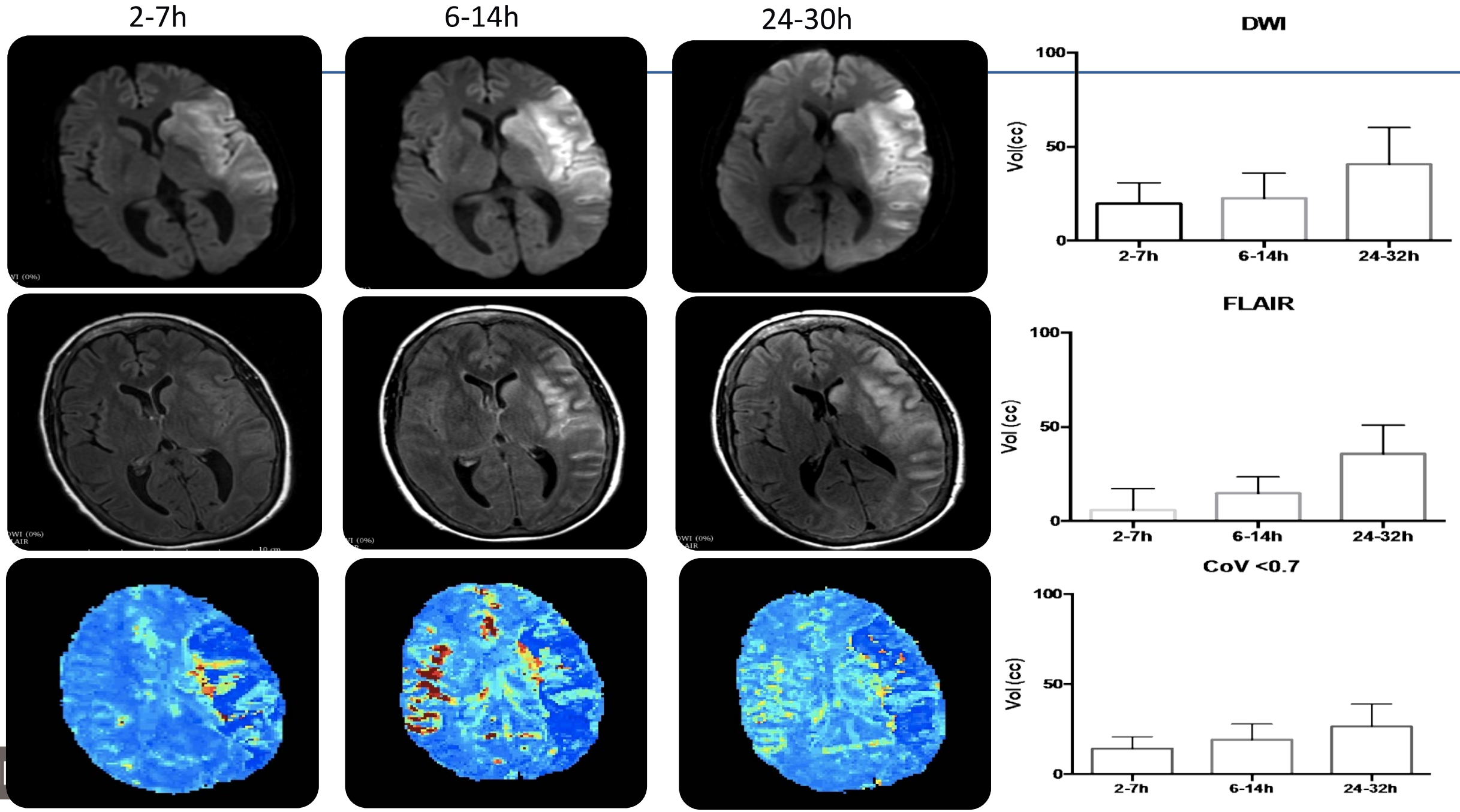
SPOTRIAS

Low CoV as Imaging Marker for Tissue Injury?



Regions with high CoV correspond to Hemorrhagic Transformation?

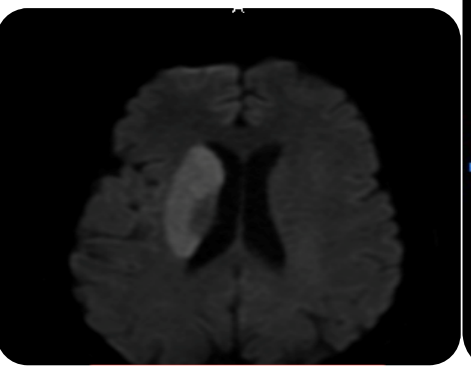
Baseline DWI

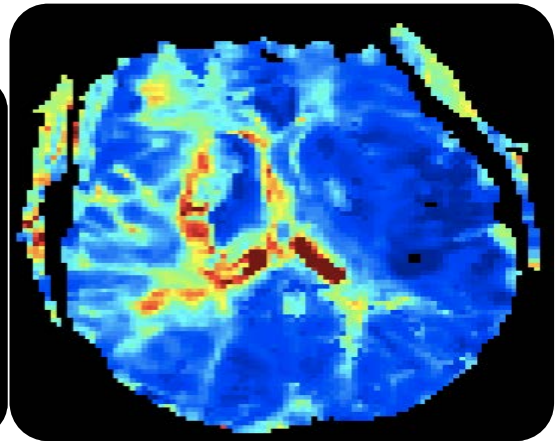
CTH

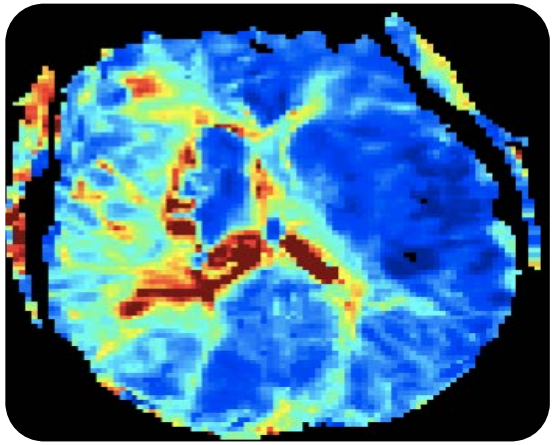
MTT

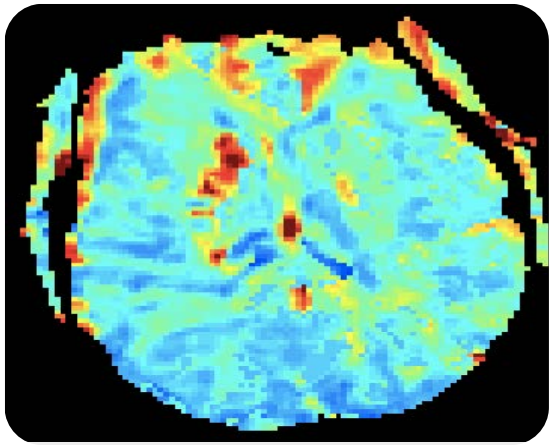
COV

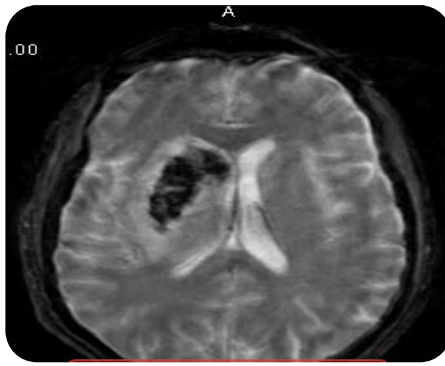
Follow Up T2*W

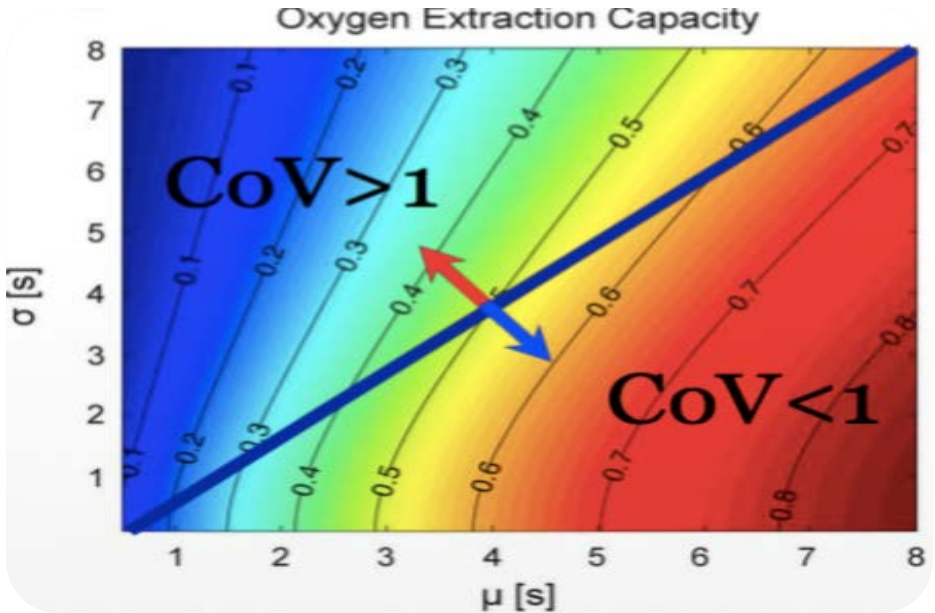












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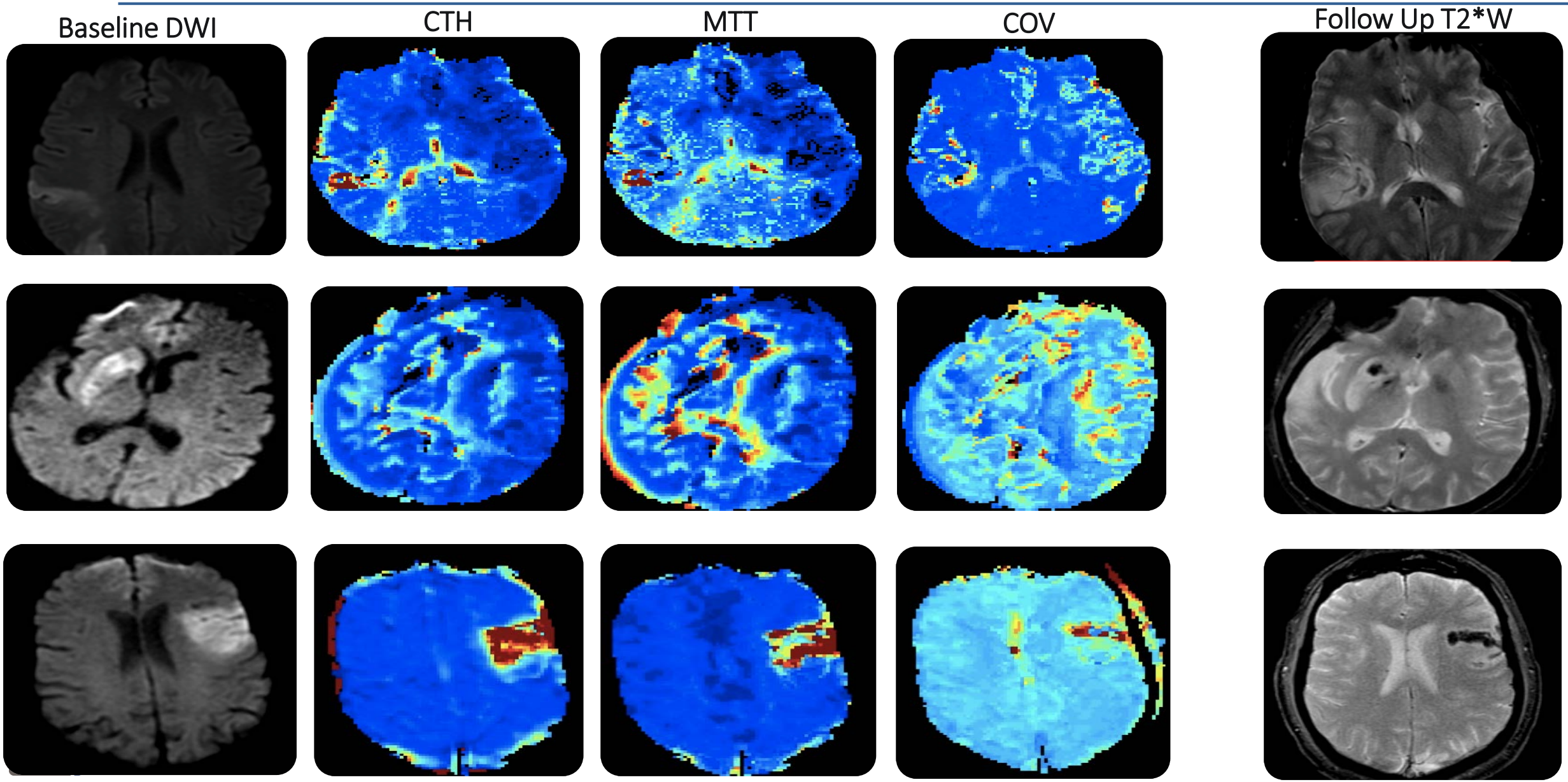
Regions with high CoV correspond to Hemorrhagic Transformation?



Project Aims:

1. Explore predictive value of CoV for hemorrhagic transformation
2. Screen plasma samples for corresponding endothelial markers
3. Assess correlations with perfusion based imaging marker
4. Evaluate performance of the perfusion algorithm comparing MRP/CTP

Future Directions:

1. Predicting stroke outcome by advanced multimodal modeling
2. Identify novel targets for intervention in acute ischemic stroke

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-R01 NS082285
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-R01 NS059775
-K08 NS0968301

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Association of Ischemic Stroke Location and Demographic Variables with Percutaneous Endoscopic Gastrostomy Placement

Michael Star[1], Heidi Sucharew[2], Sean Ruland[3], Kathy Alwell[1], Charlie Moomaw[1], Brett Kissela[1], Matthew Flaherty[1], Daniel Woo[1], Jason Mackey[4], Sheryl Martini[5], Opeolu Adeoye[6], Simona Ferioli[1], Felipe De Los Rios La Rosa[1], Dawn Kleindorfer[1]

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3. Dept of Neurology, Loyola University Stritch School of Medicine
4. Dept of Neurology, Indiana University School of Medicine
5. Michael E. DeBakey VA Medical Center
6. Dept of Emergency Medicine, University of Cincinnati

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Disclosures

- University of Cincinnati StrokeNET Fellow

Acknowledgements

- Greater Cincinnati / Northern Kentucky Stroke Study was funded by NINDS (Grant: R01 NS 30678)

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Background

- Brainstem strokes have significantly higher rates of dysphagia and aspiration[1]
- PEG used in patients with unmanageable dysphagia and severely debilitating, but survivable strokes

1. Martino, Stroke, 2005

Background (2)

- PEG is Controversial!
  - Life-sustaining/prolonging medical intervention
  - Basic humane care
  - Disability accommodation[1]
- PEG is Expensive!
  - Estimated to cost $31,832/year[2]

1. Brasher, Stroke Rehab, 2007
2. Callahan, JAGS, 2002

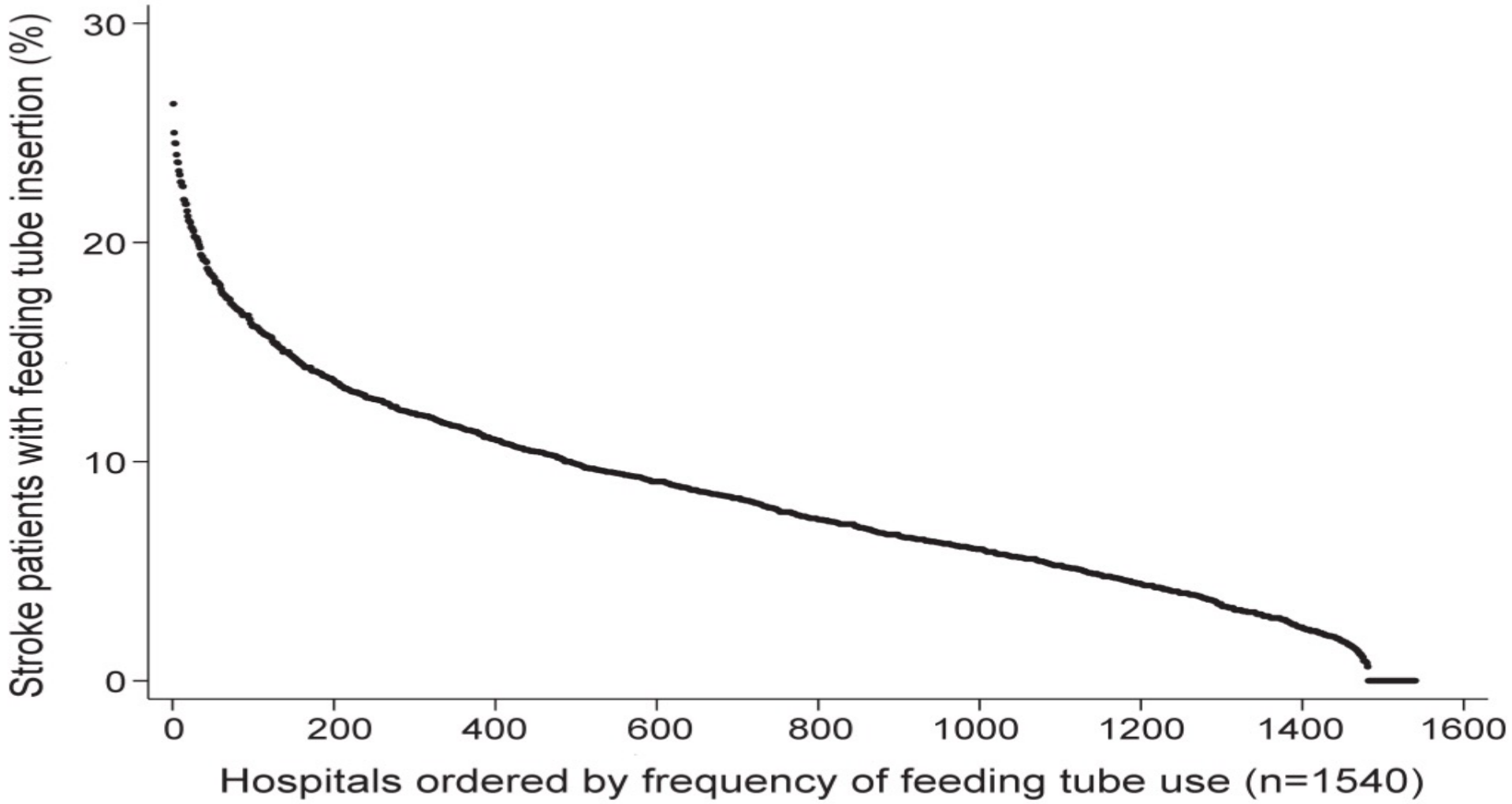
Background (3)

- FOOD Study:
  - Largest randomized, control trial to study nutrition after stroke
  - Studied:
    - Malnutrition in all stroke patients
    - Early enteral nutrition vs. “avoid tube”
    - NGT vs. PEG
  - Findings:
    - None significant

Background (4)

- Not only is there no evidence of how to practice, but there is evidence that practice varies widely and wildly

Figure 1 Rank order of frequency of feeding tube placement in acute ischemic stroke hospitalizations, 2008–2011



1. George, Neurology, 2014

Aim 1

- Determine if posterior circulation strokes were more likely to undergo PEG than anterior circulation strokes
  - Hypothesize that posterior circulation strokes would lead to more PEGs

Aim 2

- Determine clinical and demographic variables that are associated with PEG in stroke patients
  - To better understand *who* is undergoing PEG

Aim 3

- Develop “PEG Score” based on findings to determine likelihood of PEG in current practice based on demographic and clinical characteristics
  - For future research applications, not clinical use

Greater Cincinnati/Northern Kentucky Stroke Study Laboratory

- 5-county region, biracial population of 1.3 million
- Designed to study racial differences in stroke
- 1988-89, 93-94, 99, 2005, 2010[1-3]
- All local hospitals, clinics, coroners offices, sampling of nursing homes and physician offices
- TIA/IS/ICH/SAH
- ~4,000 events/year

1. Broderick,et al, Stroke 1998
2. Kissela, et al, Stroke 2004,
3. Kleindorfer, et al, Stroke 2006

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Methods

- All AIS patients >18 years presenting to emergency department or in-hospital in 2010
- GCNKSS screen hospital discharges using ICD-9 discharge codes 430-436
- Cases physician confirmed
- Stroke location by brain imaging or physician impression

Statistics

- Outcome: PEG tube placement
- Multivariable logistic regression used to evaluate associations between PEG and clinical/demographic characteristics
- Score: Points assigned to variables using beta coefficients from final multivariable logistic model

Demographic and clinical variables considered:

- Age
- Race
- Sex
- Insurance status
- rNIHSS
- Atrial fibrillation
- Dysphagia
- tPA
- Bi-hemispheric stroke
- Hospital-type
- Stroke location

Results

- 2168 ischemic strokes
  - Median age 71
  - 55% women
  - 22% black race
- 118 (5%) underwent PEG
  - Largest stroke population studied for PEG use

PEG and Stroke Location

Location	N	PEG, n (%)
Anterior only	1365	83 (6.1%)
Posterior only	457	16 (3.6%)
Posterior and Anterior	346	19 (5.5%)
Posterior		
Brainstem	173	15 (8.7%)

PEG and Demographic/Clinical Variables

Variable	PEG	No PEG	P-value
Age (median)	74	71	0.01
Black race	32%	21%	<0.01
rNIHSS (median)	14	3	<0.01
Atrial fibrillation	42%	21%	<0.01
Bi-hemispheric stroke	25%	14%	<0.01
Dysphagia	49%	15%	<0.01

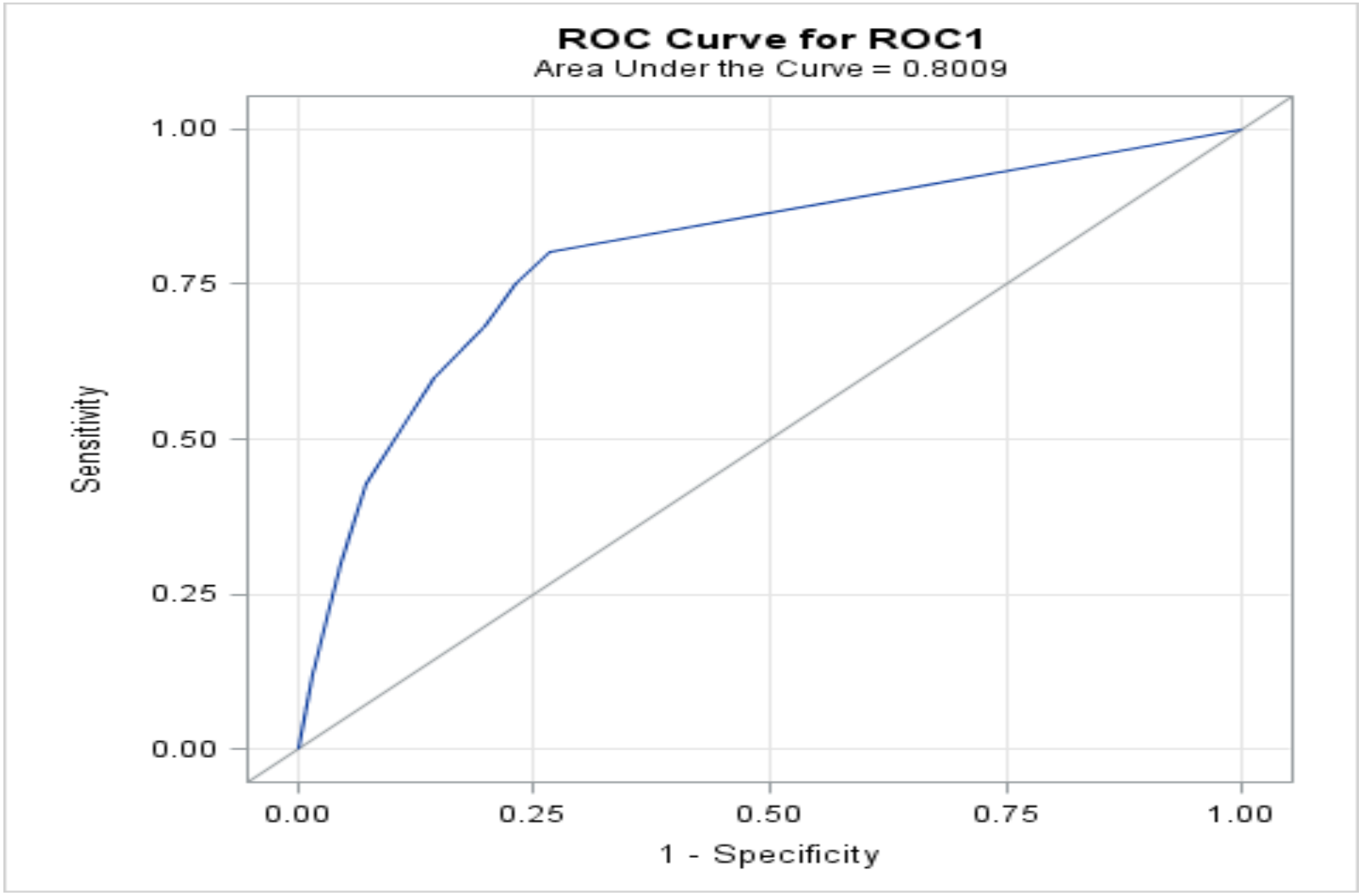
Multivariable Analysis: Factors Predicting PEG Use, $p < 0.01$

Variable	Odds Ratio	95% CI
Black Race	2.34	1.45 – 3.76
NIHSS	1.09	1.06 – 1.11
Atrial Fibrillation	2.42	1.51 – 3.88
Dysphagia	3.68	2.41 – 5.62
Hospice/Died	0.29	0.15 – 0.56

PEG Score

Item	Value	Points
History of Afib	Yes	2
	No	0
Dysphagia	Yes	3
	No	0
NIHSS Dysarthria	0 -- normal	0
	1 -- mild-moderate	2
	2 -- severe	7

- Score ≥ 3: Sensitivity = 80%, Specificity = 73%



- AUC = 0.80
  - Performs well with cross validation (0.75 AUC)

Discussion

- Posterior circulation strokes were not more likely than anterior circulation strokes to undergo PEG
  - Likely due to PEG being just as much about massive strokes as it is about dysphagia
- One possible explanation for significantly higher rate of PEG among black patient is cultural attitudes to end-of-life care

Discussion (2)

- 2 other PEG analyses with black race as independent factors[1,2]
- NY SPARCS data demonstrated lower short-term black stroke patient mortality, with associated lower use of hospice and increase in life-sustaining interventions[3]

1. Dubin, Stroke, 2013
2. Faigle, Stroke, 2015
3. Xian, Ann of Int Medicine, 2011

Limitations

- BIG caveat – this is not about who *should* get PEG, but who *does* get PEG
  - NOT to be used clinically, but instead for research
- PEG Score needs to be externally validated
- Retrospective chart review
- Stroke location based on clinical radiology reports

Future Directions

- Use PEG Score for inclusion criteria in future outcomes studies
- Separate research of enteral feeding in mild strokes with dysphagia and massive strokes
- Connection between racial disparities in end-of-life care and PEG placement

Thank you!

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Questions?

Memantine for Enhancement of Stroke Motor Recovery

Alicia Bennett, DO, StrokeNet Fellow
Lorie Richards, PhD, Occupational Therapy
K.C. Brennan, MD, Headache Neurologist
Edward DiBella PhD, Department of Radiology
Jennifer J. Majersik, MS, MD; Stroke Neurologist

Disclosures

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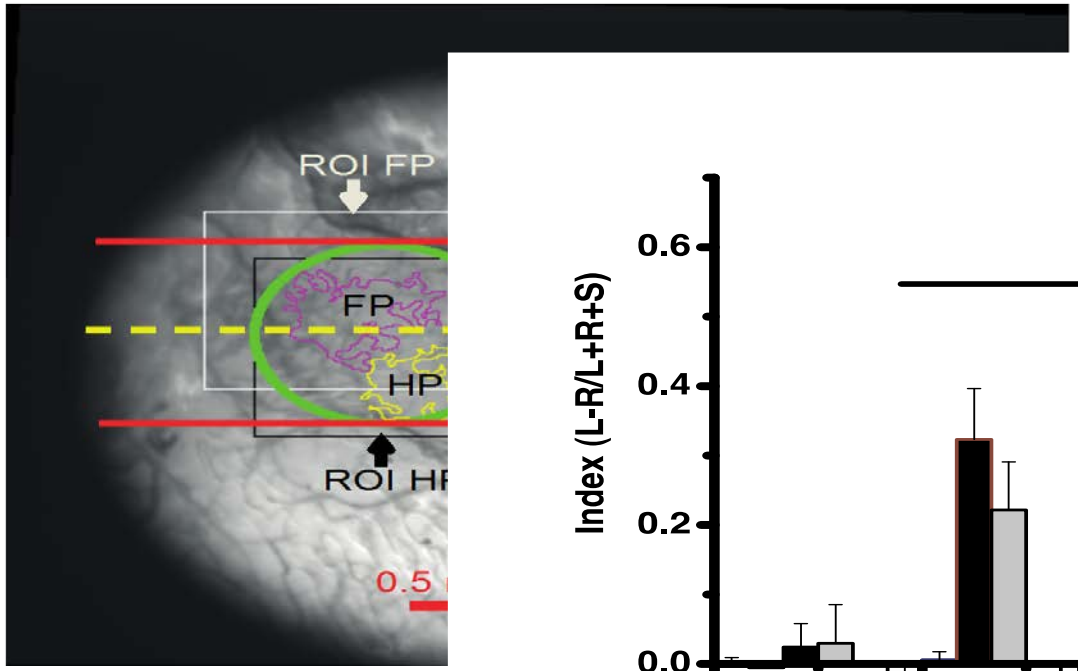
Support by the University of Utah Study CTSA (Grant 5UL1TR001067-02)

Background

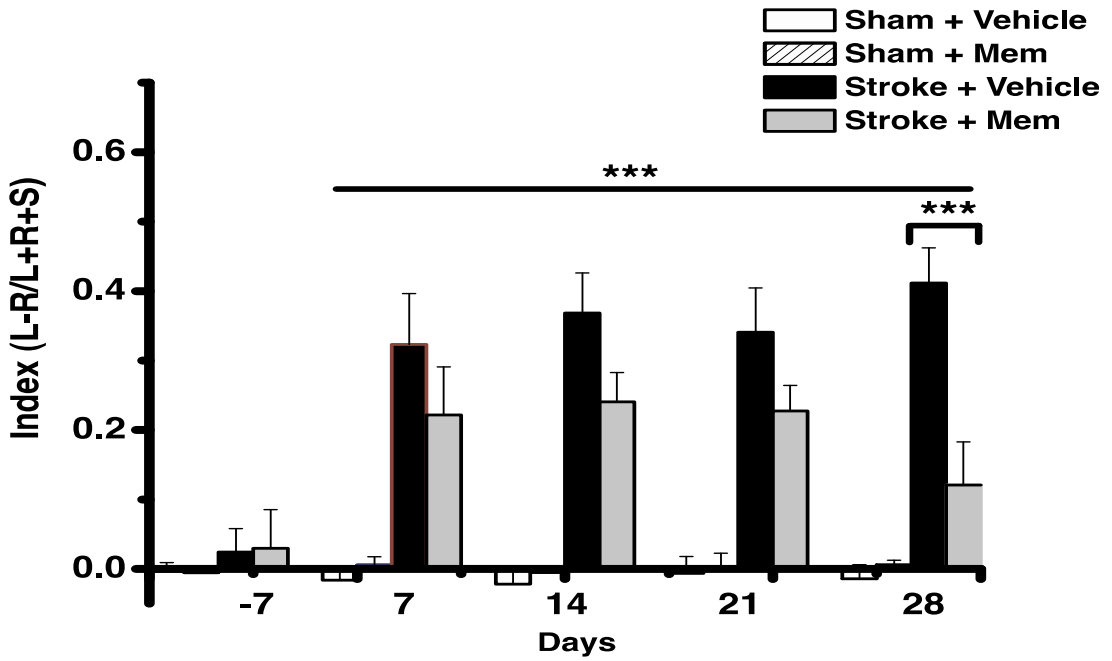
- Motor impairment is one of the leading causes of long-term disability following stroke.

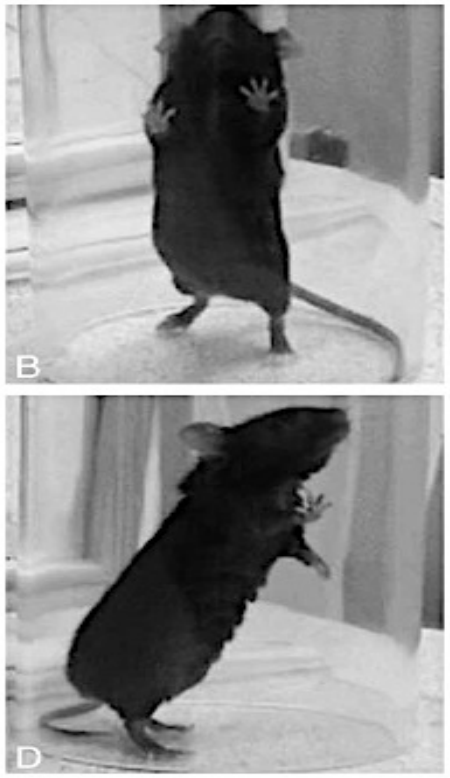
- Increasing evidence that plasticity is retained after stroke.

Memantine in Animals



Experiment



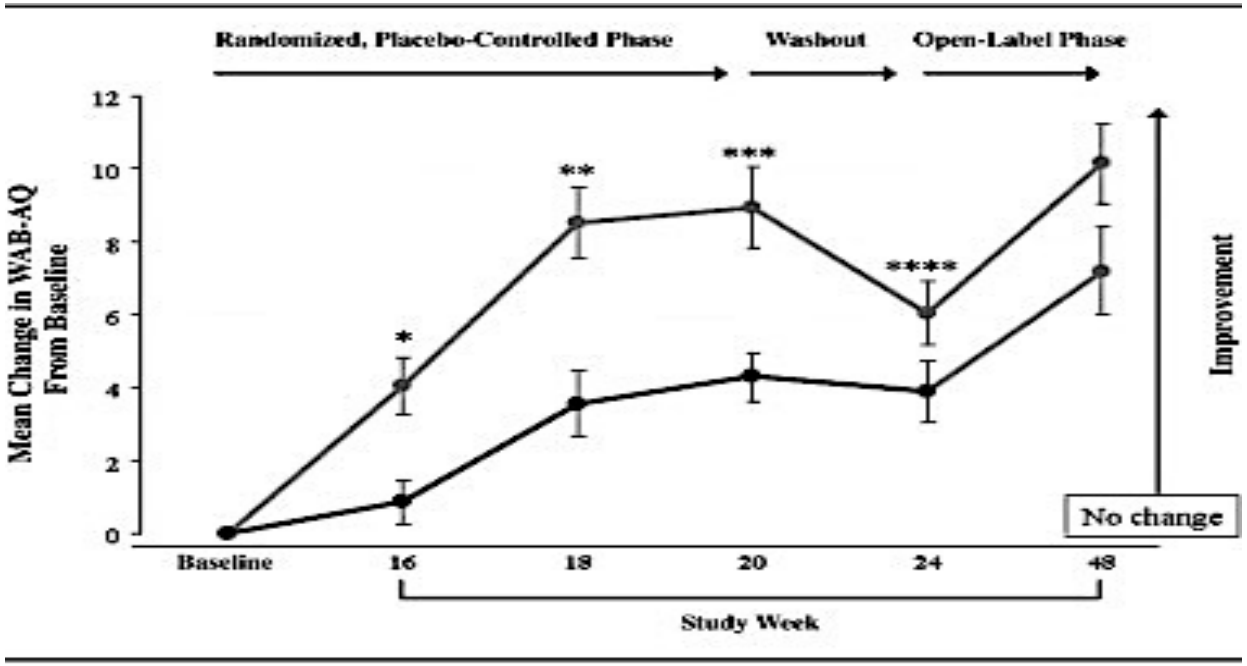


est

Lopez-Valdes et. al. *Stroke* 2C

Memantine in Humans

- 2009 Berthier et. al. studied chronic post-stroke aphasia patients
  - Placebo controlled trial
  - significant improvement in aphasia
  - No adverse effects



Hypothesis

Treatment with memantine XR for 12 weeks following an acute stroke will be feasible and associated with improvement in motor control (Fugl-Meyer Score) with no greater adverse events.

Design

- Randomized double blind placebo-controlled pilot study in which participants with acute stroke and upper extremity weakness are randomized to either drug or placebo

- Target enrollment of 10 patients per group

Aims

- Primary Aims
  - Aim 1: Measure change in Fugl-Meyer Score
  - Aim 2: Comparable adverse events
- Secondary Aims
  - Aim 3: Measure change in grip strength test and ten meter walk
  - Aim 4: Differences between groups in stroke impact scale, motor activity log

Fugl-Meyer Scale

A. Wrist control

B. Hook grasp

- Upper and lower extremity portion
- 50-item motor scale
- Scores range from 0-100

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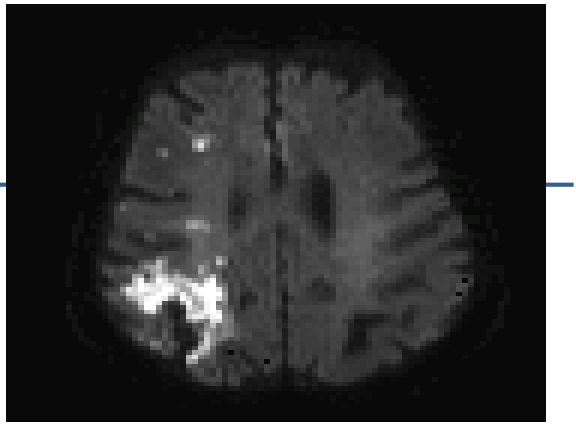
Inclusion Criteria

1. Age 18 and older
2. Acute or hemorrhagic stroke
3. Randomization between 3 days and 8 weeks of stroke symptom onset
4. Arm weakness severe enough to warrant inpatient or outpatient OT
5. Able to voluntarily move affected UE

Exclusion Criteria

1. Subarachnoid or subdural hemorrhage
2. NIH Stroke Scale ≥20
3. History of prior clinical stroke with residual symptoms on the same side as the current symptoms that would interfere with outcomes of this study

UT StrokeNet



Methods

- Baseline testing for eligibility
- Randomized
- Participants continue memantine XR or placebo for 12 weeks
- Follow-up testing at weeks 4 and 12
- Follow-up phone calls at weeks 1, 2, 3, and 8
- Optional MRI substudy at same time intervals

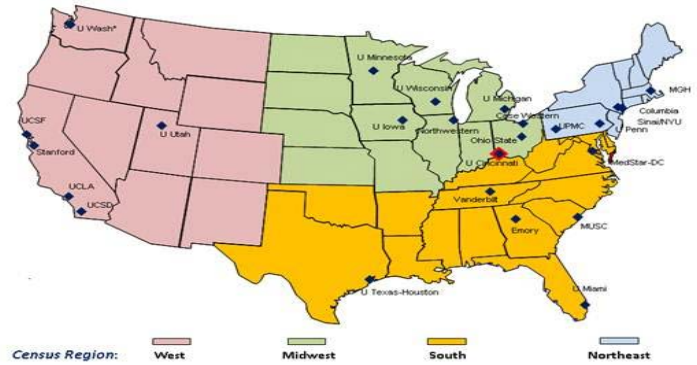
Results

- 4 subjects to date
- No difficulty with testing
- All participants have returned for testing
- No serious adverse events
- Medication adherence has been 100%

Future Direction

- Minority recruitment
- Further expansion of recruitment sites
- Feasibility assessment

National and Regional Coordinating Centers



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Thank You

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Overview of Trial Proposals

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

NIH
Funded by a grant from the National Institutes of Health

UNIVERSITY OF Cincinnati

Project Name	Protocol PI	Category	Status Update
IMPACT	Andrew Naidech	Acute	March 4-5, 2016 Study Section
PreLIMBS	Sebastian Koch	Acute	March 4-5, 2016 Study Section
CREST H	Randy Marshall, MD	Prevention	March 4-5, 2016 Study Section
Sleep SMART (C-PAP)	Devin Brown	Prevention	February 2016 grant submission.
ARREST	Robert Brown, James Torner, David Hasan	Prevention	February 2016 grant submission.
MOST	Opeolu Adeoye/ Andrew Barretto	Acute	Did not pass through Council. Will submit as an A01 in June, 2016. Endovascular issues addressed with data.
PICASSO	Marc Chimowitz	Prevention	March 2016 grant re-submission
ARCADIA	Hooman Kamel/ David Tirschwell/ Mitch Elkind	Prevention	March 2016 grant re-submission with increase in sample size. Working out budget with increased cost of the study drug due to sample size and increased drug costs.
RISiS	Julius Fridrikkson, Ron Lazar, Ed Jauch, Jordan Elm, Leonardo Bonilha	Recovery	June 2016 grant submission

Project Name	Protocol PI	Category	Status Update
SATURN	Magdy Selim	Prevention	June 2016 grant submission
ICTUS 3	Pat Lyden	Acute	June 2016 grant re-submission (possible)
I-WITNESS	Lee Schwamm	Acute	Pending CSP approval, June 2016 grant submission
DOSER	Alex Dromerick	Recovery	Pending CSP approval June 2016 grant submission
Tempo-EMS	Nerses Sanossian Administrative PI, Bill Barsan, Jeff Saver, David Hess, Ed Jauch, Rob Silbergleit	Acute	Pending CSP approval, June 2016 grant submission
ALISAH 2	Jose Suarez	Acute	Pending CSP approval, June 2016 grant submission
Dose Response Aerobic Exercise in Subacute Stroke	Sandra A Billinger, PT, PhD	Recovery	Pending CSP approval, June 2016 grant submission
SOPRANO	Karl Meisel, Wade Smith	Prevention	Under Discussion with NINDS/NHLBI as partner.

Project Name	Protocol PI	Prevention/ Acute/Recovery	Status Update
PRECISE MRI-T2	Natalia Rost	Prevention	Pending CSP approval, June 2016 grant submission
SCORPION	Kevin Sheth	Prevention	In concept development
PATCH	Maarten Lansberg	Prevention	In concept development
PHAST	Kate Amlie-Lefond, Michael Rivkin, Joan Cox Gill	Acute	In concept development
Acute Biomarker	Robert Meller	Acute	In concept development
IRIIS	Warren Lo	Recovery	In concept development
FURRThER	Bernadette Boden-Albala	Prevention	In concept development
ETOSHA	Tanya Turan,	Prevention	In concept development
TRANSPORT	Wayne Feng	Recovery	In concept development
VERiTAS II	Sepideh Amin-Hanjani	Prevention	In concept development
VAST	Adnan Qureshi	Prevention	Not approved to move forward in its current form by the ESC.

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Recruitment and Retention for Underrepresented Minorities and Ethnicities Advisory Working Group

Bernadette Boden-Albala, DrPH
MPI: NYCC-RCC (NYU)

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Advisory Working Group Members

- Maggie Baker
- Claire Binley
- Bernadette Boden-Albala (Chair)
- Devin Brown
- Dorothy Edwards
- Dawn Kleindorfer (Co-Chair)
- Michael Parides
- Jose Romano
- Patricia Tanzi
- Salina Waddy
- Olajide Williams

Working Group's Mission

- All StrokeNet PD/PI should **describe plans** to **support** and **optimize** the recruitment and retention of underrepresented groups, e.g., racial-ethnic minorities and women, in stroke clinical trials
  - Support:
    - Evaluate if investigators have access to the populations
    - To monitor recruitment of trials as they move forward to "catch" any recruitment problems as they arise
  - Optimize:
    - Provide tools needed to bring in target populations
    - Ensure that trial design, site selection,
    - statistical analysis plans are inclusive of racial-ethnic minorities and women

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Support: Minority Recruitment and Retention

- **1. Site selection guidance**
  - Evaluate if investigators have access to the populations
  - Guidance on site selection criteria

- **2. Creating minority recruitment and retention plans**
  - A. Trial mechanics
    - How your study design might influence recruitment and retention
  - B. Researcher Narrative
  - C. Statistical plan

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Site selection guidance

A. Percent of admitted patients' race-ethnicity and gender

- Information to make reasonable projections

B. Each site's feasibility to enroll

- Use ICD-9 codes
- Get with the Guidelines metrics
- Real time experience

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Minority Recruitment and Retention Plans

A. Trial mechanics

1. Trial's eligibility criteria
   - Do the criteria systematically exclude a specific group of people?
2. Patient population demographics
   - Vulnerable populations, age, sex, race, ethnicity
3. Type of recruitment sites
4. Each site's resources
   - CTSA, community outreach etc.
5. Enrollment
   - Setting, enrollment hours, language translation services
6. Retention
   - Compensation, length of follow-up

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Recommendations for Clinical Study Concept Synopsis

Briefly describe the proposed trial design:
Patient selection criteria, including window of treatment: - Inclusion/Exclusion Criteria
Describe Recruitment and Retention plans **1). Site selection criteria** **2). Considerations for underserved populations (i.e., women and racial-ethnic minorities)**
Please provide an estimate of your study sample size to assist with the feasibility assessment.
Proposed number of subjects to be enrolled: _____
Describe the statistical basis for the proposed sample size calculation:
Describe the statistical basis for inclusion of underserved populations

Minority Recruitment and Retention Plans

Review to Date

3 proposals

2 approvals

1 under review

- *"**Approach:** Provide an assessment of the outreach and recruitment needs that are unique to the center as well as to the geographical area
- **Local needs:** Coordination with others for recruitment and retention of subjects for particular research protocols and clinical trials, with a special emphasis on underserved/underrepresented populations. *An outreach plan should address the needs identified, including both strengths and barriers (e.g., parking/transportation).*
- **Recruitment methods:** 1) Descriptions of seminar or lecture series, or workshops; 2) Outreach to specific communities to publicize research; 3) collaboration with other organizations such as state and local agencies, community/service groups, hospitals, religious organizations, business groups, local medical societies, etc.; and 4) Descriptions of materials (e.g., videos and printed matter)
- **Cultural sensitivity:** information should be structured so that it can effectively reach diverse populations, including non-English-speaking people."

Key Questions

- What is the underlying minority population that could be in the study? (ex: how many people of X group pass through the doors of Y site)
- How many of out that populations would fit eligibility criteria
- What percentage of those people do investigators actually have access to?

Paradigm Shift in Clinical Trial Proposal and Planning

- Nothing can be accomplished in isolation

- Stakeholder engagement
  - NIH
  - Reviewers
  - Principal Investigators
  - Research community

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Women and Minorities in StrokeNet Trials: Plans for Analysis and Reporting

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NIH Policy and Guidelines*

- When an NIH-defined Phase III clinical trial is proposed, evidence must be reviewed to show whether or not clinically important sex/gender and race/ethnicity differences in the intervention effect are to be expected.
- Cost is not an acceptable reason for exclusion of women and minorities from clinical trials.

* http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

NIH Policy and Guidelines - Definitions

Ethnicity

- Hispanic or Latino - a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
- Not Hispanic or Latino

Minority Race

- American Indian or Alaska Native - a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
- Asian - a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
- Black or African American - a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
- Native Hawaiian or Other Pacific Islander - a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

NIH Policy and Guidelines - Definitions (cont'd)

- Significant Difference - a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference be[illegible] achieves statistical significance. Statistical significance depends upon the amo[illegible] set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

Hence, clinically driven

- Valid Analysis - an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are:
  - ✓ allocation of study participants of both sexes/genders (males and females) and different racial/ethnic groups to the intervention and control groups by an unbiased process such as randomization,
  - ✓ unbiased evaluation of the outcome(s) of study participants [such as blinded], and
  - ✓ use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the sex/gender and racial/ethnic groups.

NIH Policy and Guidelines - Scenario 1

If “Prior Studies Support the Existence of Significant Differences”:

- The primary question(s) to be addressed by the proposed NIH-defined Phase III clinical trial and the design of that trial must specifically accommodate this. For example, if [illegible] differently to an intervention, then the Phase III clinical trial [illegible] primary questions, one for men and the other for women, with ade[illegible]
- The Research Plan (for grant applications) or Proposal (for contract solicitations) must include a description of plans to conduct analyses to detect significant differences** in intervention effect.
- Inclusion of the results of sex/gender, race/ethnicity and relevant subpopulations analyses is strongly encouraged in all publication submissions. If these analyses reveal no differences, a brief statement to that effect, indicating the groups and/or subgroups analyzed, will suffice.

Recall, clinically important differences

NIH Policy and Guidelines - Scenario 2

If “Prior Studies Support No Significant Differences”:

- Sex/gender and race/ethnicity will not be required as subject selection criteria. However, the inclusion and analysis of sex/gender and/or racial/ethnic subgroups is still strongly encouraged.

NIH Policy and Guidelines - Scenario 3

If "Prior Studies Neither Suppo[rt] Significant Differences":

Vague

- Required to include sufficient and appropriate entry of sex/gender and racial/ethnic participants, so that valid analysis of the intervention effects can be performed. However, the trial will not be required to provide high statistical power for these comparisons.
- The Research Plan (for grant applications) or Proposal (for contract solicitations) must include a description of plans to conduct valid analysis (see DEFINITIONS – Valid Analysis) by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable.
- Must report in their annual Progress Report cumulative subject accrual and progress in conducting analyses for sex/gender and race/ethnicity differences.
- Inclusion of the results of sex/gender, race/ethnicity and relevant subpopulations analyses is strongly encouraged in all publication submissions. If these analyses reveal no differences, a brief statement to that effect, indicating the groups and/or subgroups analyzed, will suffice.

Comments

- Majority of the studies will fall into scenario 3.
- “Valid analysis” requirements can be met by careful planning and execution of the trial.
- Caveat – without “high statistical power”, hypothesis testing is likely to be uninformative.
- Recommended approach is to present the treatment effect estimates and their CIs by sex and minority groups, rather than doing statistical tests.
- Require clinical/epidemiological input in determining what is “sufficient and appropriate” number of subjects, and how to ensure and monitor this requirement.
- Clarification needed on how to handle race/ethnicity in non-US sites.

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Questions?

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