StrokeNet Webinar
4-14-2021

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Vision of NIH StrokeNet

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

NINDS Network Evaluation

Scott Janis, PhD

Evaluation of NeuroNEXT and StrokeNet

NINDS clinical research networks aim to facilitate efficient, high-quality clinical trials and studies.

Competitive renewals for two networks are planned for 2023:

NeuroNEXT

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NINDS will ask a **Working Group of the NANDS Council** to jointly assess these networks, using a common framework with separate attention to features unique to each program.

The Working Group will report to the NANDS Council in February 2022, and will consider:

- the extent to which the networks are meeting their goals
- how the networks engage and benefit their research communities
- changes or improvements to help the networks succeed

NIH

Evaluation Purpose

To assess processes and outcomes to date for two NINDS-supported clinical research networks, StrokeNet and NeuroNEXT, and to identify areas to improve the design of the next iterations of these programs.

The evaluation will consider:

(1) the extent to which the programs are meeting their goals
(2) the programs' research outcomes and impacts
(3) the extent to which the networks collaborate with and engage the research community
(4) what improvements to program components and operations could allow the networks to better address current or new goals.

This evaluation will assess these programs jointly using a common framework to look at overall goals, with separate attention to features unique to each network.

NIH

Membership of Committees

Membership will include one or more members of the NANDS Council

And additional adhoc members to include:

- clinical trial execution and network coordination (including familiarity with other NIH networks)
- training and career development needs for clinical research
- patient engagement in clinical research
- industry and patient organizations in research
- clinical stroke research
- adult and pediatric neurology and neurosurgery

NIH

Focus of Evaluation

1. Area of focus for evaluation of how the network has met its goals
    1. Support for high-quality trials
    2. Efficient execution
    3. Training and career development
    4. Community engagement and collaboration

2. What enhancements can be made
3. Recommendations for next iteration of the network

Data Acquisition

1. Most data will be retrieved from NINDS programs or from the coordinating centers
2. Potential for interviews with members of the network (PI's, Coordinators, Staff, etc.)
   a) If this occurs, we will provide a heads-up when and who may be contacted.

NIH

Timeline

- Committees will gather information and prepare report through 2021
- Evaluation and recommendations presented to NANDS Council for approval in Feb 2022
- Council approval of Renewal FOA in May 2022
- Anticipated publication of renewal FOA in NIH guide in August 2022
- Anticipated application due date in Oct 2022
- Review of applications Feb/March 2023
- Council approval of grants in May 2023
- Awards expected by August 2023
  - Current funding project dates end July 31, 2023
  - As needed, NCE's may be issued prior to new awards


Any
Questions


????


Any
Questions


ARE THERE ANY QUESTIONS? FEEL FREE TO ASK ANY-THING AT ALL.
WHY DO GHOSTS HAVE CLOTHES?
IF SOMEONE GIVES YOU A WEDGIE AT THE MOMENT YOU DIE, WILL YOU HAVE IT FOR ETERNITY?

StrokeNet Enrollment Recognition

Trial PIs

2020 Top Enrolling Sites

UPMC Presbyterian Hospital (3)
PI: Marcelo Rocha
Coordinator: Jason Weimer
RCC UPMC

Beth Israel Deaconess Medical Center (3)
PI: Magdy Selim
Coordinator: Sarah Marchina
RCC 04 Massachusetts General Hospital

University of Alabama Hospital (3)
PI: Angela Shapshak
Coordinator: Tammy Davis
RCC University of Alabama

Oregon Health and Science University (2)
PI: Wayne Clark
Coordinator: Amber Lee
RCC Stanford University

2020 Top Enrolling Sites

SUNY Upstate Medical University (2)
PI: Peter Abdelmalik
Coordinator: Annemarie Crumlish
RCC 02 Columbia

Harborview Medical Center (2)
PI: Rizwan Kalani
Coordinator: Allison Kunze
RCC 23 University of Washington

Prisma Health Greenville Memorial Hospital (2)
PI: Sanjeev Sivakumar
Coordinator: Sam Thavarajah
RCC 05 MUSC

2020 Top Enrolling Sites

University of Iowa Hospitals and Clinics (3)
PI: Amir Shaban
Coordinator: Heena Olalde
RCC 15 University of Iowa

Harborview Medical Center (1)
PI: David Tirschwell
Coordinator: Allison Kunze
RCC 23 University of Washington

Oregon Health and Science University (1)
PI: Wayne Clark
Coordinator: Natasha Barnhill
RCC Stanford University

Mayo Clinic Jacksonville (1)
PI: Jason Siegel
Coordinator: Meredith McDonald
RCC 16 University of Miami

ASPIRE

2020 Top Enrolling Sites

OSF St. Francis Medical Center (1)
PI: Arun Talkad
Coordinator: Madison Donaho
RCC 28 Washington University

University of Utah Healthcare (1)
PI: Safdar Ansari
Coordinator: Kinga Aitkan
RCC 22 University of Utah

UPMC Presbyterian Hospital (1)
PI: Marcelo Rocha
Coordinator: Jason Weimer
RCC 20 UPMC

Wake Forest Baptist Medical Center (1)
PI: Stacey Wolfe
Coordinator: Wendy Jenkins
RCC 27 Wake Forest

Yale New Haven Hospital (1)
PI: Guido Falcone
Coordinator: Sara Jasak
RCC 29 Yale University

2020 Top Enrolling Sites

Emory University Hospital (10)
PI: Fadi Nahab
Coordinator:
RCC: Emory University

University of Kentucky Hospital (7)
PI: Creed Pettigrew
Coordinator: Patricia Arnold
RCC: The Regents of the University of Michigan

UPMC Presbyterian Hospital (6)
PI: Matthew Starr
Coordinator: Jason Weimer
RCC: The University of Pittsburgh

Mayo Clinic, Jacksonville (6)
PI: Michelle Lin
Coordinator: Meredith McDonald
RCC: University of Miami

2020 Top Enrolling Sites

5 Randomizations

Greenville Hospital System
PI: Paulo Zortea
Coordinator: Samadhi Thavarajah
RCC: Medical University of South Carolina

OU Medical Center
PI: Evgeny Sidorov
Coordinator: April Vaughan
RCC: The University of Texas Houston

University of Nebraska Medical Center
PI: Pierre Fayad
Coordinator: Helen Obaro
RCC: University of Iowa

Methodist University Hospital
PI: Balaji Krishnaiah
Coordinator: Quentin Thacker
RCC: Washington University in St. Louis

University of Minnesota Medical Center
PI: Benjamin Miller
Coordinator: Amanda Weller
RCC: Regents of the University of Minnesota

Yale New Haven Hospital
PI: Reshma Narula
Coordinator: Sara Jasak
RCC: Yale University

2020 Top Enrolling Sites

4 Randomizations

Hospital of the University of Pennsylvania
PI: Scott Kasner
Coordinator: Devin Keating
RCC: University of Pennsylvania Institute

Memorial Hermann Texas Medical Center
PI: Anjail Sharrief
Coordinator: Gail Cooksey
RCC: The University of Texas Houston

UVA Medical Center
PI: Andrew Southerland
Coordinator: Sonya Gunter
RCC: MedStar Health Research

ARCADIA•CSI
Cognition & Silent Infarcts

2020 Top Enrolling Sites

University of Iowa (9)
PI: Enrique Leira, MD
Coordinator: Heena Olalde
RCC University of Iowa

University of Cincinnati (8)
PI: Robert Stanton, MD
Coordinator: Jennifer Powers
RCC University of Cincinnati

Greenville Hospital (8)
PI: Paulo Zortea, MD
Coordinator: Samadhi Thavarajah
RCC MUSC

OU Medical Center (5)
PI: Evgeny Sidorov, MD
Coordinator: April Vaughan
RCC University of Texas Houston

Harborview Medical Center (5)
PI: David Tirschwell, MD
Coordinator: Allison Kunze
RCC University of Washington

University of Alabama at Birmingham (5)
PI: Michael Lyerly, MD
Coordinator: Tammy Davis
RCC University of Alabama

University of Texas Health Science Center San Antonio (5)
PI: Reza Behrouz, MD
Coordinator: Jody Richardson
RCC University of Texas Houston

ARCADIA•CSI
Cognition & Silent Infarcts

2020 Top Enrolling Sites

UPMC Presbyterian Hospital (4)
PI: Matthew Star, MD
Coordinator: Jason Weimer
RCC UPMC

NYP Weill Cornell Medical Center (4)
PI: Hooman Kamel, MD
Coordinator: Carla Sherman
RCC Columbia University

Emory University (4)
PI: Fadi Nahab, MD
Coordinator: Kiva Schindler
RCC Emory University

Intercoastal Medical Group (4)
PI: Mauricio Concha, MD
Coordinator: Robynn Pannell
RCC University of Miami

Mayo Clinic (4)
PI: Michelle Lin, MD
Coordinator: Meredith McDonald
RCC University of Miami

2020 Top Enrolling Sites

Moses H. Cone Memorial Hospital
Greensboro, NC: 28
PI: Pramod Sethi, MD
Coordinators: Glynda Reaves, Rizwan Sabir
RCC 05 Medical University of South Carolina

Brooks Rehabilitation Hospital
Jacksonville, FL: 25
PI: Parag Shah, MD
Coordinators: Taisiya Matev, Eileen Daugherty
RCC 16 University of Miami

Sarasota Memorial Hospital
Sarasota, FL: 9
PI: Mauricio Concha, MD
Coordinator: Jeanette Wilson
RCC 16 University of Miami

University of Cincinnati Medical Center
Cincinnati, OH: 7
PI: Natalie Kreitzer, MD
Coordinator: Sadie Caldwell
RCC 14 University of Cincinnati

2020 Top Enrolling Sites

Oregon Health & Science University Hospital, Portland, OR: 7
PI: Hormozd Bozorgchami, MD
Coordinators: Frida Mata-Marquez, Amber Lee
RCC 10 Stanford University

Prisma Health Richland Hospital Columbia, SC: 7
PI: Souvik Sen, MD
Coordinator: Phil Fleming
RCC 05 Medical University of South Carolina

North Shore University Hospital Manhasset, NY: 7
PI: Rohan Arora, MD
Coordinators: Prat Subramaniam, Kirendra Pasram
RCC 29 Yale University

McLaren Flint Flint, MI: 7
PI: Mahmoud Rayes, MD
Coordinator: Marci Roberts
RCC 17 University of Michigan

2020 Top Enrolling Sites

Duke University Hospital, Durham, NC (6)
PI: Jody Feld
Coordinator: Kristina Balderson
Team: Pratik Chhatbar, Taewon Kim, Maggie Hoder, Janna Pogers, and Wayne Feng
RCC 27 Wake Forest University

University of Cincinnati Medical Center, Cincinnati, OH (6)
PI: Oluwole Awosika
Coordinator: Colin Drury
Evaluator: Lori McAleer
Therapists: Emily Wasik, Melinda Earnest, Matthew DeLange
RCC 14 University of Cincinnati

MedStar National Rehabilitation Network, Washington, DC (5)
PI: Richard Zorowitz, MD
Coordinator: Margot Giannetti McCloskey
Primary therapist: Abby Mitchell, MS, OTR/L
Additional TRANSPORT2 members: Shashwati Geed, PhD, Megan Grainger and Kathaleen Brady, PT, MPT and Preethy Feit, MS, CCRP
RCC 06 Medstar Health Research Institute

2020 Top Enrolling Sites

Moss Rehab at Elkins Park, Elkins Park, PA (4)
PI: Dylan Edwards
Coordinator: Sapna Kumar
Site Co-I: Dr. Ning Cao,
Assessors: Stephanie Farm, Jaun May
Therapists: Shannon Donovan, Samantha Snapp
RCC 19 University of Pennsylvania

Emory Rehabilitation Hospital, Atlanta, GA (3)
PI: Steven Wolf
Co PI: Michael Borich
Coordinator: Susan Murphy
Evaluator: Marsha Bidgood
Therapists: Theresa McLaughlin, Heather Stewart
RCC 03 Emory University

University of Alabama Hospital, Birmingham, AL (3)
PI: Chen Lin, MD
CRC: Tammy R. Davis, RN
Team: David Morris, PhD, Rodolphe Nenert, Ph.D., Ashley Parish, Ph.D., Sheree York, PhD, William Willoughby, PhD
RCC 26 University of Alabama at Birmingham

2020/21 Top Enrolling Sites

BOSTON, MA (15 CHILDREN)
Boston Children's Hospital & Mass General Hospital
PI: Laura Lehman
Co-PIs: Patricia Musolino & Michael Rivkin
Study Coordinator: Julie Swanson
StrokeNet RCC Name: RCC 04 Massachusetts General Hospital

SAN DIEGO/LA JOLLA, CA (5 CHILDREN)
UC San Diego Health
PI: Doris Trauner
Co-Is: Jeffrey Gold & Dillon Chen
Study Coordinator: Kathleen Scarvie
StrokeNet RCC Name: RCC 12 The Regents of the University of California - U.C. San Diego

COLUMBUS, OH (5 CHILDREN)
OSU & Nationwide Children's Hospital
Co-PIs: Amy Darragh, Warren Lo, & Jill Heathcock
Co-Is: Kelly Tanner & Lisa Pabst
Study Coordinator: Petra Sternberg
StrokeNet RCC Name: RCC 14 University of Cincinnati

ANN ARBOR/BRIGHTON, MI (6 CHILDREN)
University of Michigan
PI: Jessica Pruente
Co-Is: Edward Hurvitz, Megan Koss, Michelle DeMarco, Janet Santos, & Michaela White
Study Coordinators: Bre'Anna Simpson & Jacqueline Lang
StrokeNet RCC Name: RCC 17 University of Michigan

ROANOKE, VA (5 CHILDREN)
Virginia Tech
PI: Stephanie DeLuca
Co-Is: Mary Rebekah Trucks & Dory Wallace
Study Coordinators: Laura Bateman & Mary Lou Schwarzer
StrokeNet RCC Name: RCC 06 Medstar Health Research Institute

2020 Top Enrolling Sites

M Health Fairview Southdale Hospital, Minneapolis, MN: 11
PI: Oladi Bentho, MD
Coordinator: Megan Tessmer, RN
RCC 18 University of Minnesota

Memorial Hermann Texas Medical Center, Houston, TX: 10
PI: Andrew Barreto, MD
Coordinator: Jamey Franklin
RCC 21 University of Texas - Houston

University of Cincinnati Medical Center, Cincinnati, OH: 9
PI: Stacie Demel, DO, PhD
Coordinator: Abigail Vollmer
RCC 14 University of Cincinnati

McLaren Flint, Flint, MI: 8
PI: Aneil Majjhoo, MD
Coordinator: Marci Roberts
RCC 17 University of Michigan

Sarasota Memorial Hospital, Sarasota, FL: 8
PI: Mauricio Concha, MD
Coordinator: Jeanette Wilson, RN
RCC 16 University of Miami School of Medicine

2020 Top Enrolling Sites

Novant Health/Forsyth Radiology (6)
PI: Donald Heck, M.D.
Coordinator: Carla Perez

Rhode Island Hospital/Miriam Hospital, Providence RI (5)
PI: Gaurav Jindal, M.D.
Coordinator: Wendy Smith
RCC 29 Yale University

Mayo Clinic, Rochester MN (4)
PI: Giuseppe Lanzino, M.D.
Coordinator: Yeoniee Kim
RCC 18 University of Minnesota

San Francisco VA Medical Center (3)
PI: Joseph Rapp, M.D.
Coordinator: Sandra Perez
RCC 12 UCSD

Mayo Clinic Jacksonville (2)
PI: Albert Hakaim, M.D.
Coordinator: Melissa Rompola
RCC 16 University of Miami

2020 Top Enrolling Sites

University Hospitals Cleveland Medical Center (2)
PI: Vikram Kashyap, M.D.
Coordinator: Nadine Norton
RCC 14 University of Cincinnati

McLaren Flint (Michigan Vascular) (2)
PI: Robert Molnar, M.D.
Coordinator: Maureen Blewett
RCC 17 University of Michigan

Inova Fairfax Hospital (2)
PI: Dipankar Mukherjee, M.D.
Coordinator: Melissa Hockman

Lyerly Neurosurgery (2)
PI: Ricardo Hanel, M.D.
Coordinator: Nancy Ebreo
RCC University of Miami

Kaiser Permanente, Los Angeles (2)
PI: Navdeep Sangha, M.D.
Coordinator: Marissa Barron
RCC 11 UCLA

2020 Top Enrolling Sites

Novant Health, Winston Salem NC
PI: Don Heck
Coordinator: Carla Perez
RCC 27 Wake Forest

Oregon Health and Science Center, Portland OR
PI: Wayne Clark
Coordinator: Jon Foley
RCC 10 Stanford

Miriam Hospital, Providence RI
PI: Herb Aronow
Coordinator: Lina Felix
RCC 29 Yale University

Mayo Clinic, Jacksonville FL
PI: Al Hakaim
Coordinator: Melissa Rompola
RCC University of Miami

Mayo Clinic Rochester MN
PI: Giuseppe Lanzino
Coordinator: Yeoniee Kim
RCC University of Minnesota

UPMC, Altoona PA
PI: Cynthia Kenmuir
Coordinator: Kristin Kerfoot
RCC 20 UPMC

RCC Feedback from PI Calls

Joe Broderick

RCC PI and RCC Coordinators – Biggest issues

- COVID challenges to recruitment (in person versus remote), repurposing of coordinators, financial constraints in new hiring.
  - Mostly recovered but some sites still not activated for research. New hires – need to be trained.
  - Recruitment getting back closer to pre-COVID but not there yet.
- Financial limitations – supporting coordinator effort; University conversations – "is it financially worth-it to be part of network if costing monies?"
  - Pragmatic trials that have higher volume of eligible patients.
  - Increased support for coordinator effort (hourly rate increased and more hours): Particularly more monies for screening enrollments in more recent trials.
  - Higher indirect rates for all submitted StrokeNet Trials since FASTEST (50%).
  - Adding yearly amount for trial maintenance in recent trial budget applications.
  - Encouragement by NINDS to use RCC monies to help cover efforts (doesn't work for non-RCC sites)
  - Trial specific financial approaches to cover successful recruitment at sites.
  - Educate PIs more about per patient budget. Coordinators to review per patient budget.

RCC PI and RCC Coordinators - Education

- Training/certification for new StrokeNet staff/coordinators would be helpful.
  - Set up a core set of presentations and materials for new trial coordinators on StrokeNet website – in addition to trial specific information. Certification not required but going through materials should be required for new coordinators.
- "Mini-med school for project and site coordinators" – really good feedback at several sites (basic information about stroke, scales, imaging, etc.) Question could we export this to larger network?
  - Yes – incorporate this into regular coordinator meetings.

RCC PI and RCC Coordinators - Education

- Can we find a way to use monies to support multiple strokenet fellows with institutional support added – particularly with RCCs that have multiple academic programs? This wasn't allowed before but lessens potential impact.
  - Discussion with NINDS. If supplemented with institution monies, and with guaranteed of protected research time of 50%, with an approved plan, we would be in favor of this approach, but we need NINDS approval.
- Use of StrokeNet fellowship positions to support talented individuals not only in vascular neurology but also individuals in neurosurgery, neuro-critical care, PMR, PT, OT, etc. Also could be used to support just starting junior faculty but key is the 50% protected research time and well-defined plan.
- How to have other investigators break into list of trial PIs/key people for new concept proposals – rather than same old people.

RCC PI and RCC Coordinators - Education

- How can junior investigators be more credited for academic role in StrokeNet?
  - We discussed how we are strongly recommending this with the various PIs of StrokeNet trials to reward highest recruitment sites with authorship on primary paper and other papers. Also participation in various trial committees as appropriate. Should be part of the SOP for the trial writing committees.
  - Yearly awards to top recruiting sites for various trials. Can be something that site PIs can use with yearly summary to chair and also for other academic recognition.

RCC PI and RCC Coordinators – Future Issues

- Capacity with number of trials. "Can we take on another trial?" And in context of COVID.
  - Should be considered carefully and should look at whether recruitment plan that each RCC and site is required to have.
  - In future, we may have to delay start of a new trial if it overlaps greatly with ongoing large trial and in which recruitment is lagging.
  - We have gone from scarcity to some sites and coordinators being stretched.
- What happens when capacity is reached at RCC? How is that viewed?
  - Answer, for big trials we would hope to have 1-2 sites within an RCC but the RCC site itself may not participate for various reasons (example – U Pittsburgh and Emory with DEFUSE III when DAWN was going on).
- Move to virtual meetings has been very positive. Saves monies. Future of in-person meetings – further discussion about when and how? Social networking is important. For discussion this upcoming year.

Trial PIs

- Recruitment, recruitment….
  - Thoughts from ICH prevention trial PIs
  - Re-engaging sites after COVID
  - eConsent
  - Recruitment videos
  - Retraining coordinators and investigators
  - Best practices
- Website – password protection of key webinars and financial information

Considerations in Prevention Trials for ICH

Hooman Kamel, Magdy Selim

Challenges

- ICH patients are critically ill
- Patients/families are more interested in an immediate fix rather than prevention
- A large number of patients are discharged to long term care facilities
- Physicians attitudes and fixed beliefs

Questions

- How do you convincingly argue that equipoise exists and advocate for randomization with clinical colleagues?
- To what degree should there be site-level buy-in to a clinical trial question before engaging in a trial?
- How to navigate conversations with potential study patients who are hearing various viewpoints from their clinicians?

Introduction to Trainee presentations

Randy Marshall

Advances in Stroke Recovery

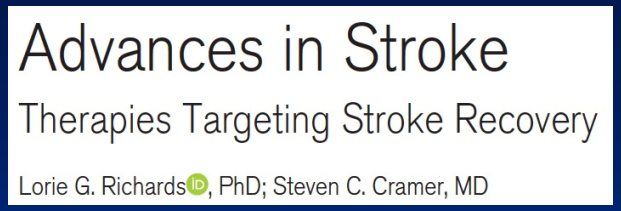
Steven C. Cramer, MD, MMSc, FAAN, FAHA

Professor, Dept. Neurology
University of California, Los Angeles

Director of Medical Research
California Rehabilitation Institute

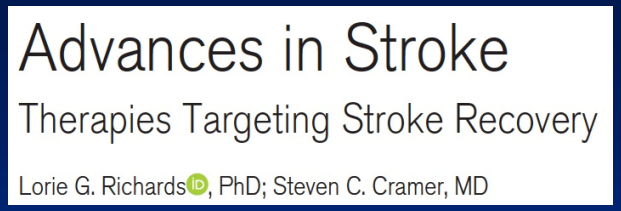
Disclosures

Dr. Cramer serves as a consultant for Abbvie, Constant Therapeutics, MicroTransponder, Neurolutions, SanBio, NeuExcell, Elevian, Medtronic, and TRCare.



Richards & Cramer. Stroke. 2021;52:348–350.

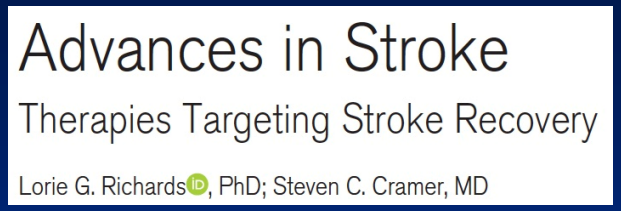
Continuum. 2020;26:415-434.



Richards & Cramer. Stroke. 2021;52:348–350.

Continuum. 2020;26:415-434.

- Advances in drugs, cells, activity-based therapies for recovery
- Includes motor, language, and hemineglect targets



Richards & Cramer. Stroke. 2021;52:348–350.

Continuum. 2020;26:415-434.

- Advances in drugs, cells, activity-based therapies for recovery
- Includes motor, language, and hemineglect targets
- 95% of patients don’t get tPA/NIR or get but remain disabled

JAMA Neurology | Original Investigation

Burden of Neurological Disorders Across the US From 1990-2017

A Global Burden of Disease Study

GBD 2017 US Neurological Disorders Collaborators

Stroke is the most burdensome neurological disorder in the U.S. in terms of disability-adjusted life-years.

JAMA Neurology. 2021;78:165-176.

StrokeNet Recovery & Rehabilitation Trials

Completed

- Telerehab Trial (clinicaltrials.gov NCT02360488)

Ongoing

- TRANSPORT-2 (clinicaltrials.gov NCT03826030)
- I-ACQUIRE (clinicaltrials.gov NCT03910075)

In process/under review

- Predictive biomarker (VERIFY Study)
- Cell therapy
- Nutrition and neuromuscular stimulation
- Intensive language therapy
- Deep brain stimulation
- Progressive exercise

Principles of Neural Repair and Their Application to Stroke Recovery Trials

David J. Lin, MD[1,4] Steven C. Cramer, MD[2,3]

Lin & Cramer. Seminars in Neurology. 2021

Principles of Neural Repair and Their Application to Stroke Recovery Trials

David J. Lin, MD[1,4] Steven C. Cramer, MD[2,3]

Table 1 Principles of neural repair

1. Neural repair is a therapeutic strategy distinct from acute stroke strategies
2. Time is a critical factor for repair-based therapies
3. Neural repair is experience-dependent
4. Measuring the effects of repair-based therapies is aided by modality-specific measures
5. Repair-based therapies are not one-size-fits-all

Lin & Cramer. Seminars in Neurology. 2021

Principles of Neural Repair and Their Application to Stroke Recovery Trials

David J. Lin, MD[1,4] Steven C. Cramer, MD[2,3]

Table 1 Principles of neural repair

1. Neural repair is a therapeutic strategy distinct from acute stroke strategies
2. Time is a critical factor for repair-based therapies
3. Neural repair is experience-dependent
4. Measuring the effects of repair-based therapies is aided by modality-specific measures
5. Repair-based therapies are not one-size-fits-all

Lin & Cramer. Seminars in Neurology. 2021

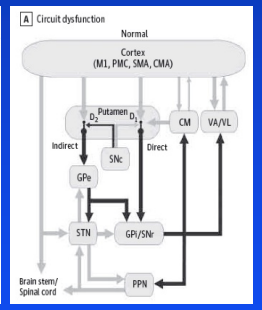
Brain repair is different from acute stroke therapy

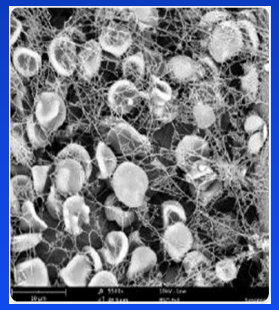
	Repair therapies	**Acute therapies**
Target	the brain	clots, arteries

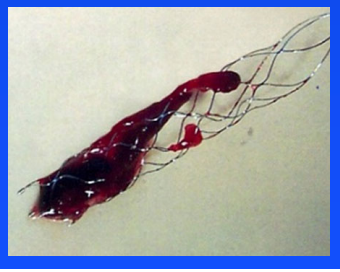
Lin et al. Stroke. 2018;49: 3107-3114

Brain repair is different from acute stroke therapy

	Repair therapies	**Acute therapies**
Target	the brain	clots, arteries







Brain repair is different from acute stroke therapy

	Repair therapies	**Acute therapies**
Target	the brain	clots, arteries
Time Window post-stroke	days-weeks +	hours
Goal	promote repair	salvage threatened tissue
Endpoints	often modality-specific	often global

Lin et al. Stroke. 2018;49: 3107-3114

Table 1 Principles of neural repair

1. Neural repair is a therapeutic strategy distinct from acute stroke strategies
2. Time is a critical factor for repair-based therapies
3. Neural repair is experience-dependent
4. Measuring the effects of repair-based therapies is aided by modality-specific measures
5. Repair-based therapies are not one-size-fits-all

Lin & Cramer. Seminars in Neurology. 2021

Table 1 Principles of neural repair

1. Neural repair is a therapeutic strategy distinct from acute stroke strategies
2. Time is a critical factor for repair-based therapies
3. Neural repair is experience-dependent
4. Measuring the effects of repair-based therapies is aided by modality-specific measures
5. Repair-based therapies are not one-size-fits-all

Lin & Cramer. Seminars in Neurology. 2021

Table 1 Principles of neural repair

1. Neural repair is a therapeutic strategy distinct from acute stroke strategies
2. Time is a critical factor for repair-based therapies
3. Neural repair is experience-dependent
4. Measuring the effects of repair-based therapies is aided by modality-specific measures
5. Repair-based therapies are not one-size-fits-all

Lin & Cramer. Seminars in Neurology. 2021

Comments, Opinions, and Reviews

The Case for Modality-Specific Outcome Measures in Clinical Trials of Stroke Recovery-Promoting Agents

Steven C. Cramer, MD; Walter J. Koroshetz, MD; Seth P. Finklestein, MD

Stroke. 2007;38:1393-1395

Comments, Opinions, and Reviews

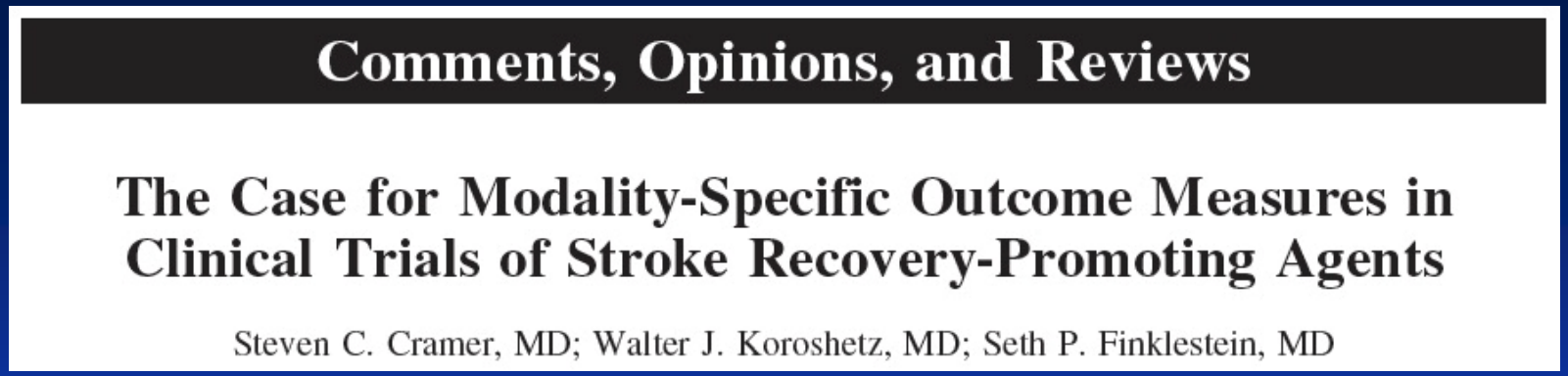
The Case for Modality-Specific Outcome Measures in Clinical Trials of Stroke Recovery-Promoting Agents

Steven C. Cramer, MD; Walter J. Koroshetz, MD; Seth P. Finklestein, MD

Often see often modality-specific
- recovery (e.g., motor gains without language gains)
- therapy (e.g., order PT but not SLT)

Modality-specific scales often have increased granularity compared to global scales

Stroke. 2007;38:1393-1395



Often see often modality-specific
- recovery (e.g., motor gains without language gains)
- therapy (e.g., order PT but not SLT)

Modality-specific scales often have increased granularity compared to global scales

Historically, neurology emphasizes both the forest and the trees.

Stroke. 2007;38:1393-1395

DISCONNEXION SYNDROMES IN ANIMALS AND MAN[1]

AND THEIR EFFECTS ON THE RANKIN SCORE

BY

NORMAN GESCHWIND

PART I

(*From the Aphasia Research Section, Neurology Service, Boston Veterans Administration Hospital and the Department of Neurology, Boston University Medical School*)

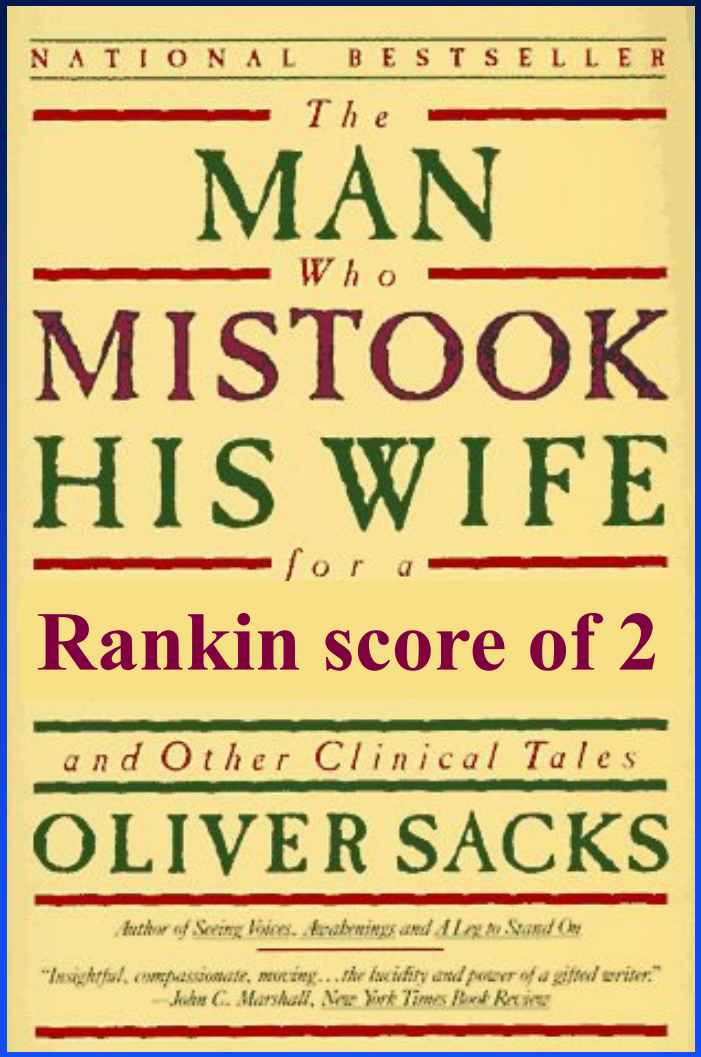
Geschwind N. Brain. 1965; 88:237-294.

Lacunes: Small, deep cerebral infarcts

Are they mRS 2 or mRS 3?

C. Miller Fisher, M.D.

Fisher CM. Neurology. 1965; 15:774-784.


NATIONAL BESTSELLER
The
MAN
Who
MISTOOK
HIS WIFE
for a
Rankin score of 2
and Other Clinical Tales
OLIVER SACKS
Author of Seeing Voices, Awakenings and A Leg to Stand On
"Insightful, compassionate, moving... the lucidity and power of a gifted writer."
—John C. Marshall, New York Times Book Review

COMMENTS AND OPINIONS

The Utility of Domain-Specific End Points in Acute Stroke Trials

Steven C. Cramer, MD; Steven L. Wolf, PhD; Jeffrey L. Saver, MD; Karen C. Johnston, MD; J Mocco, MD; Maarten G. Lansberg, MD; Sean I. Savitz, MD; David S. Liebeskind, MD; Wade Smith, MD, PhD; Max Wintermark, MD; Jordan J. Elm, PhD; Pooja Khatri, MD; Joseph P. Broderick, MD; Scott Janis, PhD; on behalf of the NIH StrokeNet Recovery and Rehabilitation Group and the Acute Stroke Group*

Cramer et al. Stroke. 2021; 52:1154–1161

The utility of domain-specific end points in acute stroke trials

Table 1. Examples of Domain-Specific End Points

Domain-specific end point	Behavioral domain assessed
Fugl-Meyer arm motor scale	Upper extremity motor deficits
Gait velocity	Functional walking ability
Western aphasia battery-revised (bedside)	Aphasia
Line cancellation test	Hemineglect
Functional Oral Intake Scale	Dysphagia
Patient Health Questionnaire-9	Depression

Cramer et al. Stroke. 2021; 52:1154–1161

The utility of domain-specific end points in acute stroke trials

Table 2. Potential Advantages and Disadvantages of Using Domain-Specific End Points in Acute Stroke Trials

Advantages
Increased resolution of measurement
Greater insight into acute therapy effects on individual brain systems
Foster a common language across all stroke trials
Better understanding of treatment mechanism
Better understanding of what goes on in the brain from acute treatment to day-90
Optimize therapeutic translation
Support therapeutic targeting of individual neural systems acutely
Capture improved outcomes in additional, patient-centered dimensions

Cramer et al. Stroke. 2021; 52:1154–1161

The utility of domain-specific end points in acute stroke trials

Table 2. Potential Advantages and Disadvantages of Using Domain-Specific End Points in Acute Stroke Trials

Disadvantages
Can require longer times to administer
Some domain-specific end points require specific testing equipment
Some domain-specific end points require specially trained personnel
Incomplete knowledge exists for the natural history of some domain-specific end points
Some domain-specific end points require further study of psychometric qualities such as validity
Experience remains limited for some domain-specific end points
Incorporating multiple domain-specific end points can increase risk of a type I error

Cramer et al. Stroke. 2021; 52:1154–1161

Bridging acute and recovery stroke trials

Bridging acute and recovery stroke trials

Intense Arm Rehabilitation Therapy Improves the Modified Rankin Scale Score

Association Between Gains in Impairment and Function

Steven C. Cramer, MD, Vu Le, MS, Jeffrey L. Saver, MD, Lucy Dodakian, MA, OTR/L, Jill See, PT, MPT, Renee Augsburger, OTR/L, Alison McKenzie, DPT, PhD, Robert J. Zhou, BA, Nina L. Chiu, BS, Jutta Heckhausen, PhD, Jessica M. Cassidy, DPT, PhD, Walt Scacchi, PhD, Megan Therese Smith, PhD, A.M. Barrett, MD, Jayme Knutson, PhD, Dylan Edwards, PhD, PT, David Putrino, PhD, PT, Kunal Agrawal, MD, Kenneth Ngo, MD, Elliot J. Roth, MD, David L. Tirschwell, MD, Michelle L. Woodbury, PhD, OTR/L, Ross Zafonte, DO, Wenle Zhao, PhD, Judith Spilker, BSN, RN, Steven L. Wolf, PT, PhD, Joseph P. Broderick, MD, and Scott Janis, PhD

Correspondence
Dr. Cramer
sccramer@mednet.ucla.edu

Neurology® 2021;96:e1812-e1822. doi:10.1212/WNL.0000000000011667

Cramer et al. Neurology. 2021;96:1812-1822

Bridging acute and recovery stroke trials

Acute trials tend to focus on mRS but not modality-specific endpoints.
Recovery trials tend to focus on modality-specific endpoints but not mRS.

Bridging acute and recovery stroke trials

Acute trials tend to focus on mRS but not modality-specific endpoints.
Recovery trials tend to focus on modality-specific endpoints but not mRS.

In the TR trial, intensive movement therapy improved arm function.
Here we asked: Did mRS also improve?

Bridging acute and recovery stroke trials

Acute trials tend to focus on mRS but not modality-specific endpoints.
Recovery trials tend to focus on modality-specific endpoints but not mRS.

In the TR trial, intensive movement therapy improved arm function.
Here we asked: Did mRS also improve?

77 patients enrolled >90 days post-stroke (historically, mRS stable by d90*)

*de Havenon et al. Variability of the modified Rankin scale score between day 90 and 1 year after ischemic stroke. Neurology: Clinical Practice. (in press).

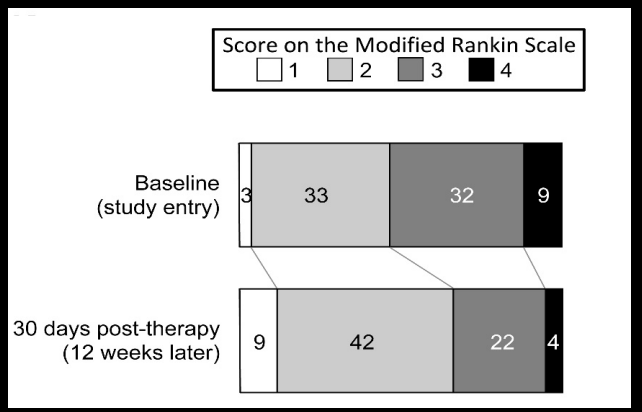
Bridging acute and recovery stroke trials

Acute trials tend to focus on mRS but not modality-specific endpoints.
Recovery trials tend to focus on modality-specific endpoints but not mRS.

In the TR trial, intensive movement therapy improved arm function.
Here we asked: Did mRS also improve?

77 patients enrolled >90 days post-stroke

mRS scores improved significantly



Median mRS score decreased from 3 to 2 ($p<0.0001$).

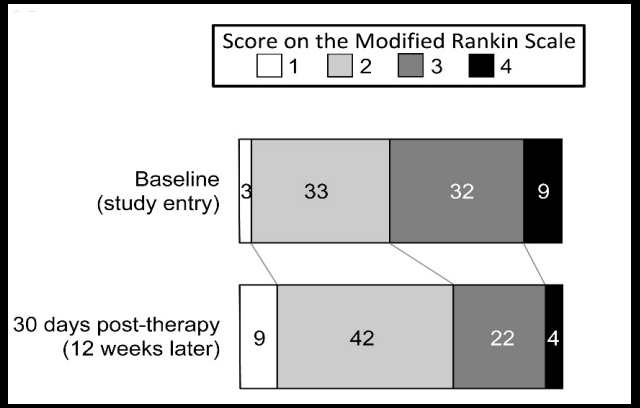
Bridging acute and recovery stroke trials

Acute trials tend to focus on mRS but not modality-specific endpoints.
Recovery trials tend to focus on modality-specific endpoints but not mRS.

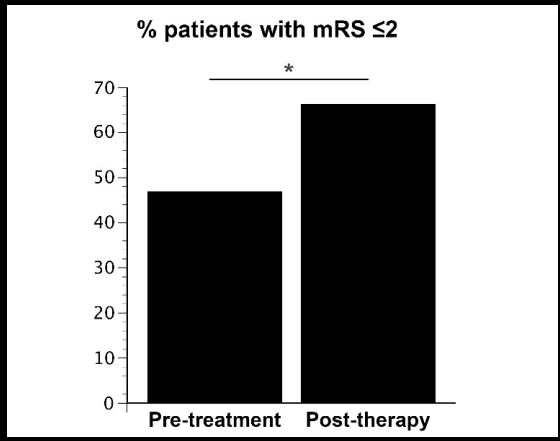
In the TR trial, intensive movement therapy improved arm function.
Here we asked: Did mRS also improve?

77 patients enrolled >90 days post-stroke

mRS scores improved significantly



Median mRS score decreased from 3 to 2 ($p<0.0001$).



Patients with mRS score 0-2 increased from 46.8% to 66.2% (*$p=0.015$).

Bridging acute and recovery stroke trials

Acute trials tend to focus on mRS but not modality-specific endpoints.
Recovery trials tend to focus on modality-specific endpoints but not mRS.

In the TR trial, intensive movement therapy improved arm function.
Here we asked: Did mRS also improve?

77 patients enrolled >90 days post-stroke

mRS scores improved significantly

Certain motor gains associated with higher odds of mRS improvement:

[1] improved finger flexion
[2] improved shoulder elevation
[3] absence of DTR hyperactivity
[4] improved wrist range of movement

Bridging acute and recovery stroke trials

Acute trials tend to focus on mRS but not modality-specific endpoints.
Recovery trials tend to focus on modality-specific endpoints but not mRS.

In the TR trial, intensive movement therapy improved arm function.
Here we asked: Did mRS also improve?

77 patients enrolled >90 days post-stroke

mRS scores improved significantly

Certain motor gains associated with higher odds of mRS improvement:

[1] improved finger flexion
[2] improved shoulder elevation
[3] absence of DTR hyperactivity
[4] improved wrist range of movement

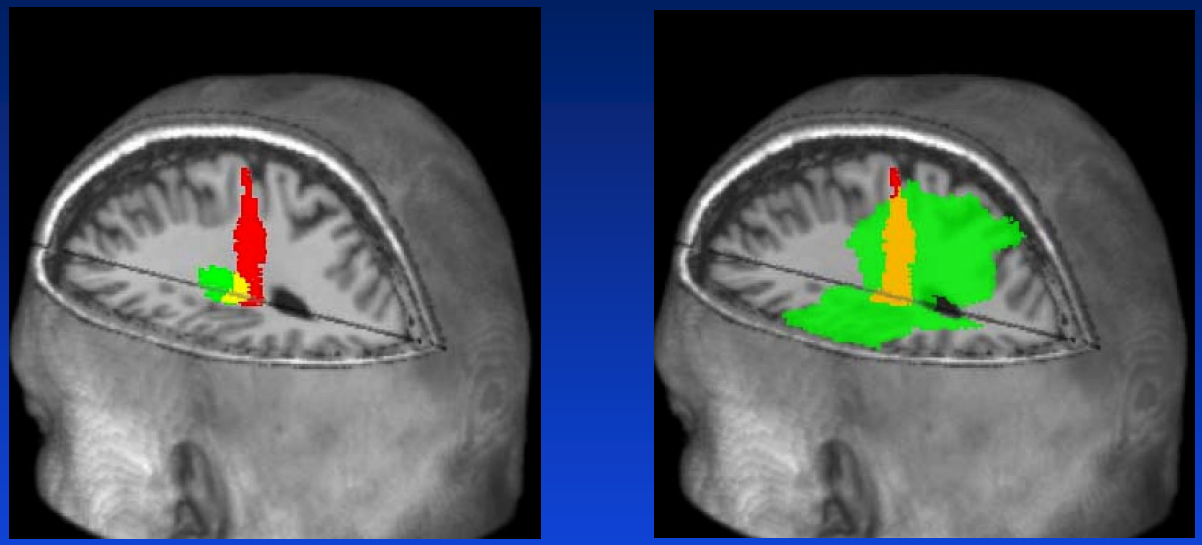
Value of a cohesive system for understanding the benefit of stroke therapeutics, from acute to recovery targets

Table 1 Principles of neural repair

1. Neural repair is a therapeutic strategy distinct from acute stroke strategies
2. Time is a critical factor for repair-based therapies
3. Neural repair is experience-dependent
4. Measuring the effects of repair-based therapies is aided by modality-specific measures
5. Repair-based therapies are not one-size-fits-all

Lin & Cramer. Seminars in Neurology. 2021

Extent of corticospinal tract injury predicts motor recovery



Riley et al, Stroke. 2011; 42:421-426

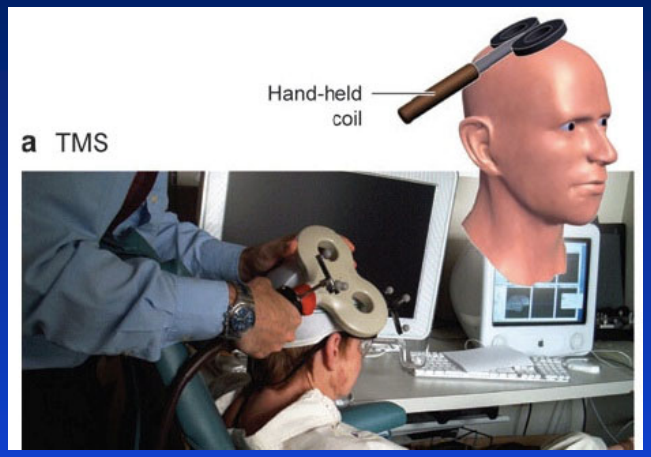
Corticospinal tract (M1)--uninjured

Corticospinal tract (M1)--injured by stroke

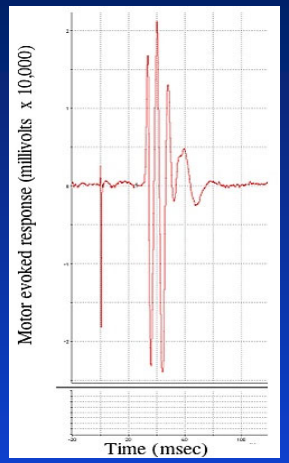
Stroke

Extent of corticospinal tract injury predicts spontaneous motor recovery as well as motor recovery with intensive therapy

Transcranial magnetic stimulation predicts motor recovery

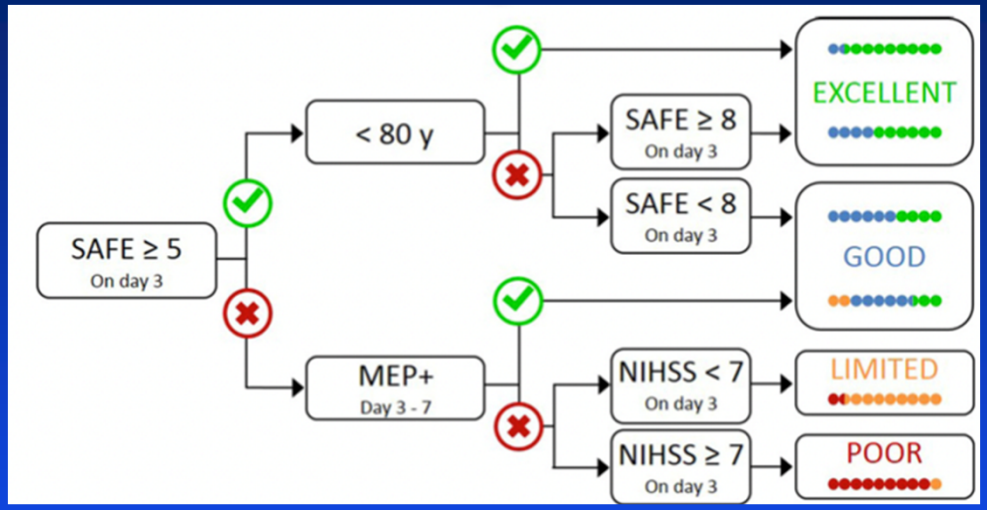


Wagner et al. Annu. Rev. Biomed. Eng. 2007. 9:527–565



- Stimulate motor cortex in stroke hemisphere
- Assess for motor evoked potential (MEP) in paretic muscle
- Presence of MEP
  - ➢Corticomotor system is functionally intact
  - ➢Predicts better spontaneous motor recovery

PREP2: predicting spontaneous arm function recovery



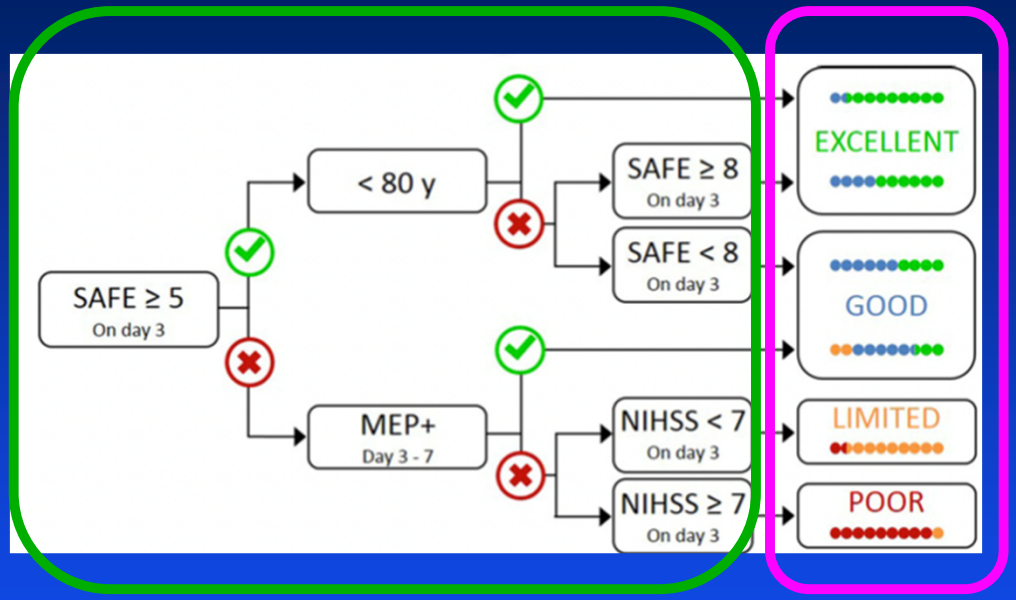
PREP
Predict Recovery Potential

SAFE
Shoulder abduction, finger extension score

NIHSS
NIH Stroke Scale

Stinear et al. PREP2: A biomarker-based algorithm for predicting upper limb function after stroke. *Ann Clin Transl Neurol*. 2017;4:811-820

PREP2: predicting spontaneous arm function recovery



Data in first week

Day 90 arm function

PREP
Predict Recovery Potential

SAFE
Shoulder abduction, finger extension score

NIHSS
NIH Stroke Scale

Stinear et al. PREP2: A biomarker-based algorithm for predicting upper limb function after stroke. *Ann Clin Transl Neurol*. 2017;4:811-820

Validation of Early Prognostic Data for Recovery Outcomes after Stroke for Future, Higher Yield Trials (VERIFY)

Aim 1: Externally validate the relationships that TMS and MRI biomarkers of corticomotor system integrity acquired < 7 days after stroke have with arm motor impairment 90 days after stroke.

Aim 2: Externally validate the PREP2 tool used < 7 days after stroke to predict 90-day functional outcomes for individual patients with stroke.

Validation of Early Prognostic Data for Recovery Outcomes after Stroke for Future, Higher Yield Trials (VERIFY)

Aim 1: Externally validate the relationships that TMS and MRI biomarkers of corticomotor system integrity acquired < 7 days after stroke have with arm motor impairment 90 days after stroke.

Aim 2: Externally validate the PREP2 tool used < 7 days after stroke to predict 90-day functional outcomes for individual patients with stroke.

During the acute admission:
Understand which patients are likely to improve and which are not.

DCU

Data Coordination Unit

MUSC Health

Medical University of South Carolina

NMDC Update

Catherine Dillon
Jordan Elm

NDMC's Biggest Challenges

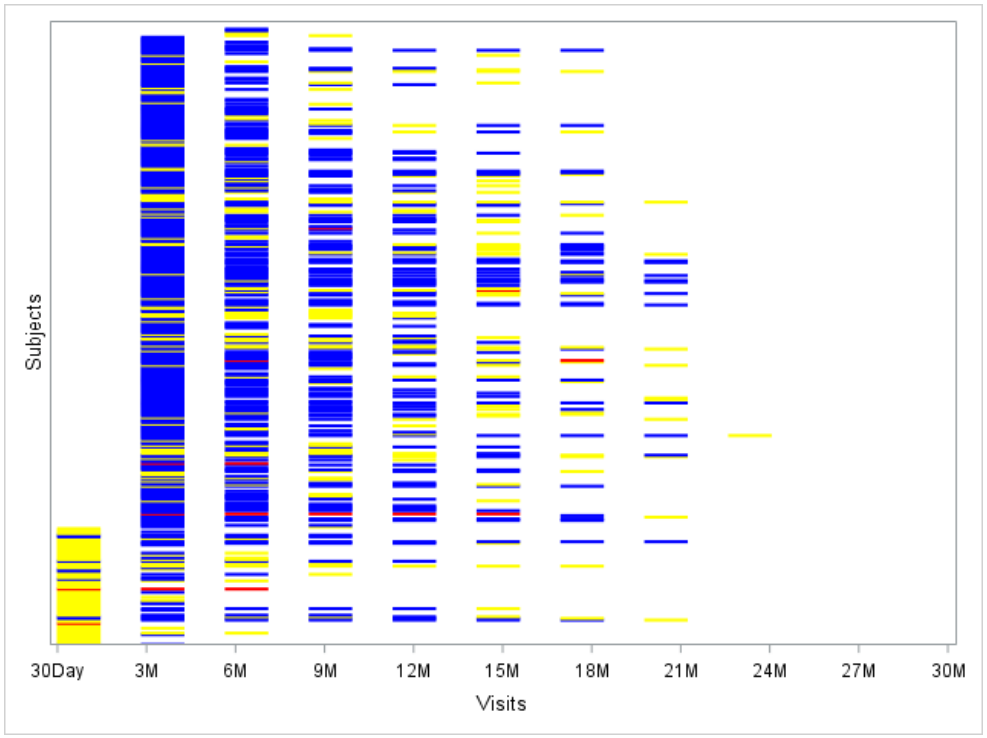
COVID-19
- New data points
- Protocol changes
- Protocol compliance

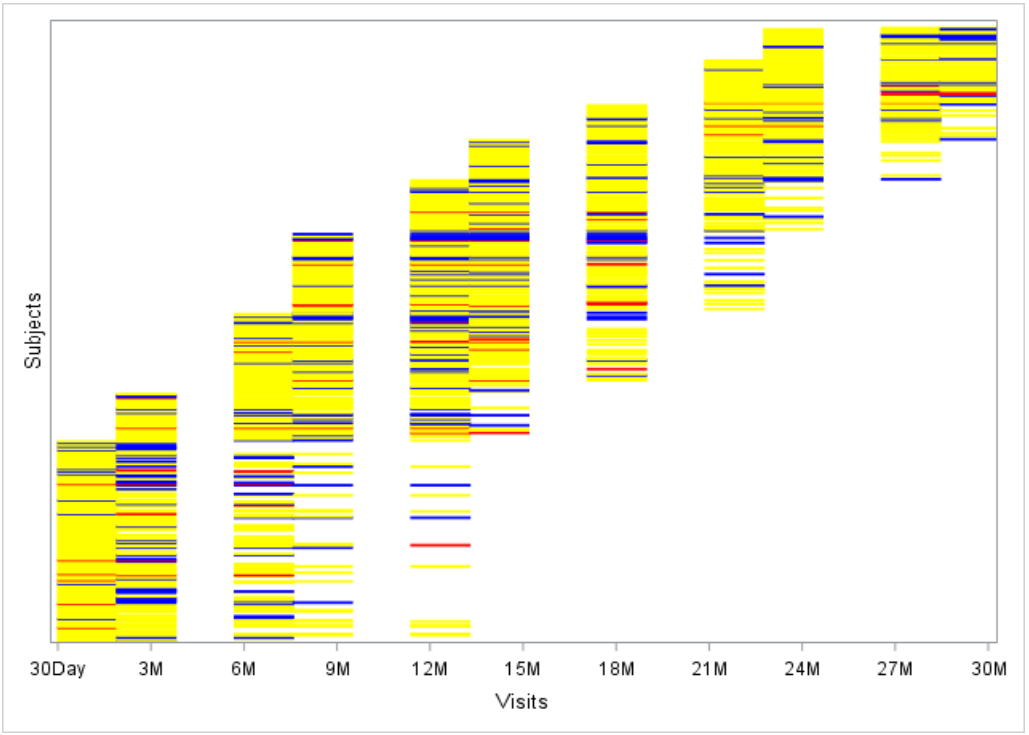
Database changes
- Un-piloted CRFs
- Study team preference
- Updates to forms are made differently across studies

Site Monitoring
- Reduced on-site access
- Study team preference

Example of Procedural Changes

Visit type before and after COVID-19
Blue: In person; Yellow: Telephone: Red: Chart review





NDMC's Response to the Challenges

Database updates:

- Creation of Library in WebDCU
- Reconciliation of forms across studies
  - CRFs (Arcadia and Aspire drug management forms)
  - Modules (drug tracking/ lab tracking)

Procedural changes to monitoring:

- Remote site visits
- Virtual check-ins

JE1

Study Supply Tracking Requirements

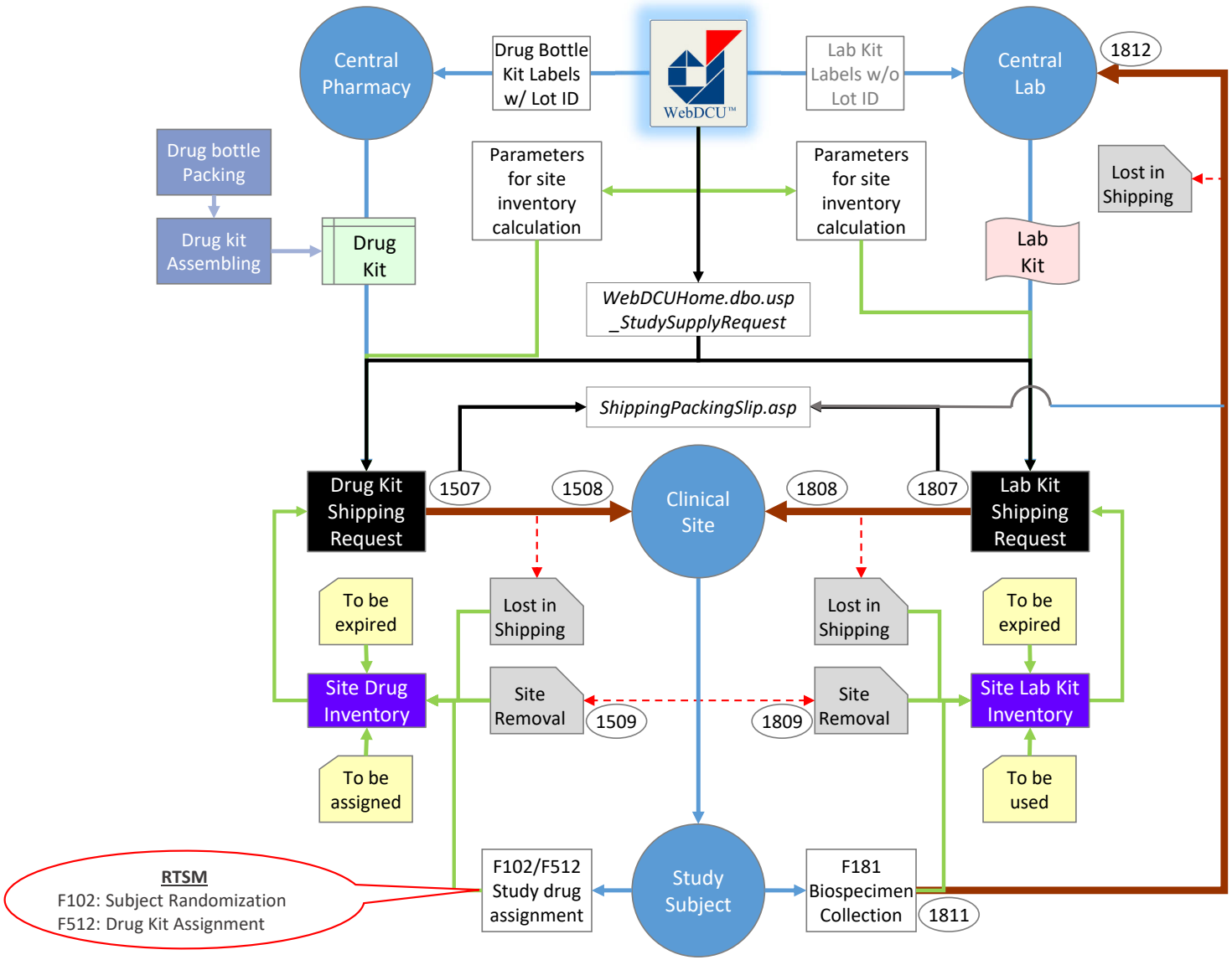
NIH StrokeNet Trials

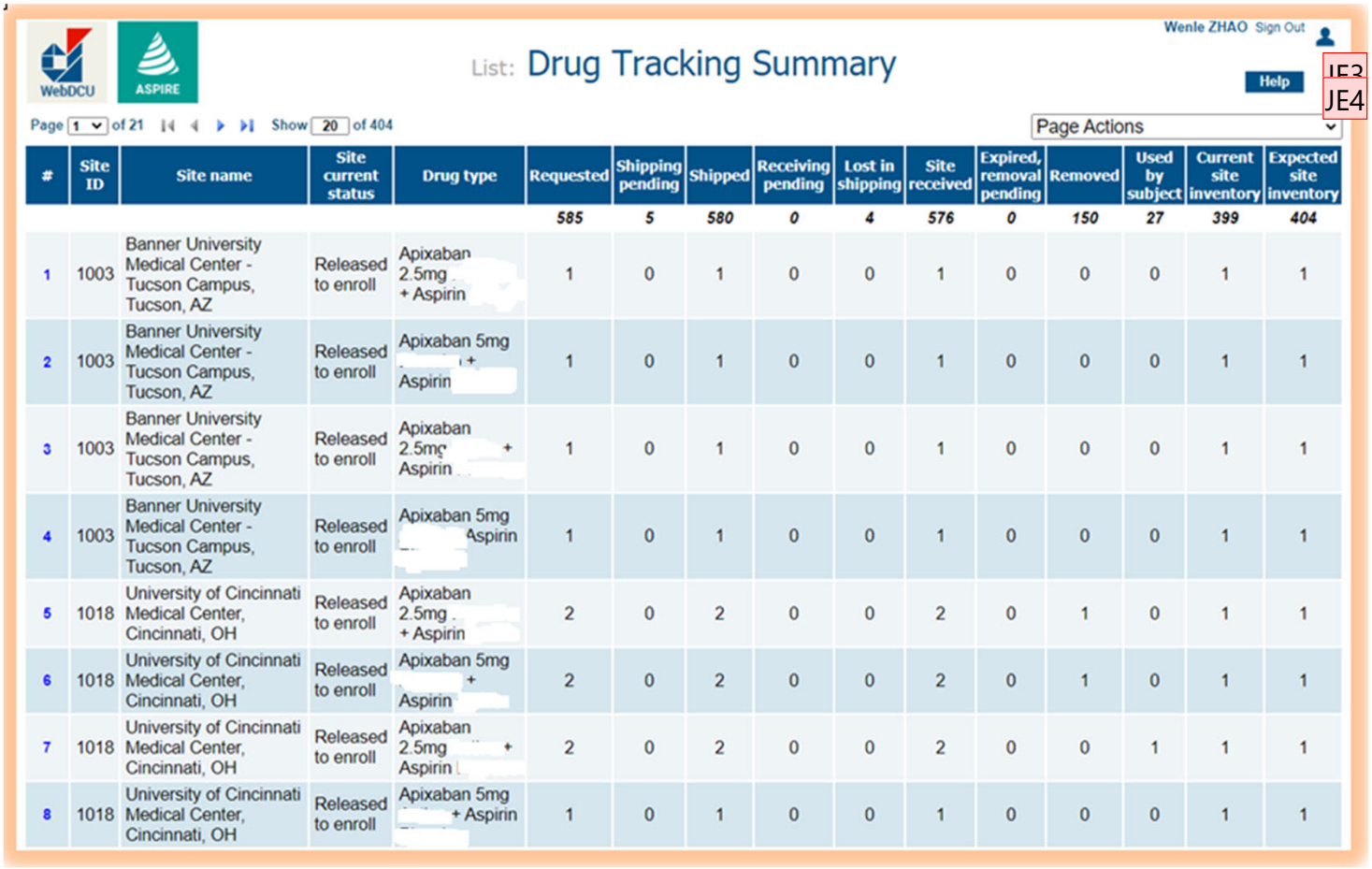
ARCADIA	ASPIRE	MOST	I-ACQUIRE	SATURN	FASTEST
					
					
Mitchell Elkind, MD	Kevin Sheth, MD	Opeolu Adeoye, MD	Sharon Ramey, PhD	Magdy Selim, MD	Joseph Broderick, MD
Columbia University	Yale University	University of Cincinnati	Virginia Tech	Harvard University	University of Cincinnati
Caitlyn Meinzer, PhD	Jordan Elm, PhD	Jordan Elm, PhD	Caitlyn Meinzer, PhD	Sharon Yeatts, PhD	Jordan Elm, PhD

NDMC, Medical University of South Carolina

Slide 87

JE1 FASTEST is a vial infusion not a pill bottle. I changed the picture
Jordan Elm, 4/12/2021


Central Pharmacy
Drug Bottle Kit Labels w/ Lot ID
WebDCU™
Lab Kit Labels w/o Lot ID
Central Lab
1812
Drug bottle Packing
Drug kit Assembling
Drug Kit
Parameters for site inventory calculation
Parameters for site inventory calculation
Lost in Shipping
Lab Kit
WebDCUHome.dbo.usp _StudySupplyRequest
ShippingPackingSlip.asp
Drug Kit Shipping Request
1507
1508
Clinical Site
1808
1807
Lab Kit Shipping Request
To be expired
Lost in Shipping
Lost in Shipping
To be expired
Site Drug Inventory
Site Removal
1509
1809
Site Removal
Site Lab Kit Inventory
To be assigned
To be used
RTSM
F102: Subject Randomization
F512: Drug Kit Assignment
F102/F512 Study drug assignment
Study Subject
F181 Biospecimen Collection
1811



WebDCU ASPIRE

Wenle ZHAO Sign Out

List: Drug Tracking Summary

Help

JE3
JE4

Page 1 of 21 Show 20 of 404

Page Actions

#	Site ID	Site name	Site current status	Drug type	Requested	Shipping pending	Shipped	Receiving pending	Lost in shipping	Site received	Expired, removal pending	Removed	Used by subject	Current site inventory	Expected site inventory
					585	*5*	*580*	*0*	*4*	*576*	*0*	*150*	*27*	*399*	*404*
1	1003	Banner University Medical Center - Tucson Campus, Tucson, AZ	Released to enroll	Apixaban 2.5mg + Aspirin	1	0	1	0	0	1	0	0	0	1	1
2	1003	Banner University Medical Center - Tucson Campus, Tucson, AZ	Released to enroll	Apixaban 5mg + Aspirin	1	0	1	0	0	1	0	0	0	1	1
3	1003	Banner University Medical Center - Tucson Campus, Tucson, AZ	Released to enroll	Apixaban 2.5mg + Aspirin	1	0	1	0	0	1	0	0	0	1	1
4	1003	Banner University Medical Center - Tucson Campus, Tucson, AZ	Released to enroll	Apixaban 5mg Aspirin	1	0	1	0	0	1	0	0	0	1	1
5	1018	University of Cincinnati Medical Center, Cincinnati, OH	Released to enroll	Apixaban 2.5mg + Aspirin	2	0	2	0	0	2	0	1	0	1	1
6	1018	University of Cincinnati Medical Center, Cincinnati, OH	Released to enroll	Apixaban 5mg + Aspirin	2	0	2	0	0	2	0	1	0	1	1
7	1018	University of Cincinnati Medical Center, Cincinnati, OH	Released to enroll	Apixaban 2.5mg + Aspirin	2	0	2	0	0	2	0	0	1	1	1
8	1018	University of Cincinnati Medical Center, Cincinnati, OH	Released to enroll	Apixaban 5mg + Aspirin	1	0	1	0	0	1	0	0	0	1	1

Slide 89

JE3 We need to cover the drug name since that is unblinding...
Jordan Elm, 4/12/2021

JE4 I've redacted it here....
Jordan Elm, 4/12/2021

Site Monitoring

- From April 1st, 2020 – March 31st, 2021:
  - Total # Monitoring Visits Conducted = **38**
    - On-site = **12**
    - Remote = **26**
  - Other Monitoring Tools Implemented this past year:
    - Virtual Site Check-in Calls
      - Total # conducted = **17**
    - Quarterly Site Metric Report Cards
      - Implemented for Sleep SMART and MOST
      - Coming soon for ARCADIA and ASPIRE

Monitoring Visits: Breakdown by Trial

	On-Site	Remote	**Total**
ARCADIA	3	11	**14**
ARCADIA-CSI	1	4	**5**
MOST	3	6	**9**
Sleep SMART	3	5	**8**
I-ACQUIRE	0	0	**0**
TRANSPORT2	2	0	**2**
ASPIRE	0	0	**0**
SATURN	0	0	**0**
TOTAL	**12**	**26**	**38**

*Monitoring visits occurring 4/1/2020 – 3/31/2021

Virtual Site Check-Ins: Breakdown by Trial

ARCADIA	5
ARCADIA-CSI	0
MOST	3
Sleep SMART	9
I-ACQUIRE	0
TRANSPORT2	0
ASPIRE	0
SATURN	0
TOTAL	**17**

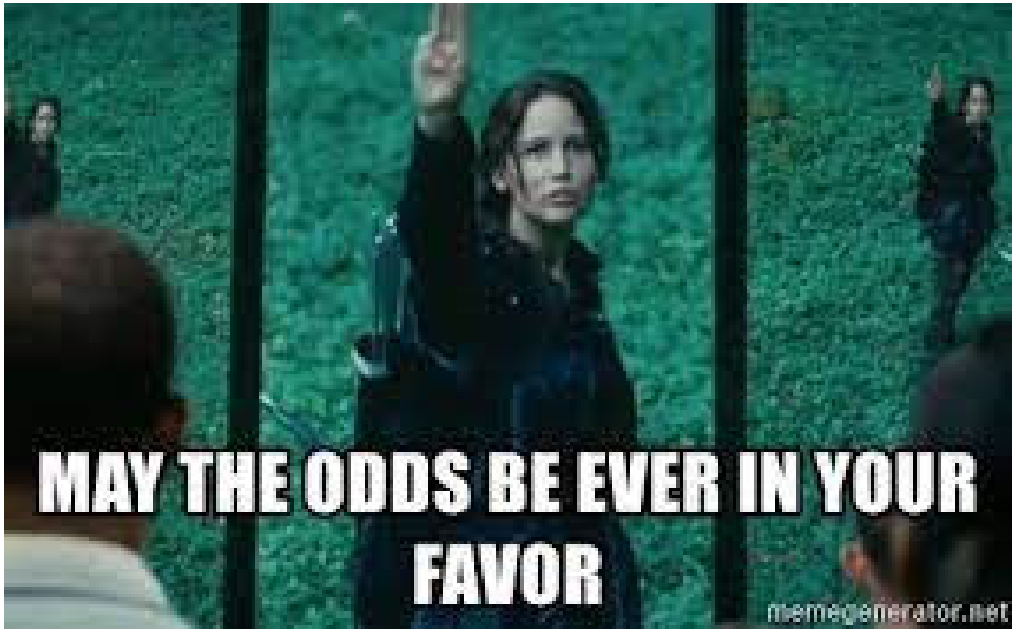
*Monitoring visits occurring 4/1/2020 – 3/31/2021

NDMC's Wishlist

- Use of standard library forms
  - Study team flexibility
  - Agreement across the network
- Maintaining consistency across studies
  - Reduce database changes
  - Implementing database changes across studies
- Maintain site monitoring flexibility
  - Increased reliance on central monitoring activities
  - Continued use of remote monitoring visits, when appropriate

Renewal

NDMC will provide standardized reports to the RCCs for renewal



NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

Goes to the MOVIES!

NOW PLAYING

- ARCADIA
- SATURN
- Sleep SMART
- MOST
- FASTEST
- CREST 2

Coming Soon!

- ASPIRE

And Lots More for your Viewing Pleasure!

Just Ask for links for more trial videos

Open Discussion