

# UC Irvine

## ICTS Publications

### Title

Stroke Recovery and Rehabilitation Research: Issues, Opportunities, and the National Institutes of Health StrokeNet.

### Permalink

<https://escholarship.org/uc/item/6xb152h7>

### Journal

Stroke, 48(3)

### ISSN

1524-4628

### Authors

Cramer, Steven C  
Wolf, Steven L  
Adams, Harold P, Jr  
[et al.](#)

### Publication Date

2017-03-07

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed



Published in final edited form as:

*Stroke*. 2017 March ; 48(3): 813–819. doi:10.1161/STROKEAHA.116.015501.

## Stroke Recovery & Rehabilitation Research: Issues, Opportunities, and the NIH StrokeNet

Steven C. Cramer, MD<sup>1</sup>, Steven L. Wolf, PhD, FAPTA, FAHA<sup>2</sup>, Harold P. Adams Jr., MD<sup>3</sup>, Daofen Chen, PhD<sup>4</sup>, Alexander W. Dromerick, MD<sup>5</sup>, Kari Dunning, PT, PhD<sup>6</sup>, Caitlyn Ellerbe, PhD<sup>7</sup>, Andrew Grande, MD<sup>8</sup>, Scott Janis, PhD<sup>9</sup>, Maarten G. Lansberg, MD<sup>10</sup>, Ronald M. Lazar, PhD, FAHA, FAAN<sup>11</sup>, Yuko Y. Palesch, PhD<sup>7</sup>, Lorie Richards, PhD<sup>12</sup>, Elliot Roth, MD<sup>13</sup>, Sean I. Savitz, MD<sup>14</sup>, Lawrence R. Wechsler, MD<sup>15</sup>, Max Wintermark, MD<sup>16</sup>, and Joseph P. Broderick, MD<sup>17</sup>

<sup>1</sup> Departments of Neurology, Anatomy & Neurobiology, and Physical Medicine & Rehabilitation; and the Sue & Bill Gross Stem Cell Research Center; University of California, Irvine; Irvine, CA

<sup>2</sup> Division of Physical Therapy, Department of Rehabilitation Medicine; Emory University School of Medicine and Atlanta VA Center for Visual and Neurocognitive Rehabilitation; Atlanta, GA

<sup>3</sup> Department of Neurology; University of Iowa; Iowa City, Iowa

<sup>4</sup> Extramural Research Program; National Institute of Neurological Disorders and Stroke; Bethesda, MD

<sup>5</sup> MedStar National Rehabilitation Hospital, Department of Rehabilitation Medicine; Georgetown University and Washington DC VA Medical Center; Washington DC

<sup>6</sup> Department of Rehabilitation Sciences; University of Cincinnati; Cincinnati, OH

<sup>7</sup> Data Coordination Unit, Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC

<sup>8</sup> Department of Neurosurgery; University of Minnesota; Minneapolis, MN

<sup>9</sup> Office of Clinical Research; National Institute of Neurological Disorders and Stroke; Bethesda, MD

<sup>10</sup> Stanford Stroke Center, Department of Neurology and Neurological Sciences; Stanford University School of Medicine; Stanford, CA

---

CORRESPONDING AUTHOR: Steven C. Cramer, MD, University of California Irvine Medical Center, 200 S. Manchester Ave, Suite 206, Orange, CA 92868, Phone: (714) 456-6876; Fax: (949) 824-5488, scramer@uci.edu.

### Disclosures and disclaimer

Steven C. Cramer has consulted for Dart Neuroscience, MicroTransponder, Roche, and Toyama. Steven L. Wolf has consulted for MicroTransponder and currently consults for Enspire. Maarten G. Lansberg has consulted for Roche. Lorie Richards has received royalties from Medbridge. Sean I. Savitz, as an employee of UT-HEALTH, serves as a site investigator in clinical trials run by industry companies (Aldagen, Athersys, Genentech, Pfizer, Dart Neuroscience) for which UT-HEALTH receives payments on the basis of clinical trial contracts; serves as an investigator on clinical trials supported by NIH grants, Let's Cure CP, the TIRR Foundation, and the Cord Blood Registry Systems; served as a PI on an NIH-funded grant in basic science research; serves as a consultant to Neuralstem, SanBio, Mesoblast, ReNeuron, Lumosa, Celgene, Dart Neuroscience, and Aldagen in which all funding goes to UTHealth; and is the PI of an imaging analysis center for two clinical trials sponsored by SanBio. Lawrence R. Wechsler has received grant funding and has served as a consultant for SanBio and Athersys. The views expressed herein are solely of the authors and do not represent the viewpoint of any entity, including the US government.

<sup>11</sup> Stroke Division, Department of Neurology; Columbia University College of Physicians & Surgeons; New York, NY

<sup>12</sup> Department of Occupational Therapy; University of Utah, Salt Lake City, Utah

<sup>13</sup> Department of Physical Medicine & Rehabilitation; Northwestern Feinberg School of Medicine; Chicago, IL

<sup>14</sup> Department of Neurology; University Texas, Houston; Houston, TX

<sup>15</sup> Department of Neurology, University of Pittsburgh Medical School; Pittsburgh, PA

<sup>16</sup> Department of Radiology, Neuroradiology Section; Stanford Healthcare and School of Medicine; Stanford, CA

<sup>17</sup> University of Cincinnati Gardner Neuroscience Institute, Department of Neurology and Rehabilitation Medicine; University of Cincinnati; Cincinnati, OH

### Keywords

stroke; recovery; rehabilitation; clinical trial

---

Stroke is the 2<sup>nd</sup> leading cause of death and the 3<sup>rd</sup> leading cause of disability-adjusted life years worldwide. While numerous therapies have been developed over the last 10 years to treat acute ischemic stroke, the stark reality remains that only 5% of these patients are so treated in the U.S.<sup>1</sup>, in part due to treatment window times < 3-6 hours post-onset, and many of these 5% nonetheless have significant long-term disability. Acute treatment options after hemorrhagic stroke remain limited<sup>2</sup>.

In parallel with efforts to further develop acute stroke interventions, researchers are studying recovery and rehabilitation treatments, which can have a treatment time window measured in days, weeks, or months post-stroke. To achieve this goal, therapies aim to maximize function in brain areas that survive the stroke, or provide compensatory approaches to improve overall function. Strategies targeting recovery and rehabilitation must be seen as distinct from acute stroke therapies such as reperfusion or neuroprotection where the strategy is to limit severity of ischemic injury including preserving penumbral tissue and reducing infarct size.

Preclinical and translational research have successfully identified numerous molecular and physiological events spontaneously arising in the nervous system during the days-to-weeks following an infarct, and, subsequently, potential restorative therapies that target these events in order to improve long-term behavioral outcomes<sup>3, 4</sup>. In parallel, a burgeoning volume of data from human subjects has emerged regarding mechanisms of recovery from stroke. Together, these efforts inform translation into clinical studies for several classes of therapy including small molecules, growth factors, stem cells, monoclonal antibodies, brain stimulation, robotics and other devices, cognitive strategies, intensive training, and telerehabilitation<sup>5, 6</sup>.

The majority of patients with stroke survives the initial event but go on to live with significant disability for many years. Indeed, there are more than 6 million stroke survivors in the U.S. alone. Thus, research on therapies that improve quality of life for patients in the chronic phase of stroke is critical. Several studies have reported significantly favorable results in this regard, such as with constraint-induced therapy<sup>7</sup>, locomotor training<sup>8</sup>, fluoxetine<sup>9</sup>, and LDOPA<sup>10</sup>. However, wide-scale adoption remains largely elusive<sup>11</sup>, and recent negative trials<sup>12, 13</sup> emphasize the need to better understand recovery/rehabilitation and its treatment.

Given the burden of stroke on patients in the U.S., the NINDS formed NIH StrokeNet<sup>14</sup>, recognizing that it is important to maintain a strategic balance of coordinated studies across research areas in prevention, acute treatment, and recovery/rehabilitation. This manuscript represents the collective thoughts of the NIH StrokeNet Recovery & Rehabilitation Working Group, with the aim to elucidate the unique challenges and potential solutions stroke recovery and rehabilitation trials face. The NIH StrokeNet is an open network; trial concepts can be initiated by investigators outside of NIH StrokeNet, as well as by NIH StrokeNet investigators, along with international and private-public partnerships facilitated through this program. Available grant targets are listed elsewhere<sup>15</sup>; phase 2 and 3 trials are encouraged. Investigative sites may participate in NIH StrokeNet trials even if not part of NIH StrokeNet. The NIH StrokeNet Recovery & Rehabilitation Working Group is available to assist investigators in applying to NIH StrokeNet with many aspects of trial design, as described below, prior to formal grant submission to study section. Engaging this approach enables the community of stroke recovery/rehabilitation investigators to pursue a new and larger opportunity to drive the science and clinical application of recovery after stroke.

Stroke recovery and rehabilitation trials are not simply acute stroke studies that are initiated at late time points. Instead, the design of recovery and rehabilitation trials must address a number of issues that are not shared with other domains of stroke research<sup>16, 17</sup>. For example, recovery and rehabilitation trials may be affected by changes in the primary provider, treatment setting, concomitant therapies, or insurance coverage; the time required to effect change in the CNS is significantly longer than with acute trials; and different endpoints are needed to capture treatment effects<sup>18</sup>. Issues related to clinical trials targeting stroke recovery and rehabilitation are considered below (see also Table 1), along with discussion of how NIH StrokeNet may address these concerns.

## **Specific issues for moving stroke recovery and rehabilitation research forward**

### **Variable patterns of post-acute stroke care delivery**

In the U.S., patients transition through numerous different care settings during the weeks-to-months following a stroke. Each new setting brings a change in personnel and in organization of care. Patients are first seen in an emergency room then admitted to an acute care hospital on average for 4-5 days; this is followed by admission to an inpatient rehabilitation facility (IRF), long-term acute care hospital (LTACH), skilled nursing facility (SNF), home health care, outpatient clinic care, or a combination of these sites. The window

for many restorative interventions occurs during the subacute (days-to-weeks) and in some cases chronic (months-to-years) phase of stroke, and consequently these shifts in care delivery can greatly impact essential recovery/rehabilitation clinical trial operations such as recruitment, treatment delivery, and subject retention. Any therapy provided in these settings will be delivered in variable doses by various personnel using varying approaches, and so may also confound the effect of an intervention tested in a given trial.

A key issue in this context is that the amount of rehabilitation care is often driven by payer rather than clinical needs. This critical issue in stroke recovery/rehabilitation research, particularly in the U.S., is not easily addressed. However, the size of the StrokeNet network might allow investigators to select sites in a manner that in part addresses this challenge. In acute stroke and prevention trials, differences in care delivery may be treated as nuisance variables or simply ignored under the assumption that differences will be equally distributed across study arms, but in recovery/rehabilitation trials any such differences may be important and integrally related to the biological mechanism underlying treatment effects. For example, one repair-based stroke clinical trial compared ropinirole+physical therapy with placebo+physical therapy. The study found that the two treatment arms did not differ in the behavioral endpoint (gait velocity), but also that the amount of outside physiotherapy (i.e., physiotherapy occurring in parallel with trial participation, but prescribed by private physicians, outside of trial jurisdiction) differed significantly between arms, with placebo receiving nearly double the amount of outside physiotherapy compared to the active treatment arms<sup>19</sup>. As was done in this study, such measures can be treated as planned covariates of interest in statistical analyses. Substantial data will be needed to potentially change patterns of post-acute stroke care delivery. NIH StrokeNet provides stroke recovery and rehabilitation investigators with new avenues for addressing such issues, with the potential to answer questions with greater speed, depth, and efficiency, aided by a large network of teams that are organized linearly across sequential treatment settings.

### **Subject recruitment challenges after discharge from the acute care setting**

Although some studies of stroke recovery therapeutics enroll patients during the initial days of the acute hospitalization, most studies to date have had a time window of weeks or months post-stroke. A time window this broad means that patients are recruited after hospital discharge, and so such trials must devise specific strategies for identifying potential study enrollees. The demands for finding potential enrollees in subacute settings, such as SNFs, and in chronic settings, such as in the community, are very different from those encountered in an acute setting, where the patients are brought directly to the investigator's Emergency Department. Furthermore, acute care often takes place at a stroke center and is provided by a specific team specializing in cerebrovascular disease. In contrast, following hospital discharge, care is provided by a range of clinicians who often are not focused on stroke or stroke research. Also, centers enrolling in clinical trials may be distant from a patient's home, limiting interest in participation due to travel time and inconvenience. Stroke survivors may withdraw from social participation for numerous reasons and may also be limited by stroke-related disabilities. All of these factors reduce the likelihood that a person who has returned to the community can and will seek out a clinical trial focused on stroke recovery/rehabilitation. Increased coordination across community-based organizations, such

as stroke support groups, might be useful to address these issues in chronic settings. At earlier stages post-stroke, a focus on patients admitted to an IRF may help address recruitment issues, and note that many such units participate in NIH StrokeNet. Overall, however, a paradigm shift is needed to improve recruitment into post-acute stroke trials<sup>20</sup>. The NIH StrokeNet, being organized across a wide range of acute and chronic settings, is positioned to support new approaches for recruiting patients into stroke recovery and rehabilitation trials, including contact and recruitment of potential subjects while they are still in the acute hospital and IRF settings. Another potential future goal for StrokeNet is to strengthen recruitment practices in LTACHs and SNFs that are affiliated with hospital systems involved with StrokeNet.

### **Subject retention challenges and social/pragmatic factors**

A patient's life can be turned upside down by a stroke. The patient trying to understand and reorder his/her life after a stroke must often deal with a host of social, marital, spiritual, occupational, legal, and fiscal issues, any of which can greatly affect retention and recruitment in a clinical trial. Similar issues often arise for family members who become caregivers, whose livelihood influences the patient's recovery, whose health is commonly adversely affected by their loved one's stroke, and whose support is often critical to subject retention in a trial focused on recovery/rehabilitation. Importantly, these societal and personal factors are not easily addressed in preclinical laboratory research although their impact on human recovery is often substantial.

These issues are exacerbated by the fact that stroke recovery and rehabilitation trials often involve multiple treatment sessions, each requiring a visit to the enrollment site. This issue is encountered much less often in acute stroke studies, which generally have only a one-time intervention. Consequently, one fundamental issue that impacts recovery trials is patient transportation. For example, if there are two-dozen treatment sessions, then there are two-dozen round trip transportations to be arranged. The routine of getting ready to leave the home, driving/parking or taking public transportation, and walking/wheeling to the clinic can last several times longer than the research visit itself. Such issues may seem banal, but the scientific method of research hypothesis testing is thus easily threatened in stroke recovery/rehabilitation trials by the added requirement that a second person, such as a spouse or child, must be simultaneously available, or that public transportation services are functioning normally and that the patient can reliably use them. Transportation costs are sometimes a leading budget line item in stroke recovery/rehabilitation trials. Creative solutions are needed to address problems arising from social/pragmatic factors to enhance enrollment and participation in recovery clinical trials. NIH StrokeNet has wide-ranging expertise to address such issues; for example, in an ongoing NIH StrokeNet trial<sup>21</sup>, satellite treatment sites are being set up to shorten transportation times.

### **Behavioral status is changing every day**

A person's behavioral state evolves rapidly during the initial days and weeks following stroke onset. Thus, for stroke recovery/rehabilitation trials recruiting during this time period, behavioral status of subjects at baseline is often evolving and not stable. This complicates many aspects of study design, clinical endpoints, and data analysis. For example, the

minimal clinically important difference, the anticipated slope of spontaneous behavioral change, and ideal choice of biomarkers all change in relation to time post-stroke. Recovery/rehabilitation trials might at times consider using longitudinal and latent class modeling to examine stability of the intervention over time and impact of incomplete treatment compliance on outcome. Substantial gaps exist in knowledge of how behavior, anatomy, and physiology evolve during the days-weeks following stroke in human subjects, yet such information may be key to optimal design and analysis of stroke recovery/rehabilitation trials during this critical period. The NIH StrokeNet network and its studies provide a platform to generate this knowledge and in parallel to pursue new trial designs and statistical approaches that are useful for addressing issues arising from a non-constant baseline among study enrollees<sup>6, 22</sup>.

### **Importance of concomitant activity and therapy**

Reperfusion with IV tPA is passive because patients need not perform a particular behavior once the drug is infused to insure treatment efficacy. Evidence suggests, however, that many stroke recovery therapies do benefit from concomitant behavioral training<sup>23</sup>--the brain circuits galvanized for rewiring need the right experience to shape them, akin to normal development. What the patient does or doesn't do, and how they are engaged during the black box between hospital discharge and study follow-up at day 90 post-stroke, may be particularly important for understanding effects of interventions targeting stroke recovery. New methods for measuring patient activity<sup>24</sup> stand to sharpen interpretation of clinical trial results.

Similarly, many patients in recovery/rehabilitation trials receive concomitant rehabilitation therapy as part of standard care. Such therapy might directly affect outcome measure scores in stroke recovery/rehabilitation trials. The amount and the type of standard of care rehabilitation therapy after stroke are quite variable<sup>13</sup>, and so controlling concomitant therapy in a clinical trial context is daunting if not unrealistic. As a result, key strategies revolve around anticipating and measuring such therapies. A further complication in the U.S. is that the amount and type of rehabilitation care vary substantially by region and by insurance reimbursement policies. Variability in patient participation also contributes to lack of uniformity. A data-driven and systematic optimization of rehabilitation therapy is needed where timing, dosing, and content of rehabilitation treatment are standardized appropriately for the billions of dollars spent on stroke rehabilitation<sup>25</sup>. In addition to optimizing clinical rehabilitation for stroke patients, such a pathway would facilitate clinical trials of restorative treatments and provide a reproducible baseline. NIH StrokeNet members with experience integrating issues related to concomitant therapy into clinical trial design will be able to help investigators address this issue.

### **Recovery and rehabilitation research competes with health care business practices and with other stroke trials**

Interventions, assessments, and study visits that are part of a stroke recovery/rehabilitation trial can impact the process of health care delivery, depending on the study and its timing post-stroke. This consideration differs from acute stroke trials, in which an experimental therapy, delivered during the initial hours after stroke onset, rarely affects flow of care in a

substantial way. Thus, recovery/rehabilitation trial processes can involve patients in ways that affect or even threaten delivery of standard of care. Furthermore, some rehabilitation clinicians might be reluctant to participate in a trial if doing so is perceived as potentially competing with critical clinical revenue.

A parallel issue is that at times a patient may be simultaneously eligible for more than one type of stroke trial, e.g., both an acute and a recovery trial, and so two studies might compete for enrolling the same patient. Rather than characterizing acute trials as diverting patients from the recovery pipeline; however, patients may be eligible to co-enroll in both if this is built into the study design. Practically, this can be characterized as a factorial-type design<sup>26</sup>, and a number of solutions have been proposed in this regard<sup>27, 28</sup>. NIH StrokeNet may have advantages for helping investigators to incorporate such designs and insure that studies are appropriately powered to enable co-enrollment given the facility of collaboration between its Recovery/Rehabilitation Working Group, Acute Working Group, and Prevention Working Group.

### **Need to target appropriate patient subgroups**

Considerable preclinical and clinical evidence indicates that recovery/rehabilitation therapies after stroke are generally not a “one size fits all” scenario<sup>29</sup>, with large inter-subject variability present in response to treatment. This variability stems from three main issues. First, stroke encompasses a broad range of clinical entities, with high variability in factors such as neural injury (e.g., stroke mechanism, location, and volume, each superimposed on differing degrees of pre-stroke vascular brain pathology) and clinical factors (e.g., age, gender, depression, and vascular risk factors such as diabetes mellitus). Second, stroke leaves some brains too devastated to respond to a restorative therapy, and so there is variability in capacity to respond to treatment. A brain that responds to a restorative therapy does so by promoting plasticity within surviving neural elements<sup>23</sup>, and so sufficient neural resource must remain in an appropriate functional state for the treatment to help<sup>30-34</sup>. Third, for studies enrolling participants during the initial days-weeks following stroke onset, the effect of time is substantial. During this interval, numerous restorative events spontaneously occur in the brain, and these evolve day-to-day<sup>3, 4</sup>. This dynamic affects behavioral recovery and, for several types of restorative therapy, has also been shown to affect responsiveness to treatment<sup>35-38</sup>. The fact that the same patient falls within the target subgroup one day but might not thereafter makes design of effective clinical interventions a challenge; this familiar theme in acute stroke medicine is no less true for many forms of restorative therapy.

To be successful, stroke recovery/rehabilitation research must better characterize the most important inter-subject differences with respect to treatment responsiveness, and clinical trials need to incorporate appropriate measures in study design and data analysis. One strategy is to enroll a carefully targeted select subgroup of patients<sup>30-34</sup>, among whom a larger effect size is expected and so ability to detect a true treatment effect is improved; later trials can explore the degree to which results generalize and the effects of widening the target population. Furthermore, improved tools are needed to distinguish between spontaneous recovery and effects of an experimental treatment, a strategy that would be facilitated by an improved means to accurately predict an individual patient's outcome in the



specific behaviors that comprise endpoints in recovery/rehabilitation trials. Additional studies are needed in this area, possibly via longitudinal measurements with fine granularity. Biomarkers might be useful for target group selection and could be incorporated into trial design, although few biomarker validation studies exist in this context. Therefore, studies with appropriate size and statistical power are needed to validate biomarkers, including with respect to key points of variability such as neural injury and time post-stroke (see below). NIH StrokeNet has hundreds of potential research participation sites and so provides an unprecedented opportunity to perform trials with investigations that address issues related to patient subgroups. Furthermore, investigators within the NIH StrokeNet network possess expertise spanning many potentially relevant fields including genetics, proteomics, bioengineering, and biomechanics; for example, the Imaging Group can advise regarding many forms of neuroimaging<sup>39</sup>. Such expertise may be incorporated into scientific aims to develop and validate best methods for understanding and defining those patient subgroups that are most likely to respond to a putative restorative/rehabilitation therapy.

### **Need to implement biomarkers**

A biomarker is an indicator of tissue state that reflects underlying molecular and cellular events<sup>40-42</sup>. Biomarkers might serve several roles such as patient selection (e.g., by providing a measure of brain function or injury) or treatment monitoring (e.g., by measuring biological effects of the therapy being studied). NIH StrokeNet provides an opportunity to develop, evaluate, and validate biomarkers in the context of stroke recovery/rehabilitation trials, much as infarct volume and perfusion measures have been advanced in acute stroke trials.

The most favorable approaches to non-invasively capturing events underlying stroke recovery in human participants remains to be determined. As a result, the investigative tools that are needed to set the stage for optimal therapeutic discovery are themselves yet to be determined. There are several promising candidate techniques, such as MRI measures of neural injury including diffusion tensor imaging (DTI), connectivity, and function; electroencephalography measures of connectivity; and transcranial magnetic stimulation (TMS) measures of motor system function<sup>42-46</sup>. Well-powered, multi-site studies examining psychometric characteristics of recovery biomarkers are sorely needed, including those that consider critical covariates such as extent, location, and timing after stroke. CT perfusion imaging was virtually unknown when the first IV tPA trial was performed but now is supported by virtually all commercial CT scanners, and indeed was central to patient selection in some recent positive acute reperfusion trials<sup>47</sup>. Similarly, if evidence continues to mount that MRI, EEG, or TMS adds value to stroke recovery/rehabilitation trials, support will be needed to insure these techniques are accessible in a standardized fashion at investigative sites across the U.S. The NIH StrokeNet is well positioned to achieve this vision and to help standardize biomarkers measurement so that they can aid in multi-site clinical trial research and become clinically useful.

### **Standardize outcome measures**

In stroke recovery and rehabilitation research there is a lack of consensus on the best measurements of improvement to use as definitive outcomes in trials. For example, a recent

review of 477 studies found that 48 different outcome measures were used to report arm motor recovery alone<sup>48</sup>. Common data elements are needed to interpret and compare findings across time, sites and interventions<sup>49</sup>, with some progress having been fostered by NIH<sup>50</sup>. In contrast with dichotomization and shift analyses often used in acute stroke study outcome measures, many of the more popular choices of outcome measures are treated as continuous variables, which introduces additional challenges in design such as the need to define the minimum clinically important improvement and the variability of the treatment effect. A parallel and equally critical issue is the need to standardize the methods by which outcome measures are scored<sup>51, 52</sup>. One study found that standardized training for the arm motor Fugl-Meyer scale improved accuracy and reduced the variance of scoring by 20%, which would decrease sample size requirements from 137 to 88 in a standard clinical trial<sup>53</sup>.

## Stroke Recovery & Rehabilitation Research Opportunities and the NIH

### StrokeNet

People disabled by stroke represent a huge opportunity for NIH and stroke researchers to improve health of stroke patients globally. There are many promising leads for recovery and rehabilitation treatments that could improve patient outcomes after stroke. NIH StrokeNet provides a platform to pursue new trial designs that better reflect the complex interventions studied in many stroke recovery and rehabilitation trials<sup>54</sup>. The study of several scientific issues, summarized above, stands to improve the ability of clinical trials to test candidate restorative interventions. Many of these issues are not shared by acute stroke or stroke prevention trials and place emphasis on the need to develop improved infrastructure and methods for performing stroke recovery/rehabilitation trials. The NIH StrokeNet represents a major avenue in this regard.

### Acknowledgments

#### Funding Sources

The NIH StrokeNet National Clinical Coordinating Center is supported by NIH U01NS086872 and National Data Management Center is supported by U01NS087748. Steve Cramer is supported by NIH K24 HD074722.

### References

1. Adeoye O, Hornung R, Khatri P, Kleindorfer D. Recombinant tissue-type plasminogen activator use for ischemic stroke in the united states: A doubling of treatment rates over the course of 5 years. *Stroke*. 2011; 42:1952–1955. [PubMed: 21636813]
2. Adams HP Jr, Nudo RJ. Management of patients with stroke: Is it time to expand treatment options? *Ann Neurol*. 2013; 74:4–10. [PubMed: 23720339]
3. Hermann DM, Chopp M. Promoting brain remodelling and plasticity for stroke recovery: Therapeutic promise and potential pitfalls of clinical translation. *Lancet Neurol*. 2012; 11:369–380. [PubMed: 22441198]
4. Carmichael ST. Emergent properties of neural repair: Elemental biology to therapeutic concepts. *Ann Neurol*. 2016; 79:895–906. [PubMed: 27043816]
5. Cramer SC. Repairing the human brain after stroke. II. Restorative therapies. *Ann Neurol*. 2008; 63:549–560. [PubMed: 18481291]
6. Carter AR, Connor LT, Dromerick AW. Rehabilitation after stroke: Current state of the science. *Curr Neurol Neurosci Rep*. 2010; 10:158–166. [PubMed: 20425030]

7. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: The EXCITE randomized clinical trial. *JAMA*. 2006; 296:2095–2104. [PubMed: 17077374]
8. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, et al. Bodyweight-supported treadmill rehabilitation after stroke. *N Engl J Med*. 2011; 364:2026–2036. [PubMed: 21612471]
9. Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): A randomised placebo-controlled trial. *Lancet Neurol*. 2011; 10:123–130. [PubMed: 21216670]
10. Scheidtmann K, Fries W, Muller F, Koenig E. Effect of levodopa in combination with physiotherapy on functional motor recovery after stroke: A prospective, randomised, double-blind study. *Lancet*. 2001; 358:787–790. [PubMed: 11564483]
11. Bayley MT, Hurdowar A, Richards CL, Korner-Bitensky N, Wood-Dauphinee S, Eng JJ, et al. Barriers to implementation of stroke rehabilitation evidence: Findings from a multi-site pilot project. *Disabil Rehabil*. 2012; 34:1633–1638. [PubMed: 22631218]
12. Winstein CJ, Wolf SL, Dromerick AW, Lane CJ, Nelsen MA, Lewthwaite R, et al. Effect of a task-oriented rehabilitation program on upper extremity recovery following motor stroke: The ICARE randomized clinical trial. *JAMA*. 2016; 315:571–581. [PubMed: 26864411]
13. Lang CE, Strube MJ, Bland MD, Waddell KJ, Cherry-Allen KM, Nudo RJ, et al. Dose response of task-specific upper limb training in people at least 6 months poststroke: A phase II, single-blind, randomized, controlled trial. *Ann Neurol*. 2016; 80:342–354. [PubMed: 27447365]
14. Broderick JP, Palesch YY, Janis LS, National Institutes of Health StrokeNet I. The national institutes of health stroke net: A user's guide. *Stroke*. 2016; 47:301–303. [PubMed: 26715457]
15. [December 13, 2016] Documents. NIH StrokeNet. [www.nihstroke.net/documents](http://www.nihstroke.net/documents).
16. Savitz SI, Cramer SC, Wechsler L. Stem cells as an emerging paradigm in stroke 3: Enhancing the development of clinical trials. *Stroke*. 2014; 45:634–639. [PubMed: 24368562]
17. Campbell GB, Skidmore ER, Whyte EM, Matthews JT. Overcoming practical challenges to conducting clinical research in the inpatient stroke rehabilitation setting. *Top Stroke Rehabil*. 2015; 22:386–395. [PubMed: 25775955]
18. Cramer SC, Koroshetz WJ, Finklestein SP. The case for modality-specific outcome measures in clinical trials of stroke recovery-promoting agents. *Stroke*. 2007; 38:1393–1395. [PubMed: 17332455]
19. Cramer SC, Dobkin BH, Noser EA, Rodriguez RW, Enney LA. Randomized, placebo-controlled, double-blind study of ropinirole in chronic stroke. *Stroke*. 2009; 40:3034–3038. [PubMed: 19520987]
20. Blanton S, Morris DM, Prettyman MG, McCulloch K, Redmond S, Light KE, et al. Lessons learned in participant recruitment and retention: The EXCITE trial. *Physical therapy*. 2006; 86:1520–1533. [PubMed: 17079752]
21. [December 13, 2016] Clinicaltrials.gov website for the study “Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke”. ID # NCT02360488. <https://www.clinicaltrials.gov/show/NCT02360488>.
22. Nowacki AS, Zhao W, Palesch YY. A surrogate-primary replacement algorithm for response-adaptive randomization in stroke clinical trials. *Stat Methods Med Res*. First published date: January-12-2015. 10.1177/0962280214567142.
23. Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, et al. Harnessing neuroplasticity for clinical applications. *Brain*. 2011; 134:1591–1609. [PubMed: 21482550]
24. Urbin MA, Bailey RR, Lang CE. Validity of body-worn sensor acceleration metrics to index upper extremity function in hemiparetic stroke. *J Neurol Phys Ther*. 2015; 39:111–118. [PubMed: 25742378]
25. Willems D, Salter K, Meyer M, McClure A, Teasell R, Foley N. Determining the need for inpatient rehabilitation services post-stroke: Results from eight ontario hospitals. *Healthc Policy*. 2012; 7:e105–118. [PubMed: 23372584]
26. Randolph AG. The unique challenges of enrolling patients into multiple clinical trials. *Crit Care Med*. 2009; 37:S107–111. [PubMed: 19104209]

27. Dennis M, Wardlaw J, Sandercock P, Signorini D, Warlow C. Families of trials: The answers to all our questions? *Cerebrovasc Dis*. 1999; 9:305–313. [PubMed: 10545686]
28. Myles PS, Williamson E, Oakley J, Forbes A. Ethical and scientific considerations for patient enrollment into concurrent clinical trials. *Trials*. 2014; 15:470. [PubMed: 25433679]
29. Cumming TB, Marshall RS, Lazar RM. Stroke, cognitive deficits, and rehabilitation: Still an incomplete picture. *Int J Stroke*. 2013; 8:38–45. [PubMed: 23280268]
30. Nouri S, Cramer SC. Anatomy and physiology predict response to motor cortex stimulation after stroke. *Neurology*. 2011; 77:1076–1083. [PubMed: 21880996]
31. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. *Brain*. 2012; 135:2527–2535. [PubMed: 22689909]
32. Crinion JT, Leff AP. Using functional imaging to understand therapeutic effects in poststroke aphasia. *Curr Opin Neurol*. 2015; 28:330–337. [PubMed: 26110806]
33. Carter AR, Shulman GL, Corbetta M. Why use a connectivity-based approach to study stroke and recovery of function? *NeuroImage*. 2012; 62:2271–2280. [PubMed: 22414990]
34. Burke Quinlan E, Dodakian L, See J, McKenzie A, Le V, Wojnowicz M, et al. Neural function, injury, and stroke subtype predict treatment gains after stroke. *Ann Neurol*. 2015; 77:132–145. [PubMed: 25382315]
35. Biernaskie J, Chernenko G, Corbett D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. *J Neurosci*. 2004; 24:1245–1254. [PubMed: 14762143]
36. Kerr AL, Cheng SY, Jones TA. Experience-dependent neural plasticity in the adult damaged brain. *J Commun Disord*. 2011; 44:538–548. [PubMed: 21620413]
37. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage. *J Speech Lang Hear Res*. 2008; 51:S225–239. [PubMed: 18230848]
38. Barbay S, Nudo RJ. The effects of amphetamine on recovery of function in animal models of cerebral injury: A critical appraisal. *NeuroRehabilitation*. 2009; 25:5–17. [PubMed: 19713615]
39. Liebeskind DS, Albers GW, Crawford K, Derdeyn CP, George MS, Palesch YY, et al. Imaging in strokeNET: Realizing the potential of big data. *Stroke*. 2015; 46:2000–2006. [PubMed: 26045600]
40. Burke E, Cramer SC. Biomarkers and predictors of restorative therapy effects after stroke. *Current neurology and neuroscience reports*. 2013; 13:329. [PubMed: 23299824]
41. Seitz RJ, Donnan GA. Recovery potential after acute stroke. *Front Neurol*. 2015; 6:238. [PubMed: 26617568]
42. Borich MR, Brown KE, Lakhani B, Boyd LA. Applications of electroencephalography to characterize brain activity: Perspectives in stroke. *J Neurol Phys Ther*. 2015; 39:43–51. [PubMed: 25522236]
43. Newton JM, Ward NS, Parker GJ, Deichmann R, Alexander DC, Friston KJ, et al. Noninvasive mapping of corticofugal fibres from multiple motor areas--relevance to stroke recovery. *Brain*. 2006; 129:1844–1858. [PubMed: 16702192]
44. Wang J, Marchina S, Norton AC, Wan CY, Schlaug G. Predicting speech fluency and naming abilities in aphasic patients. *Frontiers in human neuroscience*. 2013; 7:831. [PubMed: 24339811]
45. Corbetta M, Ramsey L, Callejas A, Baldassarre A, Hacker CD, Siegel JS, et al. Common behavioral clusters and subcortical anatomy in stroke. *Neuron*. 2015; 85:927–941. [PubMed: 25741721]
46. Liew SL, Santarnecchi E, Buch ER, Cohen LG. Non-invasive brain stimulation in neurorehabilitation: Local and distant effects for motor recovery. *Front Hum Neurosci*. 2014; 8:378. [PubMed: 25018714]
47. Campbell BC, Donnan GA, Lees KR, Hacke W, Khatri P, Hill MD, et al. Endovascular stent thrombectomy: The new standard of care for large vessel ischaemic stroke. *Lancet Neurol*. 2015; 14:846–854. [PubMed: 26119323]
48. Santisteban L, Teremetz M, Bleton JP, Baron JC, Maier MA, Lindberg PG. Upper limb outcome measures used in stroke rehabilitation studies: A systematic literature review. *PloS one*. 2016; 11:e0154792. [PubMed: 27152853]

49. Bernhardt J, Borschmann K, Boyd L, Thomas Carmichael S, Corbett D, Cramer SC, et al. Moving rehabilitation research forward: Developing consensus statements for rehabilitation and recovery research. *International journal of stroke*. 2016; 11:454–458. [PubMed: 27073187]
50. Saver JL, Warach S, Janis S, Odenkirchen J, Becker K, Benavente O, et al. Standardizing the structure of stroke clinical and epidemiologic research data: The national institute of neurological disorders and stroke (NINDS) stroke common data element (CDE) project. *Stroke*. 2012; 43:967–973. [PubMed: 22308239]
51. Duff SV, He J, Nelsen MA, Lane CJ, Rowe VT, Wolf SL, et al. Interrater reliability of the wolf motor function test-functional ability scale: Why it matters. *Neurorehabil Neural Repair*. 2015; 29:436–443. [PubMed: 25323459]
52. Yozbatiran N, Der-Yeghiaian L, Cramer SC. A standardized approach to performing the action research arm test. *Neurorehabil Neural Repair*. 2008; 22:78–90. [PubMed: 17704352]
53. See J, Dodakian L, Chou C, Chan V, McKenzie A, Reinkensmeyer DJ, et al. A standardized approach to the fugl-meyer assessment and its implications for clinical trials. *Neurorehabilitation and neural repair*. 2013; 27:732–741. [PubMed: 23774125]
54. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. *Bmj*. 2000; 321:694–696. [PubMed: 10987780]

**Table 1**

## Eight specific issues to address to move stroke recovery and rehabilitation research forward

- 
1. Patterns of post-acute stroke care delivery are highly variable, and payer rather than clinical needs often drives the amount of rehabilitation care.
  2. Acute stroke trials have a time window measured in hours and so recruit patients who have been transported to the research team's medical center, however recovery and rehabilitation trials often have a time window measured in days to months and so need to develop new recruitment strategies.
  3. Social and personal factors can have a high impact on stroke recovery in humans, affect pragmatic aspects of subject retention in trials, and are not well modeled in preclinical research.
  4. Behavioral status of potential enrollees changes rapidly for weeks after a stroke, complicating trial design, endpoint selection, and data analysis.
  5. In contrast with acute stroke therapies such as tPA, where the target is clots and patients need not perform a particular behavior to derive benefit, many stroke recovery therapies target the brain and so benefit from concomitant behavioral training-- the brain circuits galvanized for rewiring need the right experience to shape them.
  6. Recovery and rehabilitation research directly competes with health care business practices.
  7. Stroke recovery/rehabilitation research must better characterize the most important inter-subject differences with respect to treatment responsiveness, and clinical trials need to incorporate such measures.
  8. Well-powered, multi-site studies examining psychometric characteristics of recovery biomarkers are needed.
- 

NIH StrokeNet aims to help address these issues. Stroke recovery and rehabilitation investigators have a major new opportunity to move this area of clinical science forward.