Why the United States Needs a Network for Stroke Clinical Trials

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Stroke is the fourth leading cause of death in the United States, and it is a major cause of long-term disability and reduced quality of life for hundreds of thousands of Americans. Over the past decades, teams of National Institute of Neurological Disorders and Stroke (NINDS)–funded clinical trialists have consistently made major contributions toward treating stroke acutely, enhancing its prevention and rehabilitation, and thereby improving the health of the country. However, although stroke research has resulted in improved outcomes, the increasing incidence with aging of the population and substantial disability and mortality associated with stroke remain a significant burden for a growing number of stroke patients each year. At the recent NINDS stroke planning meeting, external clinicians and researchers identified that enhancing clinical trial infrastructure is one of the highest priorities for the Institute to address in its effort to advance stroke care in the United States.1

Recognizing the Challenges of Clinical Research

The NINDS typically funds between 20 and 50 phase II and III stroke trials, investing between $30 and $70 million per year. Trials are generally funded in response to investigator-initiated research proposals that are judged to be highly meritorious by a special clinical research peer review committee. Before accepting trial grants for peer review, the NINDS leadership evaluates proposals for their potential to reduce the burden of illness caused by stroke. The trials are performed by large teams self-assembled around single projects that are championed by a principal investigator and a cadre of hardworking co-investigators. However, the execution of trials requires the work of hundreds. Traditionally, necessary personnel and infrastructure are assembled anew for each trial once a grant receives funding. Trial infrastructure is then disassembled once the trial is completed. Protracted negotiations over protocols and trial agreements delay study start-up, increasing costs. In addition to the inherent inefficiency of time and resources involved in duplication of infrastructure for each trial, the current system makes it difficult to continuously improve methods or infrastructure based on lessons learned.

Enrollment into NINDS-funded stroke trials has become increasingly difficult, leading to long delays in completion. Some trials have been halted because of poor recruitment, and research resources are frequently diverted to international enrollment contracts. There are a variety of societal, regulatory, economic, and cultural factors that contribute to poor patient enrollment in the US stroke trials. Patient recruitment efforts are sporadic and dependent on intermittent support as individual trials start and stop. In the current system, incentives are not optimally aligned to engender a strong, continuous commitment by stroke experts to enroll patients in National Institutes of Health–sponsored clinical trial research. The inconstant nature of the funding and the funneling of academic rewards primarily to trial leaders make it difficult to sustain the necessary research teams or to effectively engage young stroke experts in National Institutes of Health–funded stroke research. Because of these hurdles, many large clinical trials cost millions of dollars more than originally budgeted and can take ≥10 years to complete, by which time scientific and technical advances may decrease the health impact of the trial. The high cost and long time to completion also limit the number of trials that can be performed.

Stroke clinical trial research is a true team science. Trials require the efforts of nurses, study coordinators, pharmacists, therapists, technologists, grant administrators, and other health professionals in addition to multidisciplinary teams of physicians from neurosurgery, neuroradiology, neurointervention, vascular neurology, emergency medicine, psychiatry, internal medicine, cardiology, and others. However, such research-focused, multidisciplinary relationships are difficult to establish around a discrete project. They take time to establish, and trust is enhanced by sharing responsibilities and rewards over multiple studies. The stroke research community has demonstrated that these relationships are possible, but there is often a lack of consistent support to allow them to endure. These obstacles impede the ability to sustain a successful clinical research enterprise for stroke clinical trials in the United States.

Because our ultimate goal is to test and compare therapies that will have a real impact on patient health, a coordinated and long-range approach to solving challenges in stroke trial research is sorely needed. For instance, planning through a national network would enable systematic research programs designed to distinguish among multiple potentially useful interventions in a given stroke population, or prioritization of trials based on capacity to enroll, or their health impact. National coordination could ensure that the most promising research at all stages of the clinical trials pipeline (from proof of concept to phase III trials) is efficiently moving toward clinical practice. Basic science experts in preclinical stroke research could also contribute to trial success by having a consistent means of communication with the clinical research teams.

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Trial teams in stroke prevention, treatment, and recovery, which traditionally are isolated, could explore opportunities for synergy and shared infrastructure. An effective mechanism to validate biomarkers and other technological advances is desperately needed to improve future trial methodology. This is especially the case for comparative effectiveness research, which is poised to benefit from well-designed, multicenter, electronic databases to support pragmatic, real-world clinical trials. Finally, studies designed and executed in isolation do not support metadata analysis and study comparisons. The value of data collected could be optimized through standardized data collection into widely accessible databases.

A Stroke Trial Network to Coordinate High-Quality Studies in Stroke Prevention, Treatment, and Recovery

The needs outlined above led NINDS to engage the stroke research community to establish a new coordinated network to conduct clinical trials in stroke prevention, acute treatment, and recovery.\(^1,2\) The network will partner closely with existing NINDS trial networks and will incorporate some of the successful strategies from the Neurological Emergencies Treatment Trial (NETT) network, the Specialized Programs in Translational Research in Acute Stroke (SPOTRIAS) consortium, and the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT). Over time, NINDS anticipates that the network will become the preferred system for implementing newly funded stroke trials. The long-term goal for the national stroke clinical trial network is to foster enduring collaborations, team science, infrastructure advances, collaborations with international partners, and the institutional memory to continuously improve the scientific impact of the NINDS investment in stroke clinical trials.

Promising trials are not lacking. The SPOTRIAS consortium has conducted phase II trials, many of which are now poised to enter the network as phase III studies. Investigators from within and outside of the network will be encouraged to develop original grant applications for submission to NINDS peer review. This pipeline of promising interventions and the integrated prioritization described above will ensure that the network is active and that the centers can be engaged consistently.

In support of harmonized research and robust relationships among clinicians, the new network will have strong central support and will encourage collaborative design and execution of trials. Each site will need to demonstrate commitment from multidisciplinary teams of clinicians and support staff. Collaborations will be reinforced by shared leadership, a democratic process for addressing questions from various subspecialties, and publication and data-sharing policies that serve the interests of all the team members. The network will provide opportunities to foster a model that provides sufficient incentives to the many team members required to successfully implement stroke trials; both academic credit and reimbursement for clinical research work. Creating a strong community while continuously evaluating and improving its governance and infrastructure should attract the next generation of stroke clinical researchers. Because the network centers will be involved in most, if not all, of the NINDS-funded stroke trials, they will serve as the training ground for an experienced stroke clinical trial workforce.

Similar to the NeuroNEXT model and NETT, the trial centers will use centralized institutional review board approval and master trial agreements to reduce regulatory burdens and speed trial start-up. The network will also have the opportunity to conduct studies on the basis of negotiated agreements between NINDS and industry partners who submit trial ideas for implementation by the network after accelerated peer review. In phase II trials, enrollment will be more rapid than if a trial were run primarily at one clinical site, and the decisions whether to proceed to phase III can be made more quickly. Improved efficiency and clinical trial know-how in the network should reduce the risk for the private sector to consider stroke indications and thus contribute to the eventual commercialization of novel therapies that reduce the burden of stroke.

The ability of the network to coordinate and integrate data collection across NINDS-sponsored stroke trials also presents a major opportunity. By harmonization of protocol development, the network can ensure that data are collected in a way that facilitates sharing, maximizes comparisons between studies, and builds knowledge with each ensuing trial, independent of the trial outcome. The network will provide centralized infrastructure and support for data management, integration, and opportunities for data sharing.

The stroke treatment trial network is an experiment in itself and will be evaluated on the basis of its ability to maximize the health value of the taxpayers’ investment in stroke clinical research. There are obvious performance metrics that can be easily assessed, but what matters most is that we discover and deliver as rapidly as possible the most effective treatments that science can provide to reduce death and disability from stroke. The opportunities are many and the time to act is now to reduce future stroke incidence and to improve acute and chronic outcomes for stroke patients.

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References


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