Research Priority Setting
A Summary of the 2012 NINDS Stroke Planning Meeting Report

Barbara G. Vickrey, MD, MPH; Thomas G. Brott, MD; on behalf of the Stroke Research Priorities Meeting Steering Committee and the National Advisory Neurological Disorders and Stroke Council; Walter J. Koroshetz, MD; on behalf of the National Institute of Neurological Disorders and Stroke Committee. The 9 high-priority research opportunities that resulted from this planning effort serve as an important guide for the National Institutes of Health and the international stroke research community at large. The recommendations, which are summarized below, are already shaping National Institutes of Health investments in stroke, including establishment of a new stroke clinical trials network to coordinate US stroke research, integrate activities with the Canadian stroke network, and serve as a focal point for US collaborations with our international partners. For a detailed report of the Stroke Research Priorities Meeting and a list of the planning participants, please see the NINDS Web site. An account of the rationale and expectations for the US stroke network was recently published in Stroke.

Cross-Cutting Theme—Accelerating the Translation of Preclinical Stroke Research Into Clinical Studies of Stroke Prevention, Acute Treatment, and Recovery

Development of new and more effective strategies to prevent stroke, protect the brain during ischemia and reperfusion, and facilitate its recovery after stroke hinges on high-quality basic and translational preclinical research. However, despite large investments at the bench (preclinical research) and bedside (clinical trials), investments in translation have not yielded the anticipated bounty of new, safe, and effective therapies.

Shortcomings of preclinical studies have been identified, including lack of validity, bias, narrow applicability, poor predictive value, inadequate sample size and power, lack of independent replication, and publication bias toward positive findings. There is significant momentum behind instituting higher standards for preclinical research, and the NINDS is at the forefront of this movement. However, improvements in preclinical research require a cultural shift, driven, in part, by incentives from funding sources and publishers. With systematic, evidence-based progression along the translational pathway, identification and translation of ≥1 positive, highly vetted candidates into human studies would be feasible within the next decade. Efforts to promote implementation of
quality standards for preclinical research should include the following:

- Adopt and enforce new and existing guidelines for experimental rigor.
- Enhance training in good scientific practice and experimental design.
- Implement a milestone-driven process for stroke intervention development.
- Enable data and methods sharing to facilitate independent review and replication.
- Facilitate the progression of ≥1 highly promising stroke therapies through phase II clinical trials.

**Prevention—Prevention of Vascular Cognitive Impairment**

Cerebral small vessel disease is a major contributor to stroke and age-related cognitive impairment, but it is poorly understood, and there are currently no targeted treatments.

Vascular cognitive impairment (VCI) and vascular dementia represent a large public health burden. The prevalence of stroke with VCI is estimated to be 5.7% (compared with stroke alone, with a prevalence of 6.8%), and vascular dementia is the second most common form of dementia after Alzheimer, affecting an estimated 577,000 people nationwide. Importantly, the coexistence of vascular and Alzheimer dementia (mixed dementia) is increasingly recognized as the most common forms of dementia. To address this great public health challenge, both preclinical and clinical scientific opportunities for prevention of VCI should be pursued. Major scientific goals include the identification of key biological pathways that promote small-vessel disease and the mechanisms by which it leads to VCI and interacts with the biology of Alzheimer disease. Understanding these pathways and identifying agents that attenuate their effects should inform the development of pilot clinical trials of targeted therapies using imaging biomarker outcomes.

There are major scientific gaps in our understanding of small-vessel and diffuse white matter diseases, especially in understanding the relationship between vascular damage and cognitive changes. Despite these gaps, advances in small-vessel biology, connectome analysis, blood–brain barrier, small-vessel imaging, and animal models are poised to facilitate VCI research. Recommendations for enhanced research on the prevention of VCI include the following:

- Investigate the interaction between small-vessel/microvascular damage and dementia (including Alzheimer disease).
- Define molecular and cellular pathways through human pathology studies.
- Develop and apply new animal models, including aged animals.
- Evaluate promising therapeutic agents.
- Conduct initial clinical trials.
- Encourage collaboration among scientists, funding agencies, and advocacy groups through multidisciplinary symposia and interagency partnerships.

**Prevention—Imaging Biomarkers in Stroke Prevention: From Bench to Bedside**

Advances in brain imaging have transformed medical care for stroke and many other neurological disorders, but the full potential of imaging for stroke prevention has not been realized. Subclinical infarcts could predict clinical stroke; identifying these infarcts and other subclinical risk factors through imaging would enable diagnosis and intervention before serious damage occurs. New imaging methods could noninvasively identify atherosclerotic plaque, thrombus in the heart, breakdown of the blood–brain barrier, and inflammatory cell and other cell movements, all potential biomarkers for stroke risk, onset, progression, and response to therapy. Imaging surrogate end points could improve the efficiency of clinical trials. Expensive, lengthy trials are a barrier to progress in stroke prevention. Imaging biomarkers would reveal whether experimental protective treatments are effective more quickly and with substantially fewer subjects.

The past few decades have seen rapid advances in imaging systems, imaging tracers, cerebral perfusion measurement, and knowledge of potential targets underlying disease processes. These advances have been especially useful in cancer research and clinical care, and they can now be applied to stroke research. For this to be effective, imaging scientists and stroke researchers must collaborate to adapt new imaging tools to stroke-relevant questions and targets. The following goals would facilitate the application of brain imaging for stroke prevention:

- Develop new tracers, radioligands, and MRI markers (tool development).
- Validate predictive value of preclinical and clinical imaging biomarkers, establishing correlation of imaging with outcomes (biomarker development).
- Consider all imaging modalities (magnetic resonance, nuclear magnetic resonance, computed tomography, optical, and ultrasound).
- Adapt imaging approaches from cardiovascular disease and cancer.
- Facilitate regulatory agency (Food and Drug Administration) and industry collaboration.

**Prevention—Expediting Comparative Effectiveness Research Trials in Stroke Prevention**

Existing stroke prevention strategies have not been compared in clinical evaluations to determine which are most effective in preventing strokes. Some treatments have been in clinical practice, despite limited evidence of their effectiveness and despite possible associated increased risks or higher costs compared with alternative treatment strategies (eg, endarterectomy for asymptomatic carotid stenosis, interventions for arteriovenous malformations that have never bled). A stronger evidence base is, therefore, needed on the most effective interventions for stroke to guide clinical practice. In addition, understanding which treatments work for which patients and under which circumstances could improve the delivery of high-quality patient care backed by strong clinical evidence.

Ongoing efforts in comparative effectiveness research among federal agencies include individual trials at NINDS,
the National Institutes of Health Common Fund Health Care Collaboratory Program, and the Patient-Centered Outcomes Research Institute. However, coordination among these efforts and with additional stakeholders has been suboptimal for prioritization based on public health need.

Evidence to support changes in clinical care and potentially in reimbursement could yield reduced risk, better outcomes for patients, and substantially reduced costs to the healthcare system. Recommendations for future investments in stroke comparative effectiveness research include efforts to:

- Establish infrastructure and coordinate ongoing efforts with stakeholders to encourage pragmatic clinical trials with inclusive entrance criteria to achieve a diverse population with a range of comorbidities.
- Complete ≥1 high priority, high public health impact prospective randomized trial.
- Train leaders and practitioners in the design and conduct of pragmatic clinical trials.
- Engage patients in the process of selection and design of pragmatic trials.
- Plan for effective dissemination and implementation of key results.
- Design trials to identify the subset of patients who will benefit from a stroke prevention intervention and those who will not.
- Prioritize trials based on public health impact.
- Promote unique design features and the importance of comparative effectiveness research trials.
- Encourage broader participation in pragmatic clinical trials in a real-world setting.
- Consider reimbursement strategies that are aligned with evidence development.

Treatment—Expand and Integrate Existing Stroke Trial Networks to Accelerate Translation

Substantial investments have been made by NINDS in stroke treatment trials during the past 4 decades. Networks and infrastructure are needed to maximize the efficiency of conducting these trials because by nature they are large, time-consuming, and costly. NINDS networks and consortia, such as the Specialized Program of Translational Research in Acute Stroke (SPOTRIAS), the Neurological Emergencies Treatment Trials (NETT) network, and the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT), have improved support for stroke clinical research from early phase I through phase III stages. However, these programs function quite differently and are not coordinated to support stroke trials efficiently as they move progressively through the phases of clinical testing.

Expanded, enhanced, and integrated networks could serve to streamline the transition of basic discoveries through early phase and on to large pivotal human trials. More rapid testing of potential therapies could be achieved through such coordination. For example, by allowing for innovative adaptively designed trials that begin with a phase II question and milestone-driven criteria, continuation into phase III could be more efficient. This type of network integration would also allow for coordinated and standardized data management, increasing the use and value of collected data. Such a network could improve the efficiency of all stroke trials and allow for prioritization of clinical research. Recommendations for improving infrastructure for stroke clinical trials include the following:

- Expand and improve design and network infrastructure for acute stroke phase II and III trials.
- Improve coordination and collaboration among preclinical studies, pilot studies, and pivotal human trials.
- Enhance clinical trial efficiency through centralized coordination, streamlined recruitment, use of factorial and adaptive designs, enhanced industry collaboration, and mechanisms to accelerate new study initiation.
- Facilitate stroke therapy development by accelerating the accumulation of safety and preliminary efficacy data, arriving more rapidly at go/no-go decisions in phase II and confirming or refuting efficacy in phase III.

Treatment—Preclinical and Clinical Studies to Improve Early Reperfusion Therapy and to Define the Safety and Effectiveness of Late Reperfusion Therapy (REPERFUSE)

In 1996, NINDS-sponsored stroke trials led to the first and only approved therapy for acute stroke, tissue-type plasminogen activator. However, established tissue-type plasminogen activator approaches do not meet the full spectrum of clinical needs. Tissue-type plasminogen activator is most effective if used within 90 minutes from symptom onset and is only approved in the United States for use ≤3 hours, after which the risk of hemorrhagic complication outweighs potential benefits. Even with optimal use, its success rate for unblocking the arteries is less than perfect.

Promising opportunities to improve reperfusion therapy include improved lytic drugs, imaging for selection of patients for treatment, and catheter-based approaches. Intravascular approaches, such as the use of devices to remove the blockage, have been developed. However, despite the dramatic improvement in individual patients and their clearance by the Food and Drug Administration, they have been shown not to improve clinical outcome in 2 randomized controlled trials. There is an urgent need to improve existing therapies, better define and extend the therapeutic time window, advance new therapies, and establish best practices in the clinic. These advances would expand currently available stroke therapies and increase the proportion of stroke patients who receive effective treatment.

Barriers to advancing this area include a lack of infrastructure capable of efficiently conducting phase III endovascular trials and multimodal imaging trials. Such barriers could be overcome with coordination and redesign of existing NINDS clinical trial networks/consortia. In addition, alignment of trials with reimbursement by Center for Medicare and Medicaid Services and third parties would accelerate completion of trials, because centers are often reluctant to randomize patients when device therapies are reimbursable outside of trials. Other recommendations for improving reperfusion therapy include the following:

- Expand and improve biological understanding of clot formation and dissolution and of reperfusion.
Major logistical challenges hamper the rapid delivery of reperfusion therapies within a time window sufficient to maximize the rescue of damaged brain tissue. Neuroprotective therapies are, therefore, needed to augment the benefits of reperfusion therapies and could potentially extend the therapeutic potential beyond the current time window. Preclinical evidence of the potential benefit of neuroprotective therapies has been demonstrated through individual, uncoordinated efforts, yet has not been widely validated. The scientific community is ready for a reinvigorated interest in neuroprotection research because the shortcomings of past preclinical and clinical studies in this area have been identified.

Advancing potential neuroprotective therapies will require emphasis on basic science research. Consensus among preclinical investigators around the world for increased rigor in preclinical research will improve the quality and efficiency of studies in this area. Clinical applications of neuroprotection are likely to benefit from combination therapy approaches as additions to existing reperfusion therapy. NINDS-supported clinical trial networks are well positioned to perform prehospital and emergency department treatment initiation.

New neuroprotective agents could potentially expand the availability of therapies to a larger number of stroke victims. Advances in this area may also lead to therapies for intracerebral hemorrhage, subarachnoid hemorrhage, and surgical/procedural prophylaxis for which there is no approved drug treatment. The focus of future investments in this area should be to evaluate and optimize various therapeutic and cytoprotective agents after stroke and investigate synergies with reperfusion therapy through rigorous preclinical and clinical trials. Additional recommendations for future investments in this area include the following:

- Improve preclinical rigor for selection of potential neuroprotective agents through emphasis on penetration and concentration within ischemic brain and within feasible temporal windows. Preclinical rigor also includes blinding, study of aged animals, replication in multiple laboratories, quality audits, open laboratories, robust sample size, and robust treatment effects.
- Identify informative biomarkers for neuroprotection and cytoprotection in clinical trials.

**Recovery—Translational Research Using Brain–Computer Interface Devices for Stroke and Other Neurological Disorders**

Brain–computer interfaces (BCIs) have the potential to restore function after stroke and may also be used to retrain the brain during stroke rehabilitation. BCIs have progressed to proof-of-concept studies in patients with spinal cord injuries, demonstrating their use in humans. To realize the potential of BCIs, these initial studies should be expanded to include a broader spectrum of paralytic disorders, including brain stem stroke or cortical stroke, in which damage occurs in only one side of the brain. Research in this field also provides neurophysiological insights into poststroke cortical function and plasticity that are not possible to gain by other study methods.

There are both technical and regulatory barriers to overcome for BCIs to succeed. Some of the technical and scientific hurdles that must be overcome include the following: device longevity, reliability, and performance; adequate performance, including speed, complexity, and portability; and application of a broader range of paralytic disorders. Research on neurological devices requires an iterative process very different from drug development. Device development needs a clearer translational/commercialization pathway to be able to eventually serve a broad population. The following goals would facilitate progress in this area:

- Develop ≥ 1 approved BCI device for severe paralysis (brain stem stroke, spinal cord injury, amyotrophic lateral sclerosis).
- Conduct human proof-of-concept studies for cortical stroke and hemiplegia.
- Create a rapid translational pathway for invasive neurological devices.
- Establish infrastructure for device development clinical trials, including clinical oversight and safety monitoring.
- Encourage hypothesis-driven studies in neural decoding, neural engineering, and functional neuroimaging, and focused, milestone-based studies for device development.
- Acquire fundamental knowledge on neuroplasticity from human studies with BCI devices to guide pilot trials in neuroplasticity.
- Encourage public–private partnership at early stages in device development.
- Spearhead collaboration among federal agencies, foundations, and industry partners.
Recovery—Program for Translational Research Targeting Early Recovery After Stroke in Humans

Most patients experience some spontaneous return of neurological function in the months after a stroke, but the degree and timing of recovery are variable. The biology of recovery and how it might be manipulated to improve functional recovery are poorly understood. Because of the paucity of clinical trial data for stroke recovery, the rehabilitation service industry lacks a sufficient evidence base. Understanding the biology of recovery and how to use that understanding to improve functional outcomes through specific interventions are relatively unexplored scientific areas with great public health potential.

Preclinical studies offer a wealth of promising neurorestorative approaches ready for translation to clinical trials. However, there have been almost no human studies to systematically test these approaches. The first 3 months after stroke offer the most significant window of opportunity for recovery of motor, sensory, and cognitive function. Clinical trials in stroke recovery should be prioritized, starting with early stroke recovery. Barriers to assessing these interventions systematically include the variability of rehabilitation approaches in practice and the shortage of interdisciplinary scientists focused on stroke recovery. To make substantial headway, there is a need for an integrated and coordinated approach to clinical research in stroke recovery. Scientific goals of future clinical research in stroke recovery include the following:

- Characterize the natural history of recovery.
- Assess the impact of various interventions (eg, stimulation, pharmacological agents, devices, stem cells, and combination therapies) on recovery.
- Determine the sensitive period for response to interventions.

- Enable data and sample sharing through standardization and shared infrastructure.
- Support training, career development, and interdisciplinary collaboration.

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Disclosures

None.

References


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