The 2012 National Institute of Neurological Disorders and Stroke (NINDS) Priority Setting process highlighted the need for a stable, well-organized, clinical trial organization to increase the effectiveness of NINDS in advancing stroke treatments (http://www.ninds.nih.gov/find_people/ninds/OSPP/Stoke-Research-Priorities-Meeting-2012.htm). Lessons learned from NINDS Neurological Emergencies Treatment Trials and the phase 2 biomarker-informed trials network (NeuroNext) demonstrated the value of an organization of dedicated trialists that harnessed a team science approach. In September 2013, National Institutes of Health (NIH) StrokeNet was established to conduct clinical trials in a centrally coordinated network that includes 25 regional centers that are linked to nearly 300 stroke hospitals across the United States. Busy from the start in executing NIH-funded stroke research, the group is now about to launch the first trial designed specifically for StrokeNet. The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3) trial will determine whether an imaging signature can be used to select patients who can benefit from thrombectomy treated after 6 hours of stroke onset. The trial is a result of decades of work by Dr Greg Albers and his team at Stanford University, who in DEFUSE I and II developed magnetic resonance imaging– and computed tomography–based methods that could distinguish between brain regions that can be saved by reperfusion and regions that cannot be saved.

Immediately after its initial funding, StrokeNet began to enroll in 5 recently funded NIH-funded trials. The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study (CREST-2) will inform stroke prevention decisions. The telerehabilitation trial is comparing therapy provided in a clinic with therapy at home via computer to improve arm function and is funded in large part by the Eunice Kennedy Shriver National Institute of Child Health and Human Development’s National Center for Medical Rehabilitation Research. The Minimally Invasive Surgery Plus recombinant tissue-type plasminogen activator for Intracerebral Hemorrhage Trial (MISTIE III) is testing whether clot removal yields better patient outcomes after intracerebral hemorrhage. Finally, the Intracerebral Hemorrhage Deferoxamine Trial (iDEF) is evaluating whether complexing iron improves the outcome after intracerebral hemorrhage. These trials are being executed in StrokeNet centers that span 18 states (http://nihstroke.net/the-network/about-us) and bring together teams of researchers representing every medical specialty needed for stroke care to address the 3 prongs of stroke research: prevention, treatment, and recovery. Today, >189 million Americans (60% of the population) live within 65 miles of a StrokeNet center.

**Revolutionizing Treatment of Acute Stroke**

In the 1990s, NINDS-funded investigators pioneered intravenous therapy of tissue-type plasminogen activator, a thrombolytic agent that became standard of care in acute stroke treatment after publication of the clinical trial in 1995 (http://www.ncbi.nlm.nih.gov/pubmed/7477192). At the 2015 International Stroke Conference, 4 landmark randomized controlled clinical trials demonstrated the striking benefit of catheter-based clot removal to restore blood flow in brain arteries in patients with the most severe strokes (http://www.ninds.nih.gov/about_ninds/message/message-2015-AcuteStroke.htm). In combination with advanced imaging that allows fast and easy identification of large artery blockages, endovascular therapy is a breakthrough in treating patients at the greatest risk for severe disability. Many questions remain, particularly how to best choose patients who can benefit from thrombectomy and avoid endangering those in whom the damage is so severe that there is no chance of benefit. The DEFUSE 3 trial will determine whether physicians can identify stroke patients who can benefit from thrombectomy as much as 6 to 16 hours after stroke onset (https://clinicaltrials.gov/ct2/show/NCT02586415). Those who meet inclusion criteria will undergo either computed tomographic perfusion/computed tomographic angiogram or magnetic resonance diffusion weighted imaging/perfusion weighted imaging/magnetic resonance angiography studies before randomization. Patients who present with evidence of an internal carotid artery or middle cerebral artery M1 occlusion and a target mismatch profile will be randomized in a 1:1 ratio with ≥1 Food and Drug Administration-approved thrombectomy devices versus medical therapy alone, in a maximum of 476 patients in 45 StrokeNet sites over 4 years. The primary end point will be the distribution of scores on the modified Rankin Scale at 90 days.

**DEFUSE 3’s Potential to Transform Acute Stroke Research**

If the DEFUSE 3 trial successfully identifies patients who can benefit from recanalization in 6 to 16 hours, many patients
will avoid a life of disability as a result of severe stroke. This is DEFUSE 3’s primary goal. However, a validated predictive signature of ischemic but still salvageable brain tissue also opens the door to novel research. The failed efforts of the 1990s to demonstrate clinical benefit of neuroprotective drugs that worked in animals could have benefited tremendously from a powerful imaging technique paired with thrombectomy. Without the ability to distinguish irreparably damaged versus still salvageable tissue, and not knowing if and when recanalization occurred, it was not possible to ascertain whether a drug decreased stroke damage in patients. DEFUSE 3’s imaging method will allow the former, and thrombectomy enables the latter. These combined technologies offer a tremendous opportunity to slow the process of ischemic tissue injury and prevent reperfusion injury and have the potential to transform acute stroke care and ultimately save the lives of millions of Americans.

Disclosures
None.

Key Words: clinical trial ■ image-guided intervention ■ National Institute of Neurological Disorders and Stroke ■ reperfusion injury ■ thrombectomy
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Meghan Mott, Scott Janis and Walter J. Koroshetz

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