National Institutes of Health StrokeNet During the Time of COVID-19 and Beyond

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The National Institute of Neurological Disorders and Stroke (NINDS) established the National Institutes of Health (NIH) StrokeNet in the fall of 2013 to facilitate the rapid initiation and efficient implementation of small and large multisite exploratory and confirmatory clinical trials of stroke prevention, treatment, and recovery, as well as validation studies of biomarkers or outcome measures. NIH StrokeNet sprang from an earlier NINDS-funded clinical trial network called Specialized Programs of Translational Research in Acute Stroke that focused only on phase II clinical trials and biomarker studies of acute stroke. Since the publication of the NIH StrokeNet User Guide in 2016 that detailed the organizational structure, as well as the development and implementation of trials within the network,1 NIH StrokeNet has grown substantially in the number of participating clinical sites, the number of ongoing trials, and scientific and educational impact. We provide a summary of the first 7 years of the network, the completed and ongoing trials, the recent impact of coronavirus disease 2019 (COVID-19) on the network, and a blueprint for reinstitution of clinical trial enrollment following the COVID-19 pandemic. Detailed information regarding the NIH StrokeNet, its ongoing trials, and educational webinars can be found at the website https://www.nihstrokenet.org/.

Key Words: biomarkers ▪ data management ▪ therapeutics ▪ United States

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Nonstandard Abbreviations and Acronyms

| Abbreviation | Description |
|--------------|-------------|
| ARCADIA      | Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke |
| ARCADIA-CSI  | Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke—Cognition and Silent Infarcts |
| ASPIRE       | Anticoagulation for Stroke Prevention and Recovery After Intracerebral Hemorrhage |
| COVID-19     | Coronavirus disease 2019 |
| DEFUSE 3     | Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 |
| FASTEST      | FVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time |
| I-ACQUIRE    | Infant ACQUIRE |
| MOST         | Multi-Arm Optimization of Stroke Thrombolysis |
| NETT         | Neurology Emergencies Treatment Trial |
| NIH          | National Institutes of Health |
| NINDS        | National Institute of Neurological Disorders and Stroke |
| NT-proBNP    | N-terminal pro-B-type natriuretic peptide |
| SATURN       | Statins Use in Intracerebral Patient |
| Sleep SMART  | Sleep for Stroke Management and Recovery Trial |
| TRANSPORT2   | Transcranial Direct Current Stimulation for Post-Stroke Motor Recovery A Phase II Study |

Since the process began, 109 unique concept proposals have been submitted of which 37 were submitted to NIH for formal review by NIH Study Section (3 are currently pending review). Of these, NINDS has funded 10.

The NINDS designed the NIH StrokeNet to support phase II and phase III stroke trials. During the first years of the network, NIH StrokeNet focused on developing infrastructure and new proposals and assisting in the completion of trials already funded by NINDS. These previously funded trials included the following trials completed with NIH StrokeNet assistance: the NETT (Neurology Emergencies Treatment Trial) Network supported POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke)\(^2\) and SHINE trials (Stroke Hyperglycemia Insulin Network Effort)\(^3\), the NeuroNEXT (Network for Excellence in Neuroscience Clinical Trials) supported RHAPSODY trial (Safety Evaluation of 3K3A-APC in Ischemic Stroke)\(^4\) and the MISTIE 3 (Minimally Invasive Surgery Plus r-tPA for ICH Evacuation)\(^5\) and i-DEF trials (Intracerebral Hemorrhage Deferoxamine)\(^6\). Additionally, the NIH StrokeNet continues to assist ongoing studies funded before initiation of the network: CREST 2 (Carotid Revascularization Endarterectomy vs Stenting)\(^7\) and CREST H.\(^8\) The first 3 trials implemented fully by StrokeNet were DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3),\(^9\) Telerehab,\(^10\) and ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke).\(^11\) For DEFUSE 3 and ARCADIA, the design, funding, and implementation occurred entirely within StrokeNet. Telerehab was originally designed outside the network framework and approved for funding as a single-center study and then adapted and implemented into StrokeNet after the funding decision.

The first of these multicenter trials fully designed within the network, DEFUSE 3 (Table 1),\(^9\) was funded in September 2015. This phase 3 randomized trial compared thrombectomy and standard medical therapy versus standard medical therapy alone in patients 6 to 16 hours after they were last known to be well and who had remaining ischemic brain tissue that was potentially salvageable. DEFUSE 3 stopped early in the summer of 2017 for overwhelming efficacy. In 2019, the trial received a Distinguished Clinical Research Achievement Award. This award was presented to the top 2 studies among all nominated clinical trials in the United States in 2018, “that show creativity, innovation, or a novel approach which demonstrated an immediate impact on the health and well-being of patients.”

The second trial, the Telerehabilitation trial, was the first multicenter trial of telerehabilitation versus standard in-person physical therapy.\(^10\) The trial demonstrated that 6 weeks of intensive therapy substantially improved function and that telerehabilitation was not inferior to traditional in-clinic rehabilitation for improving motor status (Fugl-Meyer arm motor scale). The trial design was prescient given the social distancing required during the ongoing COVID-19 pandemic and likely represents the digital future of ambulatory physical therapy for certain groups of patients.

The ongoing third trial, ARCADIA, tests the hypothesis that apixaban is superior to aspirin for the prevention of recurrent stroke in participants with cryptogenic ischemic stroke and atrial cardiopathy, as defined by 1 of 3 cardiac markers: P-wave terminal force \(>5000\) \(\mu\)V\(\times\)ms in ECG lead V\(_1\), serum NT-proBNP (N-terminal pro-B-type natriuretic peptide)\(>250\) pg/mL, and left atrial diameter \(\geq 3\) cm/m\(^2\) on echocardiogram (Table 1).\(^11\)

Since 2018, when NINDS renewed funding of the network for 5 additional years, the number of funded trials and active clinical trial sites in the network increased markedly (Table 1). At the time of the COVID pandemic, 6 trials were recruiting: MOST (Multi-Arm Optimization of Stroke Thrombolysis), Sleep SMART (Sleep for Stroke Management and Recovery Trial), I-ACQUIRE (Infant
Table 1. Current Status of StrokeNet Trials (Enrollment Suspended for All Trials Because of COVID-19 on March 24)

| NIH StrokeNet Trials | Primary Study Question | Notice of Award | Date of First Enrollment | Planned Sites | Target Number of Randomized Participants | Randomized Participants |
|----------------------|------------------------|-----------------|--------------------------|---------------|------------------------------------------|------------------------|
| ARCADIA* phase III   | Is apixaban superior to aspirin for the prevention of recurrent stroke in participants with cryptogenic ischemic stroke and atrial cardiopathy? | May 2017 | March 12, 2018 | 120 (now 180) | 1100 | 441 |
| MOST phase III       | Does epifibatide, argatroban, or placebo added to IV tPA, started within 3 h of onset, improve outcome in ischemic stroke subjects at 90 d? | June 2018 | October 15, 2019 | 110 | 1200 | 33 |
| Sleep SMART* phase III | Does treatment of OSA with positive airway pressure starting shortly after acute ischemic stroke or high-risk TIA (1) reduce recurrent stroke, acute coronary syndrome, and all-cause mortality during 6 mo after the event and (2) improve stroke outcomes at 3 mo in patients who experienced an ischemic stroke? | August 2018 | May 31, 2019 | 110 (now 140) | 3062 | 253 |
| TRANSPORT2 phase II  | Do 3 dose regimens of noninvasive brain stimulation (including sham stimulation) plus modified constraint-induced movement therapy lead to a differential change in motor impairment in the upper extremity after a 10-session intervention? | August 2018 | September 9, 2019 | 12 (now 15) | 129 | 12 |
| I-ACQUIRE phase III  | In 8- to 36-mo-old children with perinatal arterial stroke, does intensive pediatric rehabilitation at either 3 h/d (moderate dose) or 6 h/d (high dose) for 5 d/wk for 4 wk improve outcome at 7 d after treatment and at 6 mo, as compared with usual and customary treatment? | February 2019 | October 10, 2019 | 12 | 240 | 22 |
| ARCADIA-CSI* phase III ancillary | Do patients in the ARCADIA trial on apixaban experience less cognitive decline and fewer silent infarcts than those on aspirin therapy? | July 2019 | November 14, 2019 | 100 | 500 | 52 |
| ASPIRE phase III     | Is apixaban superior to aspirin for prevention of the composite outcome of any stroke (hemorrhagic or ischemic) or death from any cause in patients with recent ICH and atrial fibrillation? | July 2019 | May 26, 2020 | 125 | 700 | 1 |
| SATURN phase III pragmatic | Whether continuation vs discontinuation of statin drugs after spontaneous lobar ICH is the best strategy, and whether the decision to continue/discontinue statins should be influenced by an individual’s APOE genotype? | September 2019 | NA | 140 | 1456 | 0 |
| FASTEST* phase III   | Does treatment with rFVIIa within 2 hours of onset in appropriately selected patients with spontaneous ICH improve outcome, as measured by the ordinal distribution of the mRS at 180 d, as compared with placebo? | February 2020 | NA | 115 | 860 | 0 |

Completed trials

| DEFUSE 3* phase III  | Is thrombectomy plus standard medical therapy superior to standard medical therapy alone in improving outcome at 90 d, in patients 6 to 16 h after they were last known to be well and who have remaining ischemic brain tissue that was potentially salvageable? | September 2015 | May 6, 2016 | 45 | 476 | 182 |
| Telerehab phase II   | Whether a 6-wk course of intensive home-based telehealth therapy targeting arm movements after stroke would provide rehabilitation benefits that are comparable with those derived from dose-matched traditional in-clinic rehabilitation therapy? | September 2015 | May 6, 2016 | 45 | 476 | 182 |

APOE indicates apolipoprotein-E; ARCADIA, Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke; ARCADIA-CSI, Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Intracerebral Hemorrhage; COVID-19, coronavirus disease 2019; DEFUSE, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; FASTEST, FVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time; I-ACQUIRE, Infant ACQUIRE; ICH, intracerebral hemorrhage; IV tPA, intravenous tissue-type plasminogen activator; MOST, Multi-Arm Optimization of Stroke Thrombolysis; mRS, modified Rankin Scale; NA, not applicable; NIH, National Institutes of Health; OSA, obstructive sleep apnea; rFVIIa, recombinant factor VIIa; SATURN, Statins Use in Intracerebral Patient; Sleep SMART, Sleep for Stroke Management and Recovery Trial; TIA, transient ischemic attack; and TRANSPORT2, Transcranial Direct Current Stimulation for Post-Stroke Motor Recovery A Phase II Study. *Industry partnership.
Stroke Administered at Earliest Time) was funded on February 28, 2020, with enrollment planned to start in the early fall.

EDUCATIONAL CORE
Since the beginning of StrokeNet, the educational mission of the network has been a priority. StrokeNet includes yearly-designated StrokeNet clinical research fellowships at each regional center across the United States, and our Educational Core leadership coordinates this education program and mentoring process across the network. The activities and outcomes of educational core have been detailed in an article published recently in *Stroke.*

IMAGING CORE
Since the beginning of StrokeNet, the imaging core has been providing support to the clinical trial design in terms of imaging protocols and homogenization of imaging across sites. In addition, StrokeNet offers a common mechanism for central collection of images for all clinical trials. Combined with the use of common data elements in the coding of these images, the central collection of images allows for increased standardization of imaging across trials and for pooled analyses in the future. Such efficiencies are highly desirable considering the high cost of imaging in clinical trials.

IMPACT OF COVID-19 ON NIH STROKENET
COVID-19 represents a once-in-a-lifetime event that profoundly affects all clinical research now and going forward.

| Guidance to Trial Sites | Table 2. Initial Guidance From StrokeNet Leadership to Trial PIs Regarding COVID-19 |
|-------------------------|------------------------------------------------------------------------------------------------|
| Monitoring and following all CDC and local recommendations regarding good hygiene, avoidance of major gatherings (social distancing), travel, etc | | |
| Adherence to local institution recommendations regarding research in the COVID-19 environment, including screening or enrollment into research trials. Some institutions had already suspended screening and enrollment, whereas others had not | | |
| Maintenance of patient follow-up for those participants already enrolled in trials and use of telemedicine and telephone interactions whenever possible to obtain study data. Per FDA guidance, these changes could happen even if the protocol had not yet been amended | | |
| Amendment of all trial protocols to allow for remote patient visits for outcomes, study medications, etc, for situations like COVID-19 and communication of the amendment to the CIRB | | |
| Use of an unblinded assessor as needed for those studies that require blinded outcome assessors if designated person was not available | | |
| Completion of outcome assessments outside of the prescribed windows as needed (because of illness) | | |
| For studies requiring study medication, mailing of study medication, even if not detailed in protocol | | |
| For trials requiring physical or hands-on therapy and in-clinic or at-home visits, suspension of therapy when a patient or therapist is COVID-19 positive or is possibly infected and restarting therapy only when the participant is no longer contagious | | |
| Crafting of plans by trial PIs regarding COVID-19 issues unique to their trial | | |
| Suspension of any in-person StrokeNet meetings until the situation has changed to minimal risk | | |
| Communication of COVID-19 infection in a study patient or study investigator to the trial PIs as allowed by HIPAA | | |

CDC indicates Center for Disease Control; CIRB, central institutional review board; COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; HIPAA, Health Insurance Portability and Accountability Act; and PIs, principal investigators.
suspended in StrokeNet trials on March 24 while maintaining follow-up of participants, to the extent possible, within ongoing trials. While the primary goal of suspension of enrollment was safety of relevant parties during the peak of the pandemic, StrokeNet leadership and the trial principal investigators used this time to redesign processes and protocols within the trials that would enable safely restarting enrollment in the trials as quickly as possible, while recognizing the local conditions and requirements at a given site. Within a month of suspension of enrollment, 2 trials had submitted a plan to the central institutional review board for reopening enrollment, and a template letter for restarting trials was provided to all trial principal investigators to assist them in crafting a trial-specific plan and request to central institutional review board to restart enrollment (http://nihstrokenet.org/documents).

Table 3 describes some of the specific impacts of COVID-19 and the proposed solutions by the network to address these issues. Solutions include increased and innovative use of telemedicine and digital technologies, flexible approaches for interactions of the study teams with participants or perform prescribed therapies

| COVID-19 Impact on Trials | Planned and Implemented Solutions |
|--------------------------|----------------------------------|
| Protocols required in-person screening and enrollment | Investigator-participant interactions by telemedicine; multiple methods of remote consent including eConsent, as well as a centralized eConsent process and platform for entire trial and not just at individual sites (REDCap database). |
| Protocols required in-person visits for distribution of study medication (eg, ARCADIA, ASPIRE) | Direct shipping of study medication to patient homes with revised timeline and assurance of patient’s receipt of study medication. |
| Protocols required in-person outcome assessments (eg, MOST, I-ACQUIRE, and TRANSPORT2) | Outcomes by telemedicine and recorded video. Audio recording if video not possible. Therapy trials that require in-person assessment must adopt precautions that mirror recommendations for COVID-19 patient care. |
| Central cognitive assessment for ARCADIA-CSI trial had to be onsite at institution | Technology amended to allow cognitive assessment from test administrators’ homes. |
| Centralized laboratory for trial closed for non-COVID research activities (eg, ARCADIA, SATURN) | Discussions with laboratories to consider restart receipt of laboratory samples (rate-limiting step for trials to reopen). |
| Therapy trials that require close-contact multisession rehabilitation therapy or the use of tools and devices in combination with the rehabilitation therapy on a daily basis (eg, TRANSPORT2 and I-ACQUIRE) | Plan for use of daily COVID-19 screening questionnaire to assess risk of exposure and infection and PPE (eg, masks and gloves) for both staff (eg, therapists/trainers) and study subjects that mirror clinical recommendations. Disinfect/clean the rehabilitation and assessment tools and machines/devices (such as tDCS/TMS/MRI) after each visit. |
| Inability for children (ages 8 mos to 3 y) to see faces of therapists wearing facemasks during therapy (I-ACQUIRE) | Transparent masks designed for the hearing-impaired purchased for trial to allow visualization of facial expressions to help with communication and therapy. |
| Inability to do typical in-person focus groups or to survey large groups of community members in person as required by exception from informed consent or EFIC (FASTEST) | Centralized online survey tool using REDCap for all participating sites in the United States that can be used for several sites within same community. Online focus groups—regionally and nationally. Discussion with Advarra the CIRB for FASTEST regarding implementation. |
| Sleep.SMART—Concern for aerosolization of viral particles by CPAP | Provision of clinical guidance to participants regarding mitigation of risk to household members, circumstances under which CPAP use may merit review with local physician. |
| Less study activity at trial sites with suspension of enrollment | Maintenance of screening for potential participants even though patients cannot be approached for enrollment. Focus on completing outstanding queries and study start-up. Educational efforts by the network to improve coordinator knowledge base. Update certification and training if expiring soon. With restarting trials, creating flexibility so that project coordinators may reenter physical clinical space in accordance with local practice but for minimal time periods and with maximum physical distancing. |
| Lack of monies to support research coordinators or therapists at trial sites since they cannot enroll new participants or perform prescribed therapies | Encouragement of coordinators to assist on other available funded research activities and to document all unfunded activities for potential financial assistance in future. I-ACQUIRE addressed this issue, in part, by providing additional ongoing training and interactive Webinar sessions and paying for therapists’ time to do this. Institutional responses varied greatly with some coordinators furloughed, some redeployed to clinical duties when qualified, some required to take paid time off, and some having salaries cut. These latter issues have slowed ongoing processes such as study start-up activities during shutdown and will slow restart enrollment initially at some sites. |
| Suspension and delay of site monitoring visits | Simplified visits, conducted online and by virtual communication. |
| Suspension of in-person, hands-on study staff training near Atlanta on technical aspects of Sleep SMART protocol | It is not clear that virtual demonstration can substitute, but we plan video conferencing alternatives. |

ARCADIA indicates Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke; ARCADIA-CSI, Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke—Cognition and Silent Infarcts; ASPIRE, Anticoagulation for Stroke Prevention and Recovery After Intracerebral Hemorrhage; CIRB, central institutional review board; COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; EFIC, exception from informed consent; FASTEST, FVila for Acute Hemorrhagic Stroke Administered at Earliest Time; I-ACQUIRE, Infant ACQUIRE; MOST, Multi-Arm Optimization of Stroke Thrombolysis; MRI, magnetic resonance imaging; PPE, personal protective equipment; REDCap, Research Electronic Data Capture; SATURN, Statins Use in Intracerebral Patient; Sleep SMART, Sleep for Stroke Management and Recovery Trial; IDCS, transcranial direct current stimulation; TMS, transmagnetic stimulation; and TRANSPORT2, Transcranial Direct Current Stimulation for Post-Stroke Motor Recovery A Phase II Study.
COVID-19 represents a unique and rare external event that requires the full attention of our clinical and research infrastructure. The interaction of COVID-19 and stroke is proving to be a very active area of research that NIH StrokeNet is poised to help address, as we begin to collect data to quantify the impact of COVID-19 across our trials. Most importantly, the COVID-19 pandemic, like any critical external event, provides NIH StrokeNet and clinical researchers everywhere the opportunity to rethink how we can do research better.

ARTICLE INFORMATION

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