Stroke

SPECIAL REPORT

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/.

EVOLUTION OF STROKENET AND STROKENET TRIALS

The initial task of the first years of StrokeNet was development of the network infrastructure including the National Coordinating Center; National Data Management and Statistical Center; 25 participating regional coordinating centers, sites within each regional network; a central institutional review board for all participating clinical research sites; a central research pharmacy; prevention, acute stroke, and recovery working groups; education and imaging cores; key committees; and the NIH StrokeNet Data and Safety Monitoring Board. The network has grown dramatically with 27 regional coordinating centers and over 500 clinical research sites throughout the United States.

While the infrastructure was under development, StrokeNet also solicited, developed, and submitted clinical trial proposals for potential funding. Investigators refine concept proposals as they deem fit and submit to the NINDS to determine alignment with programmatic priorities. If NINDS approves concept proposals, investigators return to the network for assessment of feasibility through both detailed surveys of StrokeNet sites and a population-based epidemiological assessment, before the final trial submission to the NIH for peer review.

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

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For Sources of Funding and Disclosures, see page XXX.

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SPECIAL REPORT

Nonstandard Abbreviations and Acronyms

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 2 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 μV×ms in ECG lead V_1, serum NT-proBNP (N-terminal pro-B-type natriuretic peptide)>250 pg/mL, and left atrial diameter index≥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

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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 eptifibatide, 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 18, 2015	5	124	124

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 Cryptogenic Stroke–Cognition and Silent Infarcts; ASPIRE, Anticoagulation for Stroke Prevention and Recovery 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.

ACQUIRE), TRANSPORT2 (Transcranial Direct Current Stimulation for Post-Stroke Motor Recovery A Phase II Study), ARCADIA, and ARCADIA-CSI (ARCADIA-Cognition and Silent Infarcts). In addition, 2 trials had been ready to open enrollment, ASPIRE (Anticoagulation for Stroke Prevention and Recovery After Intracerebral Hemorrhage) and SATURN (Statins Use in Intracerebral Patient). The FASTEST trial (FVIIa for Acute Hemorrhagic

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*.[12]

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. Stroke research has unique challenges since patients often have communication issues requiring consent from legally authorized representatives, severely ill stroke patients may require intubation, stroke patients often move across several healthcare settings before returning home, and stroke patients frequently need transportation to health care or research facilities. Organized research networks like the NIH StrokeNet are uniquely positioned to address unforeseen challenges such as COVID-19. The response to an extraordinary situation can be coordinated across all trials and trial sites in the network while communicating best practices, innovative approaches, and the changing environment among the national principal investigators of all ongoing trials, as well as site principal investigators from hundreds of recruitment sites.

By February, recruitment had been accelerating in many of the trials, some of which had just begun enrollment in the prior months, and was poised to start in 2 of the trials. The events surrounding COVID-19 impacted clinical trials by closing clinical research activities at many institutions nationally and internationally in March 2020. The NIH StrokeNet leadership met regularly with the central institutional review board leadership to discuss the situation across the network. Concerns pertinent to the rapidly evolving situation included the safety of current and potential research participants and research staff, as well as the potential impact of research activities to the clinical care and resources available to potential COVID-19 patients. On March 13, detailed guidance regarding the COVID situation from StrokeNet leadership, the central institutional review board, and the NINDS was sent to StrokeNet trial investigators (Table 2).

In consideration of the safety of patients, study investigators, and the clinical resources and personnel needed for clinical care of COVID-19, and after discussions with the StrokeNet leadership, all study enrollment was

Table 2. Initial Guidance From StrokeNet Leadership to Trial PIs Regarding COVID-19

Guidance to Trial Sites
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.

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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

Table 3. COVID-19 Impact on Trials and Implemented Solutions

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 mo 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, FVIIa 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; tDCS, transcranial direct current stimulation; TMS, transmagnetic stimulation; and TRANSPORT2, Transcranial Direct Current Stimulation for Post-Stroke Motor Recovery A Phase II Study.

participants, a centralized approach to electronic and remote consent across all trial sites rather than each individual site, innovative approaches to online survey and focus groups for studies using exemption from informed consent, clear masks for therapy with infants and young children to allow perception of facial expressions, and reconsideration of all study processes including timing of enrollment from onset and outcome assessments. Some of these changes had already been initiated earlier in the year but were accelerated by the COVID-19 pandemic. Many of the changes will be positive changes for our clinical research platform going forward.

One additional challenge is that the COVID-19 pandemic may alter the standard of care or usual and customary care for control groups, particularly in our rehabilitation therapy trials. Changes in care may include less in-person and less frequent therapy, less home care, less social support, etc. Thus, we plan to document these changes over time to measure their potential impact on the interpretation of study results.

As of initial submission of this report on May 18, 2020, 55 days after suspension of trial enrollment, all of the trials have officially reopened for enrollment except for I-ACQUIRE, with 3 trials having enrolled new participants. Yet, while trials have officially reopened centrally, only a small number of individual trial sites are approved currently to enroll research participants by their institutions.

SUMMARY OF LESSONS LEARNED

One major strength of a large network such as StrokeNet is the substantial number of talented and collaborative clinical research investigators in StrokeNet institutions across the United States. Working with the larger stroke community, such a coordinated talent pool generates many trial ideas (109 proposals thus far) and spurs innovation: adaptive trial design of multiple therapies (MOST), the first phase III multicenter infant stroke recovery trial (I-ACQUIRE), a combined stroke prevention and outcome trial (Sleep SMART), a pragmatic trial (SATURN), and the first exception from informed consent trial of spontaneous intracerebral hemorrhage with use of mobile stroke units (FASTEST).

Perhaps the greatest strength of NIH StrokeNet and its investigators is the ability to respond quickly and collaboratively to external events. Most commonly, scientific advances can impact the design or conduct of large phase III trials that often take ≥10 years for investigators to plan, successfully navigate NIH review, obtain funding, and complete enrollment. For example, DEFUSE 3 investigators extensively redesigned the trial within 2 to 3 months after the late 2014 and early 2015 presentations of 5 positive endovascular trials that led to an immediate change in clinical practice. The redesigned DEFUSE 3 trial also led to a major change in clinical practice.

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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Disclosures

Dr Broderick is the principal investigator (PI) of the National Institutes of Health (NIH)–funded FASTEST trial (FVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time) that receives in-kind study medication from Novo Nordisk and monies to Department of Neurology and Rehabilitation Medicine from Genentech for his role on Steering Committee of TIMELESS trial (Tenecteplase in Stroke Patients Be-

tween 4.5 and 24 Hours) and from Ono Pharmaceuticals for role as consultant. Dr Wolf serves on the Scientific Advisory Board of SAEBO, Inc, and is a paid consultant to Motus Nova, Inc. Dr Kamel is a co-PI for the NIH-funded ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke) that receives in-kind study drug from the Bristol-Myers Squibb-Pfizer Alliance for Eliquis and ancillary study support from Roche Diagnostics, deputy editor for *JAMA Neurology*, Steering Committee member of Medtronic Stroke AF trial (uncompensated), end point adjudication committee for a trial of empagliflozin for Boehringer Ingelheim, and advisory board for Roivant Sciences related to Factor XI inhibition. Dr Elkind is a co-PI for the NIH-funded ARCADIA trial that receives in-kind study drug from the Bristol-Myers Squibb-Pfizer Alliance for Eliquis and ancillary study support from Roche Diagnostics and reports royalties from UpToDate for chapter on cryptogenic stroke. Dr Tirschwell is a co-PI for the NIH-funded ARCADIA trial (NINDS [National Institute of Neurological Disorders and Stroke] U01 NS095869) that receives in-kind study drug from the Bristol-Myers Squibb-Pfizer Alliance for Eliquis and ancillary study support from Roche Diagnostics. Dr Longstreth is a co-PI for the NIH-funded ARCADIA trial that receives in-kind study drug from the Bristol-Myers Squibb-Pfizer Alliance for Eliquis and ancillary study support from Roche Diagnostics. Dr Cramer is a consultant for Abbvie, Constant Therapeutics, MicroTransponder, Neurolutions, Regenera, SanBio, Stemedica, Fujifilm Toyama Chemical, Co, Biogen, and TRCare. Dr Sacco reports research grants from NIH and FL Department of Health; institutional support from Boehringer Ingelheim for role on executive committee of RE-SPECT ESUS trial (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source); and personal fees, Editor-in-Chief, *Stroke*. Dr Johnston reports research grants from NIH and Virginia Catalyst, consulting for Food and Drug Administration, member of NIH-NINDS council, grant funding and consulting for Diffusion Pharmaceutical, and Data Safety Monitoring Boards for Biogen and Rivanna Medical–joint research program. Dr Albers reports equity and consulting for iSchemaView and consulting for Genentech. Dr Adeoye is a cofounder and equity holder for Sense Diagnostics, Inc, and belongs to the Scientific Advisory Board for Acticor. Dr Barreto reports nonfinancial support from Glaxo-Smith-Kline, Inc, and Mitsubishi Pharma EU and consulting fees from Cerevast Therapeutics, Inc, and Genentech, Inc. Dr Grotta is a PI of Patient-Centered Outcomes Research Institute-funded BEST-MSU study (Benefits of Stroke Treatment Delivered Using a Mobile Stroke Unit) that receives study medication from Genentech and CSL Behring; co-PI of NIH-funded MOST trial (Multi-Arm Optimization of Stroke Thrombolysis) and FASTEST trial, the latter which receives study medication from Novo Nordisk; Scientific Advisory Board for Haemonetics and Acticor; and consultant for Frazer, Ltd. Dr Chervin reports research grants from NIH; he has served as a consultant for Zansors and editor and author for UpToDate; he has produced copyrighted material, patents, and patents pending, owned by the University of Michigan, focused on assessment or treatment of sleep disorders; he has served on the Boards of Directors for the American Academy of Sleep Medicine, Associated Professional Sleep Societies, International Pediatric Sleep Association, and the nonprofit Sweet Dreamzzz and on an advisory board for the nonprofit Pajama Program; and reports personal fees from Cambridge Press for role as editor. Dr Schlaug reports research grants from NIH and is an associate editor for *Annals of Neurology*. Dr Lansberg is a consultant for Biogen, Genentech, NuvOx Pharma, and Nektar Therapeutics. Dr Sheth reports research grants from NIH and the American Heart Association, Hyerfine, Novartis, Biogen, and Bard; is a consultant for Zoll; and reports equity in Alva. Dr Khatri reports funds from Cerenovus (Investigator Initiated Study grant multiple principal investigator), Nervive (NINDS grant coinvestigator), Bayer (Trial National PI), Lumosa (consultant), Diamedica (Scientific Advisory Board), and UpToDate (royalties). The other authors report no conflicts.

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