**Report of the Clinical Networks Evaluation Working Group**
**of the**
**National Advisory Neurological Disorders and Stroke (NANDS) Council**

February 7, 2022

## Contents

## Purpose of the evaluation

The National Institute of Neurological Disorders and Stroke (NINDS) supports clinical research networks to facilitate efficient, high-quality clinical trials and research studies. Anticipating renewal of two of these networks - NIH StrokeNet and the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) - NINDS established the Clinical Networks Evaluation Working Group of the NANDS Council to assess network processes and outcomes to date and to identify areas for improvement in the design of the next iterations of these programs. The Working Group was charged to consider:

(1) the programs' outcomes and impacts;
(2) the extent to which the programs are meeting their goals;
(3) the extent to which the networks collaborate with and benefit the research community; and
(4) what improvements to program components and operations could allow the networks to better address current or new goals.

The Working Group evaluated these programs jointly using a common framework to assess overall goals, with separate attention to features unique to each network.

## Clinical Networks Evaluation Working Group Roster

The Working Group included one member of the NANDS Council, investigators with expertise in clinical trial execution and network coordination, investigators with expertise in research areas addressed by the networks, and representatives from industry and a patient organization.

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## Evaluation process and timeline

The Working Group reviewed documents about both networks prepared by NINDS staff with input from network investigators. These materials covered network structure and operations, funding, study portfolios and outcomes, training and educational activities, engagement with the research community, patients and patient advocacy organizations, and industry, as well as prior recommendations made to the networks by their external oversight boards. NINDS also conducted a survey of hundreds of network leadership, staff, and participating investigators to gather feedback on the implementation of the two programs to inform future improvements and provided the responses to the Working Group for consideration. In addition, working group members conducted six small group discussions with network leadership, staff, and participating investigators for more direct dialog about the strengths of the programs and areas for improvement.

Between May 2021 and January 2022, the Working Group met by Zoom on six occasions. These meetings focused on (1) the goals of the evaluation; (2) network structure and proposal development; (3) network costs, efficiency, data quality, and study portfolio and outcomes; (4) training and community engagement; (5) results from the survey and discussion groups and group deliberation around findings and recommendations; and (6) finalizing the Working Group report. In addition to materials prepared for the Working Group in advance of each meeting, the Working Group heard presentations from NINDS program staff for the networks at the initial two meetings and met without program staff for the remaining meetings. The group also heard a presentation from a former NCI staff member about changes made to NCI clinical trial processes to speed trial development and initiation, promote collaboration in study development, and increase patient and community engagement.

## Summary of high priority recommendations

While recognizing the value of the networks and their many accomplishments, **the Working Group has concerns that the networks as they currently function are not well-positioned to drive impactful advances in neurotherapeutics into the future**. Through extensive review and deliberation described above, the Working Group identified opportunities for significant, meaningful improvements that would better position NeuroNEXT and StrokeNet to drive such advances going forward. The two top recommendations of the Working Group (# 1 and #2 below) are to initiate proactive, priority-setting processes to guide potential applicants toward areas of high unmet need and therapeutics with strong scientific promise; and to design and implement significantly streamlined and agile processes for assessing, developing, approving, and initiating projects. The combined effect of substantial improvement in these two areas could be significant, by energizing the research community, encouraging more impactful proposals, focusing network resources on projects more likely to be initiated, and generating research results in a more timely fashion. Additional recommendations target enhanced community engagement, diversity, equity and inclusion, workforce development, and more effective continuous improvement.

1. **Proactively identify and direct priorities for NeuroNEXT and StrokeNet studies, by developing and implementing a multi-stakeholder process to prioritize topics, questions, technologies, and/or scientifically-promising therapeutics for trials and clinical studies that have the potential for high-impact. These identified priorities should be communicated by NINDS through dedicated funding opportunities,** supplementing the current exclusive reliance on unsolicited, investigator-initiated proposals.
   1.1 Because of the importance of studies in pediatric populations, the Working Group specifically recommends prioritizing support for studies in pediatric populations, with a goal to conduct at least two new pediatrics studies in each network during the next funding period.

2. **Monumentally improve efficiency by shortening the average time from initial receipt of study concept to notice of grant approval by at least 50%. This should be accomplished in part by moving peer review for significance and impact earlier in the process, in order to focus time-intensive network and investigator protocol development efforts on studies much more likely to be conducted.** Not only would this improve efficient use of network resources, it would have the additional benefit of maintaining energy, morale, and engagement of the investigator community. To accomplish this goal, NINDS should also consider alternatives to reviewing and funding studies as separate grant applications through the study section process, which currently occurs after an already time-consuming, in-depth internal Network proposal vetting and development process.

3. **Strengthen internal and external community engagement by adding formal requirements to the next 5-year funding cycle:**
   3.1 Elevate the role of patient advocacy groups (PAGs) in both Networks to the program leadership level, and integrate the patient voice into all stages of project development, execution, analysis, and reporting, including reporting back to communities affected by trial results.
   3.2 Establish an industry consultant board(s) to develop strategies to more meaningfully engage biopharmaceutical companies in each Network's activities.
   3.3 Ensure adequate resourcing of clinical sites and hubs to more effectively support study participant recruitment, research coordinator retention, and community engagement.

4. **Set an explicit goal to achieve by the end of the next 5-year cycle a distribution of study participants, investigators, trainees, and staff that each reflect at least the proportions of individuals from non-White groups by race, and of Hispanic ethnicity, per the 2020 census.** One strategy to help achieve that goal is to require an equity, diversity, and inclusion (EDI) action plan for each network and to establish accountability for its implementation and for attainment of the goals. People with appropriate expertise to help achieve these goals should be required at each Network's leadership level and adequately resourced in the funding announcement.

5. **Enhance clinical trial investigator workforce development, readiness, and retention in the network renewal by (i) establishing specific expectations and deliverables for NeuroNEXT and StrokeNet Fellows programs and (ii) ensuring sufficient resources to achieve the specified deliverables** (for example, at least 50% salary and benefit support for Fellows).

6. **Institute processes for (i) at least annual input from all levels of 'frontline' (site, spoke, hub) investigators and staff on what is working well and what should be improved, and (ii) accountability on an annual basis for considering, responding to, and implementing solutions to input from both frontline investigators and staff AND annual recommendations of the Network Oversight Boards.** Leadership from both the Networks AND NINDS should be involved in consideration and response to identified needed improvements.

**In addition, the Working Group also discussed two additional major strategic considerations for NINDS leadership:**

- We recommend NINDS leadership ask the question: **"If we were designing networks for clinical trials in the neurosciences for the 21st century, is the current organization optimal?"**
- Even among leadership within the cores, there seemed to be uncertainty **whether trials focused on developing the *tools of experimental neurotherapeutics* is in scope for NeuroNEXT and StrokeNet**. Given the criticality of new technology and improved methodology to advancing treatments for neurological disorders, NINDS leadership should clarify whether development and validation of tools is in scope, and if so, what proportion of the portfolios should be so targeted.

## Program Overviews

**StrokeNet:**

NINDS established StrokeNet in 2013 to promote and conduct high-quality, multi-site, exploratory phase 1 and 2 and confirmatory phase 3 clinical trials focused on promising interventions, as well as validation studies of biomarkers or outcome measures immediately preparatory to trials. The objective was to have a balanced portfolio across stroke prevention, treatment, and recovery. StrokeNet is an open network; trial concepts can be initiated by investigators outside of the network or by StrokeNet investigators. NINDS expects that StrokeNet is the primary and first-line infrastructure involved in implementing all multi-site stroke trials submitted to the NINDS.

The StrokeNet infrastructure, now in its second five-year funding cycle, consists of a national coordinating center (NCC) at the University of Cincinnati, a national data management and statistical center (NDMC) at the Medical University of South Carolina, and 27 academic regional coordinating centers (RCCs) across the United States (Appendix 1), each with respective clinical performance and satellite sites representing approximately 500 stroke hospitals. Additionally, StrokeNet has partnered with the Global Alliance of Independent stroke Networks (GAINS) and includes international sites in Canada, Germany, United Kingdom, Spain, and Japan. Centralized resources include a central IRB (cIRB), central research pharmacy, imaging core, and a training and education core. Each RCC is provided funds to annually support a network trainee who can dedicate at least 50% protected time to train and engage in stroke research.

A total of 14 trials have been run through the network (Appendix 1), including 4 that were already underway and 10 trials that have been fully developed and awarded through StrokeNet. To date, StrokeNet has contributed to 7 completed trials, including the Telerehab and Defuse 3 trials, which were the first two trials that began in StrokeNet.

Across the eight fiscal years of 2013 to 2020, trial costs were $164 million, RCC costs were $67.5 million, NCC costs were $19 million, and NDMC costs were $8 million, for total costs to NIH over eight years of $258.5 million (Appendix 1).

**NeuroNEXT:**

NeuroNEXT develops and conducts exploratory clinical trials evaluating promising therapies for neurological disorders other than stroke, whether from academic, foundation, or industry discoveries. Examples include Phase 2 clinical trials, as well as clinical studies to validate biomarkers and clinical outcomes in preparation for clinical trials. The network consists of a Clinical Coordinating Center (CCC), a Data Coordinating Center (DCC), and 25 clinical sites throughout the US (Appendix 2). NeuroNEXT was among the first networks at NIH to establish a Central Institutional Review Board (cIRB), and it uses Master Clinical Trial Agreements (MCTAs) between the CCC and each of the clinical sites. NeuroNEXT was established in 2011 and first renewed in 2018. The 2nd renewal of the NeuroNEXT infrastructure is planned for FY 2023-27.

Through NeuroNEXT, NINDS aims to support exploratory trials and biomarker validation studies that can provide more rapid preliminary testing of new treatments to help identify those that merit further testing, such as through Phase 3 trials. NeuroNEXT is designed to increase the efficiency of clinical trials, facilitate patient recruitment and retention, increase the quality of neuroscience clinical trials, and enable public-private partnerships between NINDS and industry, foundations, or academia. The renewal of the program in 2018 strengthened emphasis on training and career development activities, adding a Fellows program with funds for partial support ($20,000/year) of one fellow at each clinical site and integrating support for the NINDS Clinical Trials Methodology Course (CTMC) into NeuroNEXT.

Like StrokeNet, NINDS supports clinical trials and studies conducted through the NeuroNEXT network separately from the infrastructure, through peer-reviewed funding mechanisms open to investigators from academia, foundations, or industry. To date, ten studies have been conducted or are in various stages in NeuroNEXT, testing biomarkers or therapies for GNE myopathy, cryptogenic sensory peripheral neuropathy (CSPN), Fragile X Syndrome, glioblastoma, Huntington's disease, ischemic stroke, myasthenia gravis, multiple sclerosis, and Parkinson Disease (Appendix 2).

Across the 10 fiscal years of 2011 to 2020, trial costs were $65 million, site costs were $73.9 million, CCC costs were $25.8 million, and DCC costs were $16.8 million, for total costs to NIH over 10 years of $181.6 million (Appendix 2).

## Evaluation findings

### Accomplishments and Strengths

The Working Group finds overall that continued support is justified for NeuroNEXT and StrokeNet, which have executed and completed several trials that have had a significant impact on clinical practice and patient outcomes. Further, staff in each network have built the infrastructure from the ground up, often expanding to include additional, local practice communities to engage in these studies.

**Programs' outcomes and impacts**: Both networks have developed the capacity to plan and efficiently execute impactful clinical studies. Notable successes from NeuroNEXT include a longitudinal observational study of infants with SMA that informed clinical trials and contributed to the approval of nusinersen, one of the most efficacious targeted therapies in neurology; and a phase 2 trial that provided evidence for a promising therapy for progressive MS, a type of MS with limited treatment options. The NIH StrokeNet DEFUSE 3 trial showed that imaging could identify acute stroke patients who could benefit from endovascular thrombectomy beyond previously recognized time windows, leading to rapid changes in clinical guidelines to allow more patients to receive therapy.

**Extent to which programs are meeting goals related to efficiency:** The networks have to a considerable extent developed and provided leveraged resources for trials, *once they are activated*. Following study section review, Institute approval, and funding allocation, trial initiation and implementation are efficient and generally on par with benchmarks for clinical trials in industry. At this point, both networks consistently track measures of efficiency and data quality and share results regularly with sites to encourage good performance and ongoing improvement. Similarly, the overall cost of trials conducted within the networks appears to be reasonable. Both Networks have shown an ability to make improvements over time. Examples include development of central IRBs, Standard Operating Procedures, data sharing standards, and enhanced community engagement. NINDS recently issued a Research Opportunity Announcement (ROA) for establishing initial plans for running platform trials to address expanded use of thrombectomy and related questions in acute stroke management, using a rolling approach within the existing NIH StrokeNet infrastructure.

**Extent to which networks collaborate with and benefit the research community:** NeuroNEXT and StrokeNet have convened expertise across relevant disciplines, and the programs provide some research training opportunities and partial support for new clinical investigators. Both networks have engaged with their broader academic research communities and have received and funded proposals from investigators within and outside their sites (Table 1). The networks recognize the important role of the patient perspective in their clinical studies, and they have collaborated with patients and patient advocacy groups (PAGs) to a variable extent across individual studies, particularly around recruitment and retention. Two NeuroNEXT trials were led or co-led by industry sponsors, and in both networks, companies have provided study medications, placebos, and devices for interventional trials, and in some cases, financial support for certain trial activities (note that this support is not reflected in the cost tables in Appendices 1 and 2).

**Table 1. NeuroNEXT and StrokeNet Proposals Reviewed and Funded, through May 2021.**

| | Initial proposals assessed by network | Funded studies |
|---|---|---|
| **NeuroNEXT** | | |
| From NeuroNEXT site | 77 (47%) | 3 (33%) |
| From non-NeuroNEXT site | 87 (53%) | 6 (67%) |
| **StrokeNet** | | |
| From Funded RCC PI or Co-PI | 38 (31%) | 7 (43%) |
| From Investigator without StrokeNet funding at an RCC | 45 (37%) | 6 (43%) |
| From Investigator at a non-RCC site | 38 (31%) | 2 (14%) |

Excludes proposals for studies developed prior to the networks' establishment of proposal development processes.

## Opportunities for Improvement and Recommendations

While recognizing the value of the networks, and their many accomplishments, **the Working Group has concerns that the networks as they currently function are not well-positioned to drive impactful advances in neurotherapeutics into the future**. Through extensive background review, presentations, interviews, and internal discussion, the Working Group identified a number of opportunities for significant and meaningful improvements that would better position NeuroNEXT and StrokeNet to achieve more impact. First and foremost, the Working Group recommends proactive priority setting to guide potential applicants toward areas of high unmet need and therapeutics with strong scientific promise; and to design and implement significantly streamlined and agile processes for assessing, developing, approving, and initiating projects. The combined effect of substantial improvement in these two areas would be significant, by energizing investigators and securing and executing more impactful proposals in a more timely fashion. Additional recommendations target enhanced community engagement, diversity, equity and inclusion; workforce development; and more effective continuous improvement.

1. **Proactively identify and direct priorities for NeuroNEXT and StrokeNet studies, by developing and implementing a multi-stakeholder process to prioritize topics, questions, technologies, and/or scientifically-promising therapeutics for trials and clinical studies that have the potential for high-impact. These identified priorities for desired studies should be communicated by NINDS through dedicated funding opportunities,** supplementing the current exclusive reliance on unsolicited, investigator-initiated proposals.

   To select studies for NeuroNEXT and StrokeNet, NINDS has relied nearly entirely on investigator-initiated proposals from the academic community, as opposed to also systematically identifying priorities and encouraging proposals in those high-priority areas. While the Working Group recommends that an investigator-initiated mechanism be continued, we strongly recommend that approach be supplemented by identifying and encouraging proposals addressing conditions with high unmet need and therapeutics with high scientific promise and potential impact. The current approach has resulted in a dearth of projects addressing high-priority research needs.

   For example, no trials for epilepsy have been conducted in NeuroNEXT, and StrokeNet trials have not included a focus on vascular contributions to dementia. In addition, the networks have conducted very few studies in pediatric populations (see recommendation 1.1). Feedback from network participants reflected a perception that well-established or well-connected investigators are more likely to receive support for their proposals, leading to a concentration of focus in certain conditions of interest to those investigators (e.g., over-representation of trials in neuromuscular disorders in NeuroNEXT). Inclusive and transparent priority-setting may counter such perceived biases while encouraging more compelling and innovative applications.

   Proactive priority setting, with input from the community, might also encourage investigators to work together as teams to address identified goals as opposed to competing across disciplines for support. Feedback from StrokeNet investigators and staff noted concerns that ongoing trials compete for the same patient populations; more proactive priority setting could be part of a strategy to manage eligibility overlap among concurrently recruiting trials. When setting priorities for the networks, NINDS should also consider studies and trials in important but underfunded areas less likely to receive industry support, such as stroke rehabilitation and prevention research.

   A systematic process to identify and communicate translational scientific advances emanating from NCATS and other translational research programs would enhance the likelihood that promising discoveries are moved forward into subsequent trials. Another consideration for priority-setting for StrokeNet is whether the current balance of Phase 1 and 2 versus Phase 3 trials reflects where the strongest opportunities are to advance our knowledge, or whether a portfolio with more early phase trials is optimal, based on current scientific opportunities.

   For both Networks, the priority-setting process should also ensure that Phase 2 trials not only provide information about safety and dosing, but also generate stronger conclusions about proof of concept and phase 3 readiness, by requiring the use of sensitive measures of efficacy and by incorporating new assessment approaches (e.g., home blood tests, computer-based, wearable, portable, home-based). This is because a primary goal of Phase 2 trials is to provide clear evidence as to whether an intervention warrants further testing in Phase 3, and neurology clinical trials have a high rate of failure in expensive Phase 3 trials.

NINDS should also proactively seek and continue to expand the use of innovative study designs, such as platform and virtual trials, as well as novel technologies to expand study scope and potential impact and to accelerate innovation in research methods. Trials that purposefully incorporate telemedicine and digital devices enable capture of objective, real-world data in trials and enable remote assessments for screening participants and for long-term follow-up, especially for biological or high risk treatments. Decentralized ("siteless") studies are very well suited for rare, geographically dispersed, disabling conditions.

**1.1 Because of the importance of studies in pediatric populations, the Working Group specifically recommends prioritizing support for studies in pediatric populations, with a goal to conduct at least two new pediatrics studies in each network during the next funding period.**

Although both networks have committees or working groups focused on pediatric research and NINDS has begun more outreach to pediatric-focused investigators, only two of 10 ongoing or completed studies in NeuroNEXT and one of 15 in StrokeNet have addressed conditions in pediatric populations. More intentional work and input from experts in pediatric clinical research are needed to address barriers to conducting pediatric trials in NeuroNEXT and StrokeNet and to ensure that more pediatric trials are supported in subsequent funding periods. For example, strong adult clinical sites are often not strong pediatric sites, and adult-dominated networks and coordinating centers/cores cannot easily meet the needs of pediatric clinical trials. Also, neurodevelopmental testing and scoring of results require coordinating center skills not always present in adult trial coordinating centers. Neuroimaging in infants, toddlers, school-age children, and adolescents are each different, and neuroimaging cores within adult networks often do not have adequate expertise. Adult-oriented clinical neurophysiology cores are often not capable of managing the different data norms, methods of data collection, and technical standards across different ages of children. Finally, outcome measures often are more complex and need additional centralized expertise not available in adult-oriented data coordinating centers (e.g., qualitative data from parents, school performance data).

Particularly in pediatric neurology, research is needed not just on the short-term efficacy of an intervention but also on long-term impacts on the developing brain and later functional outcomes. The Working Group suggests that NINDS consider support for converting some of the populations in clinical trials that demonstrate efficacy or effectiveness into cohorts that can address longer term outcomes and preparing for this possibility as part of a planning process at the outset of funded pediatric trials, where relevant.

**2. Monumentally improve efficiency by shortening the average time from initial receipt of study concept to notice of grant approval by at least 50%. This should be accomplished in part by moving peer review for significance and impact earlier in the process, in order to focus time-intensive network and investigator protocol development efforts on studies much more likely to be conducted.** Not only would this improve efficient use of network resources, it would have the additional benefit of maintaining energy, morale, and engagement of the investigator community. To accomplish this goal, NINDS should also consider alternatives to reviewing and funding studies as separate grant applications through the study section process, which currently occurs after an already time-consuming, in-depth internal Network proposal vetting and development process.

Both networks invest significant effort in developing proposals for potential clinical studies prior to their submission as grant applications for peer review. This process can provide useful feedback to investigators, and it may strengthen eventual grant applications. However, the overall funding rate is low, and most proposals that progress to study section peer review require resubmission (Table 2).

**Table 2. Number of proposals submitted and funded through NeuroNEXT and StrokeNet, through 2020.**

| Network | Initial proposals assessed by network* | Grant applications reviewed** | Number funded after 1st submission | Resubmitted applications reviewed | Number funded after resubmission | Total grants funded |
|---|---|---|---|---|---|---|
| NeuroNEXT (2012-2020) | 164 | 28 | 2 | 14 | 7 | 9 |
| StrokeNet (2015-2020) | 122 | 28 | 2 | 19 | 9 | 11 |

* Excludes proposals for studies developed prior to the networks' establishment of proposal development processes.

**Excludes applications withdrawn prior to review or for which review or funding decision is pending.

Moreover, the process from concept submission to grant funding is prohibitively long (Tables 3 and 4). In NeuroNEXT, the mean time from initial proposal to the network to grant application is 434 days (range 137-1392), and the mean time from initial proposal to grant funding is 957 days (range 550-1614). In StrokeNet, the mean time from initial proposal review to grant application is 365 days (120-978), and the mean time from initial proposal review to grant funding is 612 days (237-1486).

**Table 3. NeuroNEXT proposal development and review timeline**

| | Days from initial proposal submission to the NeuroNEXT executive committee (NEC) to: | | | |
|---|---|---|---|---|
| | NEC Decision | Grant Application | Grant Application Resubmission | Budget Start |
| Min | 10 | 137 | 339 | 550 |
| Max | 1056 | 1392 | 1083 | 1614 |
| Median | 57 | 356 | 682 | 925 |
| Mean | 111 | 434 | 680 | 957 |

Descriptive statistics for the length of time (days) lapsed from initial proposal submission to the NeuroNEXT executive committee (NEC) to NEC decision, grant application submission to NINDS, grant application resubmission (if applicable), and start of funding for awarded applications; for proposals submitted to NeuroNEXT NEC from 2011- June 2021.

**Table 4. StrokeNet proposal development and review timeline**

| | Days from initial proposal review by StrokeNet Work Group to: | | | |
|---|---|---|---|---|
| | NINDS ESC Review | Grant Application | Grant Application Resubmission | Budget Start |
| Min | 0 | 120 | 417 | 237 |
| Max | 560 | 978 | 1619 | 1486 |
| Median | 98 | 288 | 752 | 405 |
| Mean | 147 | 365 | 897 | 612 |

Descriptive statistics for the length of time (days) lapsed from initial proposal review by a StrokeNet Work Group (prevention, acute, or recovery) to NINDS Extramural Science Committee (ESC) review, first grant application submission to NINDS, final grant resubmission (if applicable), and start of funding for awarded applications; for all StrokeNet proposals submitted from 2015 - June 2021.

Researchers do not know whether their proposals will move forward as grant applications until late in this process, often extending for 2 years or more. At the same time, Network staff and investigators spend substantial time working on many proposals that are never initiated. Feedback from investigators indicates that the low success rate coupled with the long timeline – including prolonged time and effort before concepts are turned down – has diminished enthusiasm among many researchers. These factors also affect the networks' ability to attract innovative and important studies. Feedback suggests that some researchers submit their best ideas elsewhere due to the lengthy proposal evaluation period and low chance for success. Working Group members were also concerned that the review of potential trials may be overly conservative, potentially discouraging newer investigators or submission of more ambitious ideas.

NINDS should revamp the proposal development and review processes in NeuroNEXT and StrokeNet to screen and triage proposals based on significance at earlier stages, in order to focus on proposals that have the greatest potential impact and that are more likely to receive funding. This should be a central and essential part of a multi-pronged strategy to shorten the average timeline from concept submission to trial funding by at least 50%. NINDS should learn from approaches used in other NIH clinical networks and consider alternatives to reviewing and funding studies as separate grant applications. For example, NCI networks use a team approach to develop brief letters of intent that focus on justifying significance, scientific plausibility of the treatment, potential impact, and alignment with priority areas as principal criteria for early peer review. NCI and the NIH Early Phase Pain Investigation Clinical Network (EPPIC-Net) also include early review of study concepts (the science, target, and intervention mechanism of action) and then allow the network to design and execute studies approved to move forward.

3. **Strengthen internal and external community engagement by adding formal requirements to the next 5-year funding cycle:**

   **3.1. Elevate the role of patient advocacy groups (PAGs) in both Networks to the program leadership level, and integrate the patient voice into all stages of project development, execution, analysis, and reporting, including reporting back to communities affected by trial results.**
   Both networks recognize the benefits of patient and PAG engagement. However, most patient engagement has centered around recruitment and retention, and the type and level of engagement appears to have varied considerably across trials. Meaningful PAG involvement should be an intrinsic component of the networks, led from the top, to maximize the value the patient voice can bring at all stages of clinical research, including project development, determining clinical endpoints, and study execution, analysis, and reporting, including publication. Patient engagement in rare disease research may provide a useful model, and the Working Group also suggested that sites be encouraged to work more with organized patient groups to receive broad perspectives, in addition to working with individual patients who speak from their individual experience. Importantly, elevating patient engagement in the networks will require additional resources at the Core Level and at the RCC and site levels.

   **3.2. Establish an industry consultant board(s) to develop strategies to more meaningfully engage biopharmaceutical companies in each Network's activities.**
   Companies are not likely to engage in projects testing their investigational assets via NeuroNEXT and StrokeNet because of the excessively long study development timelines and the need for independent peer review. However, the Working Group felt that industry engagement would bring considerable benefits to the networks and believes there may be ways for companies to engage with the networks and achieve mutual benefits. For example, industry consultants advise on study design/outcomes and regulatory issues, identify promising compounds that are off patent or might benefit from collaboration, mentor investigators, provide network trainees with industry experiences, and the like. The networks should also increase efforts to partner with companies that can donate product or bring in funding for later stage trials. In addition, the Working Group suggests that NINDS revisit possible mechanisms to allow companies to use the network's infrastructure but bring their own funding for the trial, potentially with a different review process than that used for academic trials.

   **3.3. Ensure adequate resourcing of clinical sites and hubs to more effectively support study participant recruitment, research coordinator retention, and community engagement.**
   The Working Group observed that support for sites for conducting trials is marginal or inadequate for certain purposes. Feedback from the networks noted that sites are losing money by participating in network trials, with some reporting that they effectively 'subsidize' their network study participation by participating in industry and other trials, which were perceived as not as scientifically interesting or engaging but necessary in order to be able to maintain a research staff workforce to participate in network studies. The Working Group recommends NINDS increase dedicated funding and other resources to clinical sites and hubs, for example by providing stable support for clinical coordinators, managers, and other staff/activities critical for maintaining trial infrastructure and implementation. The Working Group found that high coordinator turnover is particularly problematic, as coordinators are vital to study execution activities. NINDS and the networks should find ways to better resource and recognize the role of clinical coordinators. Potential solutions include providing bridge funding to site coordinators in between active trials, creating modest 'scholarships' in recognition of clinical research staff, and enhancing the career development opportunities for coordinators. Retention and turnover of coordinators working on network trials should be tracked for improvement (not judgment) purposes.

   Network participants noted that recruitment and retention activities, in particular, also need more resourcing. Outreach and engagement with patients, especially with those from underrepresented groups, is substantially constrained at current support levels. More funding could be used, for example, to increase per patient fees, and in some cases, support recruitment and retention specialists that are well-trained in community engagement. There is also a need for the networks to provide more instruction on advancing equity, diversity, and inclusion, including proactively disseminating existing toolkits on recruitment and enrollment of underserved populations.

4. **Set an explicit goal to achieve by the end of the next 5-year cycle a distribution of study participants, investigators, trainees, and staff that each reflect at least the proportions of individuals from non-White groups by race, and of Hispanic ethnicity, per the 2020 census.** One strategy to help achieve that goal is to require an equity, diversity, and inclusion (EDI) action plan for each network and to establish accountability for its implementation and for attainment of the goals. People with appropriate expertise to help achieve these goals should be required at each Network's leadership level and adequately resourced in the funding announcement.

NIH is committed to supporting clinical research that benefits individuals of all sexes/genders, races, ethnicities, and ages, and to fostering a diverse and inclusive research workforce. Despite efforts and with the exception of enrollment of Black/African American participants in StrokeNet, the recruitment of minority participants in NeuroNEXT and StrokeNet clinical trials is well below aspirations for achieving health equity goals (Tables 5-6; Appendix 3), suggesting the need for more proactive community engagement and other strategies to improve inclusion. The Working Group notes that the geographic distribution of StrokeNet sites does not match the epidemiology of stroke incidence, where risk is higher in the stroke belt and in populations with health inequities. The networks need to identify and implement ways to meaningfully increase racial and ethnic diversity of enrolled study participants so that results are generalizable and applicable to the population more broadly.

**Table 5. Percentages of trial participants by ethnicity for NeuroNEXT and StrokeNet as of July 2021, and 2020 US Census data**

| | Hispanic or Latino | Not Hispanic or Latino | Unknown or Not Reported |
|---|---|---|---|
| **NeuroNEXT trial participants, %** | **7%** | **90%** | **4%** |
| **StrokeNet trial participants, %** | **8%** | **91%** | **1%** |
| **2020 US Census, 18 years or older*** | **17%** | **83%** | n/a |
| **2020 US Census, under 18 years*** | **26%** | **74%** | n/a |

*from https://www.census.gov/library/stories/2021/08/improved-race-ethnicity-measures-reveal-united-states-population-much-more-multiracial.html

**Table 6. Percentages of randomized participants by race for NeuroNEXT and StrokeNet as of July 2021, and 2020 US Census data**

| | American Indian/AK Native | Asian | Black or African American | Native Hawaiian or Other PI | White** | More than one race | Unknown or not reported |
|---|---|---|---|---|---|---|---|
| **NeuroNEXT trial participants, %** | **0%** | **1%** | **6%** | **0%** | **87%** | **2%** | **4%** |
| **StrokeNet trial participants, %** | **0%** | **3%** | **21%** | **1%** | **74%** | **0%** | **2%** |
| **2020 US Census, 18 years or older*** | **1%** | **6%** | **12%** | **0.2%** | **64%** | **9%** | n/a |
| **2020 US Census, under 18 years*** | **1%** | **6%** | **14%** | **0.3%** | **53%** | **15%** | n/a |

*from https://www.census.gov/library/stories/2021/08/improved-race-ethnicity-measures-reveal-united-states-population-much-more-multiracial.html

**In the 2020 US Census, 'Some Other Race Alone' (not shown in Table 6) were 8% among those 18 years and older and 11% of those under age 18; 94% of these individuals also reported Hispanic or Latino ethnicity, so among network trial participants, these individuals would likely have been classified as White race.

Consistent with NIH/NINDS goals to promote diversity and inclusion in the research workforce, the Working Group also sees opportunities to strengthen NeuroNEXT and StrokeNet by increasing diversity among their leadership, investigators, and staff, which may in parallel aid in efforts to increase the diversity of study participants. The

networks should conduct outreach, encourage, and mentor a diverse group of potential trial investigators, especially younger ones who may come from groups underrepresented in medicine. At a minimum, the networks should create such opportunities for co-PIs.

Network EDI plans should outline goals, gap analysis, desired outcomes, and processes and metrics to measure progress and promote accountability. Importantly, these plans will also require additional resources for successful implementation.

5. **Enhance clinical trial investigator workforce development, readiness, and retention by (i) establishing specific expectations and deliverables for NeuroNEXT and StrokeNet Fellows programs and (ii) ensuring sufficient resources to achieve the specified deliverables** (for example, at least 50% salary and benefit support for Fellows). It is recommended that this be implemented with the renewal of the networks.

   The networks seeks to contribute to the development of the next generation of clinical trial investigators. Each network has a program to support clinical research fellows at its clinical sites, and these programs also include some central training activities. Both programs have been well-received by participants, but the Working Group identified several opportunities for improvement.

   First, NINDS and the networks should clarify the goals of the Fellows programs and the expectations for the participants. For example, are these intended for post-residency trainees, for junior faculty, or for both? The Working Group recommends more explicit description of program components, including fellow selection, training objectives and plans, and mechanisms for tracking participant satisfaction and outcomes. Central network oversight of the Fellows programs appears somewhat loose and should be more rigorous. The Working Group recommends that the networks expand program offerings for NeuroNEXT and StrokeNet Fellows, to include more opportunities to gain exposure to industry research and development, stronger mentorship, and more leadership opportunities, which may include serving on network committees and working groups, or as co-PIs on network studies. NINDS and the networks should also clarify how the goals and content offerings of the Clinical Trials Methodology Course (CTMC) relate to the Fellows programs and ensure that the CTMC is available as an opportunity to all Fellows across NINDS-supported networks.

   As part of network goal-setting to meet the distribution in the US population of minority investigators and trainees (Recommendation 4), NINDS and the networks should make explicit commitments to fostering diversity and inclusion within both the CTMC and fellows training programs. There should be ongoing tracking and transparency about central tracking tools used to ensure sites offer these opportunities equitably to individuals from underrepresented groups and do outreach to help ensure meeting goals for inclusion of individuals from underrepresented groups.

   Importantly, NINDS should provide adequate financial support to support the goals and expectations of the network Fellows programs, including increased salary support and appropriate enforcement of protected time for research training and network activities. The current level of support of $20,000 for a NeuroNEXT Fellow is insufficient to expect meaningful impact, while the current level of support for StrokeNet Fellows could support 50% of a post-residency fellowship, but would not provide adequate support for junior faculty. The Working Group recommends that NINDS and the networks implement these improvements to training programs in the next five-year funding cycle.

6. **Institute processes for (i) at least annual input from all levels of 'frontline' (site, spoke, hub) investigators and staff on what is working well and what should be improved, and (ii) accountability on an annual basis for considering, responding to, and implementing solutions to input from both frontline investigators and staff <u>AND annual recommendations of the Network Oversight Boards</u>.** Leadership from both the Networks AND NINDS should be involved in consideration and response to identified needed improvements.

   In the process of conducting this program evaluation, the Working Group was struck by two observations. First, a meaningful number of the recommendations we are making were recommended over the years by one or both Network External Oversight Boards (EOB). A summary document from the NeuroNEXT EOB listed 6 separate meetings between 2/26/13 and 5/14/21. The document stated that EOB had met with investigators and program

officials after each meeting, conveying their recommendations. The summary document lists recommendations that are strikingly similar to those provided by the current review panel. However, it is unclear what changes, if any, were made based on the EOB observations and recommendations. Similarly, the StrokeNet EOB met with staff from StrokeNet NCC and NDMC as well as NINDS staff 4 times between 2015 and 2019. The summary document lists numerous recommendations that closely align with recommendations from the current panel. Again, it is not clear what changes were made in response to the observations and recommendations from StrokeNet EOB, but the current Working Group is not confident that EOB recommendations have led to substantive as opposed to incremental or no changes.

Second, data from the surveys and discussion groups with site, spoke, and hub investigators and staff often (although not uniformly) reflected a perception that Network leadership structure(s) were insular and that there needed to be substantively more engagement and inclusiveness.

NINDS and the networks should establish more systematic processes to monitor performance across program goals that will drive accountability and transparency and aid ongoing evaluation, incorporate diverse perspectives, and ensure continuous learning. At the outset of the next phase of each network, NINDS should work with network staff to establish a 5-year evaluation plan, including short, medium, and longer-term evaluation metrics and pre-established timelines for data collection and review. These processes should include the development of target timelines for the steps of proposal development and funding; metrics for assessing training programs and efforts in diversity and inclusion and in community engagement; and a means for obtaining in-depth feedback from a representative sample of network participants on at least an annual basis. Evaluative activities should not be seen as punitive but rather should inform course-correction and continuous learning. Summaries and other read-outs of network performance should be disseminated regularly throughout the networks. The process for NINDS program and Network leadership review and strategizing of responses to EOB recommendations should be formalized in a way that ensures transparency related to the recommendations and responses, and that provides accountability.

## Additional Major Strategic Considerations for NINDS Leadership

Beyond the 6 recommendations listed above, which target the next iterations of StrokeNet and NeuroNEXT, the Working Group discussed two additional major strategic questions for consideration by NINDS leadership. Though a bit beyond the scope of the Working Group's charge, these additional considerations are warranted given the increasingly important role of neurotherapeutics, and the already substantial investments in these NINDS flagship networks.

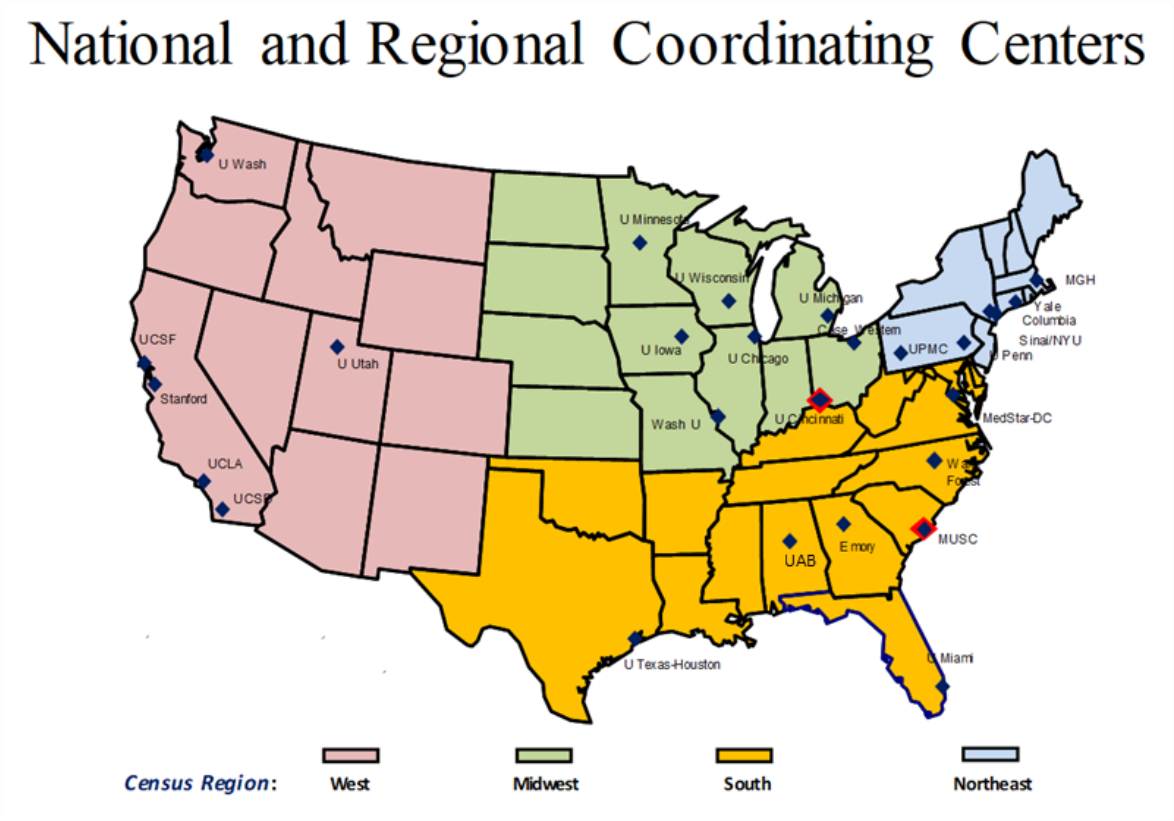
First, NINDS might revisit the current approach of organizing support for clinical trials in the neurosciences with two networks—one network focused on stroke studies at all phases and another focused on phase 2 studies for all other neurological conditions. NINDS leadership could ask the question: "If we were designing networks for clinical trials in the neurosciences for the 21st century, is the current organization optimal?" Additionally, with rapid scientific and technical advances in data management, bioinformatics, analytic sciences including AI, biomarkers, imaging, and the like, there will be cases in which complex, cutting edge trials require expertise and resources beyond the networks' standing capabilities. NINDS should consider approaches to improve network organization and function to ensure effective flow of ideas and optimal collaboration and integration of special expertise and capabilities in the research community—both within and external to the networks—throughout the conception, planning, and implementation of trials.

Second, the review panel sensed some confusion, or at least ambiguity related to scope for each of the networks. Clinical trial evolution in the neurosciences will almost certainly be dependent on advances in assessment technology, development and validation of biomarkers, new imaging technology, better understanding of disease evolution, and innovative trial design, including virtual trials and increased reliance on patient reported outcomes (among others). Even among leadership within the core facilities, there seemed to be uncertainty whether trials focused on developing the *tools of experimental neurotherapeutics* is in scope for NeuroNEXT and StrokeNet. Given the criticality of new technology and improved methodology to advancing treatments for neurological disorders, NINDS leadership may wish to clarify whether clinical research protocols specifically designed to advance clinical trial tools and methods are in scope for NeuroNEXT and StrokeNet, and if so, what proportion of the portfolios should be so targeted.

## NANDS Council deliberation

The Working Group co-chairs presented the findings and recommendations in this report during the open session meeting of the NANDS Council on February 2, 2022. All Council members voted to accept the report's recommendations. In their discussion, Council members provided comments in support of the Working Group's top two recommendations (recommendation 1, priority setting to supplement investigator-initiated proposals; and 2, improved efficiency for the process from trial concept to initiation), as well as recommendations for more support for sites and coordinators and strengthening community engagement, including with the patient community and industry (recommendation 3). They also shared suggestions for additional opportunities to consider in implementing the recommendations. One suggestion was to look beyond the patient community to include other potential end-users of clinical study data (e.g., primary care providers and insurers) to facilitate impact. Another noted that many investigators do not have expertise in community engagement and that both resources and training may be needed to support effective community engagement that can drive improvements in recruitment, diversity, and other aspects of trials. In addition, the use of Exception From Informed Consent (EFIC) processes (with appropriate community engagement) was suggested as an opportunity to enhance enrollment, particularly for stroke trials. Council members also discussed the feasibility of conducting at least two pediatric stroke trials in the next funding period. Given the general challenge that the best sites for adult clinical research may not be the best sites for pediatric research, this may be an area where flexibility to engage expertise outside of the established infrastructure could be helpful.

## Appendix 1: StrokeNet center locations, costs, and trials




| Network Component | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | Grand Total |
|---|---|---|---|---|---|---|---|---|---|
| NCC | $2,472,191 | $2,367,154 | $2,347,302 | $2,361,126 | $2,361,126 | $2,489,388 | $2,417,137 | $2,393,054 | $19,208,478 |
| NDMC | | $1,421,391 | $1,157,142 | $1,071,983 | $1,069,932 | $1,101,875 | $1,077,384 | $1,054,812 | $7,954,519 |
| RCCs | $9,830,495 | $9,535,930 | $7,092,586 | $9,531,379 | $9,384,623 | $7,619,006 | $6,847,345 | $7,625,939 | $67,467,303 |
| Trials (number ongoing) | $7,947,611 (2) | $15,214,179 (4) | $14,407,370 (5) | $17,851,393 (5) | $22,257,623 (5) | $32,932,392 (7) | $7,146,895 (6) | $46,072,182 (9) | $163,829,645 (14 Total) |
| **Grand Total** | $20,250,297 | $28,538,654 | $25,004,400 | $30,815,881 | $35,073,304 | $44,142,661 | $17,488,761 | $57,145,987 | **$258,459,945** |

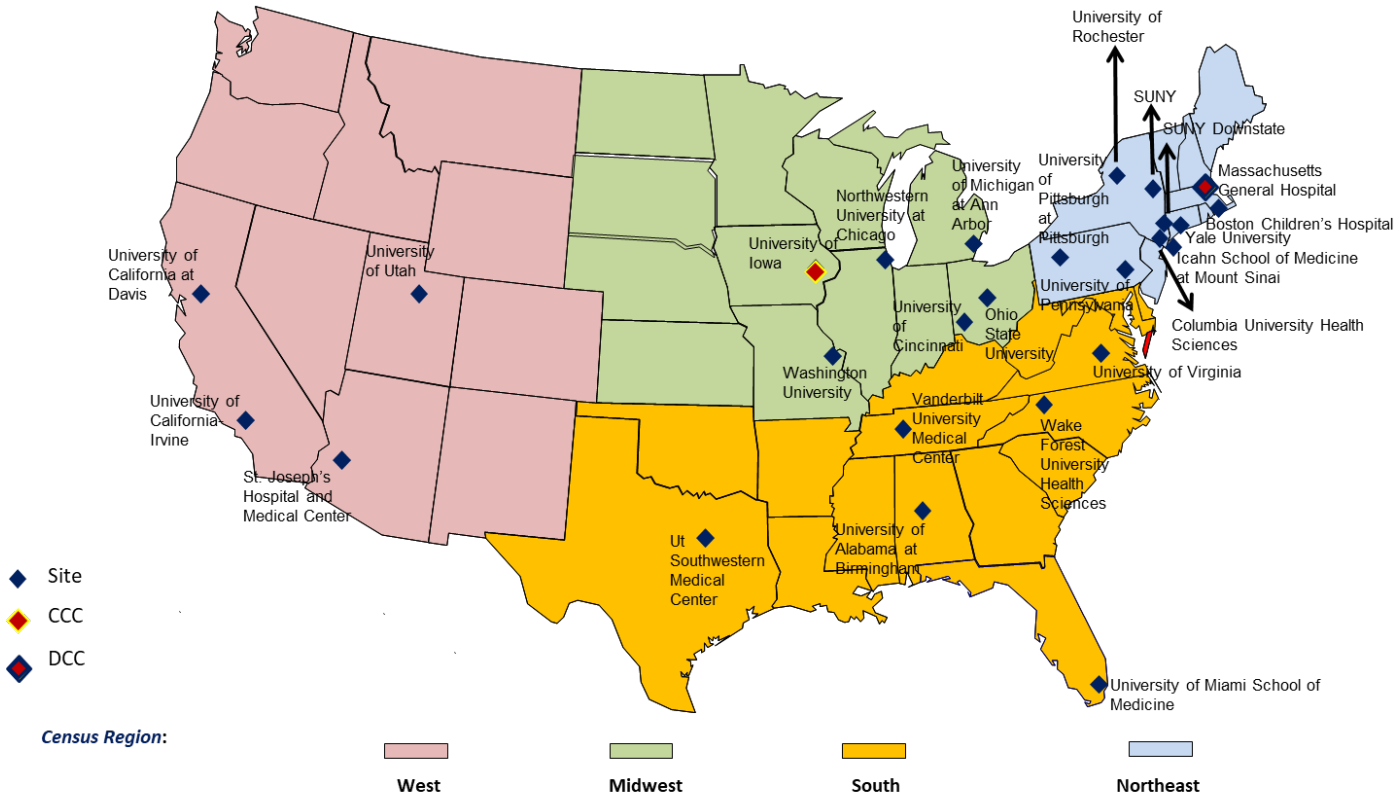
**Studies Supported by NIH StrokeNet (2013-2020)**

| Study name (Link to CT.gov) | Study Name (short) | Phase | Prev/Acute/Recovery | Intervention type | Enrollment target | Number of sites | Trial Start | Trial End (or status) | Primary Publication |
|---|---|---|---|---|---|---|---|---|---|
| Minimally Invasive Surgery Plus Rt-PA for ICH Evacuation Phase III* | MISTIE3 | 3 | Acute | rt-PA | 500 | 78 | 12/30/2013 | 9/1/2018 | Publication Link |
| Futility Study of Deferoxamine Mesylate in Intracerebral Hemorrhage* | iDEF | 2 | Acute | Deferoxamine Mesylate | 294 | 40 | 10/1/2014 | 5/30/2018 | Publication Link |
| Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial* | CREST-2 | 3 | Prevention | Carotid endarterectomy/ stenting | 2480 | 147 | 12/2/2014 | ongoing | |
| Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke | Telerehab | 2 | Recovery | Telerehabilitation Therapy | 124 | 11 | 9/1/2015 | 4/1/2018 | Publication Link |
| Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke | Defuse-3 | 3 | Acute | Endovascular Thrombectomy | 476 | 38 | 4/1/2016 | 8/23/2017 | Publication Link |
| AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke | ARCADIA | 3 | Prevention | Apixaban | 1100 | 165 | 1/19/2018 | ongoing | |
| ARCADIA CSI (Cognition and Silent Infarcts) | ARCADIA-CSI | ancillary | Prevention | n/a | 500 | 92 | 7/1/2019 | ongoing | |
| Sleep for Stroke Management And Recovery Trial | Sleep-SMART | 3 | Prevention/Recovery | CPAP | 3062 | 110 | 5/9/2019 | ongoing | |
| Multi-arm Optimization of Stroke Thrombolysis | MOST | 3 | Acute | Argatroban/ Eptifibatide | 1200 | 112 | 10/19/2019 | ongoing | |
| Transcranial Direct Current Stimulation for Post-stroke Motor Recovery | TRANSPORT-2 | 2 | Recovery | tDCS | 129 | 16 | 9/1/2019 | ongoing | |
| Perinatal Arterial Stroke: A Multi-site RCT of Intensive Infant Rehabilitation | I-ACQUIRE | 3 | Recovery | Pediatric Constraint-Induced Movement Therapy | 240 | 12 | 10/10/2019 | ongoing | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Anticoagulation in ICH Survivors for Stroke Prevention and Recovery | ASPIRE | 3 | Prevention/Recovery | Apixaban | 700 | 140 | 1/28/2020 | ongoing | |
| Statins In Intracerbral Hemorrhage | SATURN | 3 | Prevention | Statins | 1480 | 140 | 6/10/2020 | ongoing | |
| Recombinant Factor VIIa (rFVIIa) for Hemorrhagic Stroke Trial | FASTEST | 3 | Acute | Recombinant Activated Factor VII (rFVIIa) | 860 | 120 | In start-up | ongoing | |

*Three trials (MISTIE3, iDEF, and CREST-2) were approved before NIH StrokeNet was initiated but used network resources to conduct or complete the study.

## Appendix 2: NeuroNEXT center and site locations, costs, and trials




| Network Component | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | Grand Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CCC | $2,740,976 | $2,755,158 | $2,742,199 | $2,663,374 | $2,703,973 | $2,618,494 | $2,322,084 | $2,450,857 | $2,398,805 | $2,395,171 | $25,791,091 |
| DCC | $1,776,295 | $1,760,159 | $1,665,128 | $1,605,564 | $1,601,880 | $1,561,366 | $1,514,273 | $1,795,894 | $1,763,568 | $1,763,568 | $16,807,695 |
| Sites | $7,817,572 | $7,658,514 | $6,166,168 | $6,859,069 | $6,308,534 | $7,633,224 | $7,634,310 | $8,063,196 | $7,938,376 | $7,847,629 | $73,926,592 |
| Trials (number ongoing) | | $823,453 (1) | $5,168,265 (3) | $8,006,845 (4) | $7,131,119 (4) | $11,825,655 (6) | $10,957,752 (7) | $6,901,997 (4) | $6,587,228 (4) | $7,637,579 (4) | $65,039,893 (10 total) |
| **Grand Total** | **$12,334,843** | **$12,997,284** | **$15,741,760** | **$19,134,852** | **$17,745,506** | **$23,638,739** | **$22,428,419** | **$19,211,944** | **$18,687,977** | **$19,643,947** | **$181,565,271** |

**Studies conducted through NeuroNEXT**

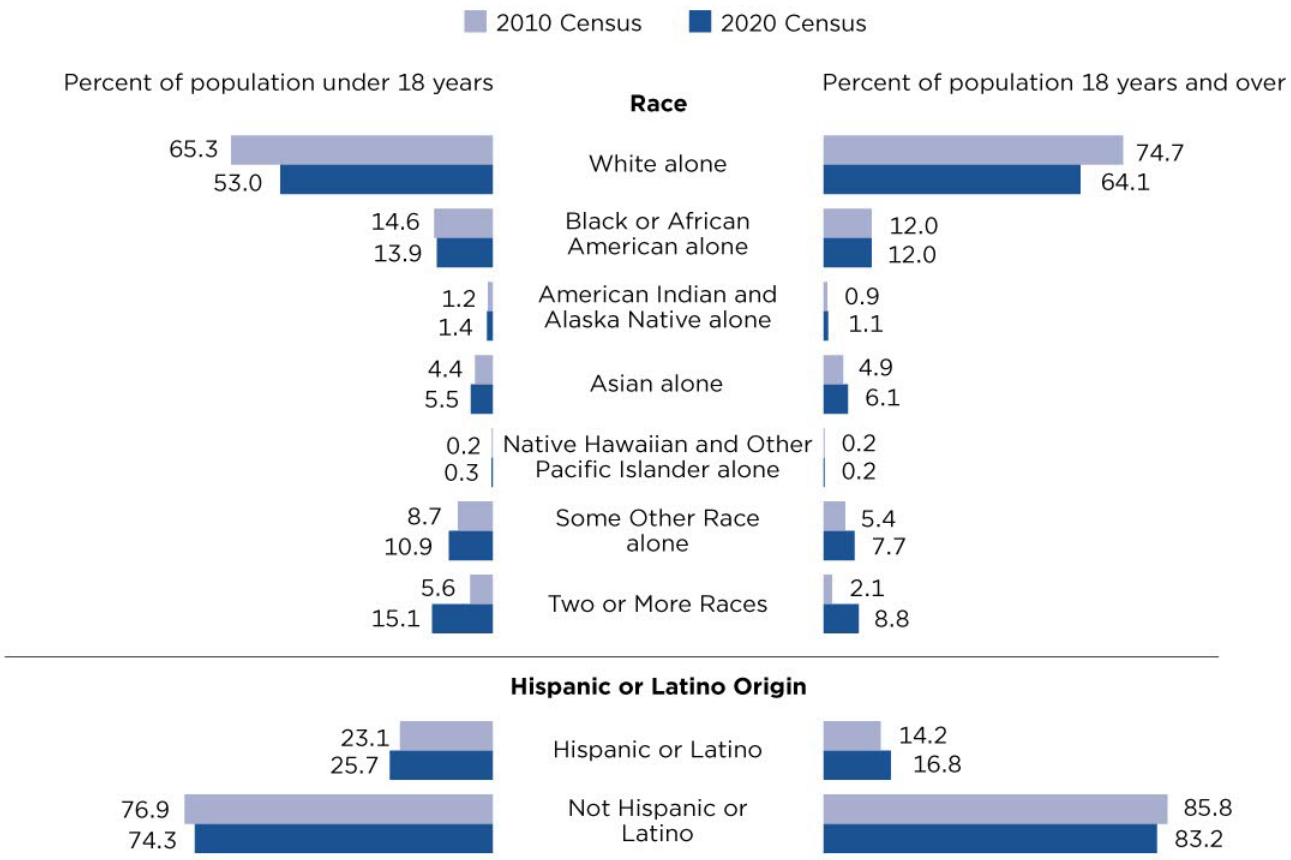
| Study # | Title | Disease | Age group | Study Type | Intervention Type | Organization Type | Enrolled (actual) | Number of sites | Trial grant start | Trial grant end (or status) | Primary Publication |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NN101 | SMA Biomarkers in the Immediate Post-natal Period of Development (Super Baby) | Spinal muscular atrophy | 0-6 mos | Observational (biomarker) | N/A | Academic | 53 | 15 | 12/1/2012 | 9/1/2015 | Publication Link |
| NN102 | Ibudilast Phase II trial in progressive MS (SprintMS) | Progressive multiple sclerosis | 21-65 | Interventional | small molecule | Academic/ Industry | 255 | 28 | 11/1/2013 | 12/1/2017 | Publication Link |
| NN103 | A Phase II Trial of Rituximab In Myasthenia Gravis (BeatMG) | Myasthenia gravis | 21-90 | Interventional | biologic (mAb) | Academic/ Industry | 52 | 26 | 5/1/2014 | 5/1/2018 | Publication Link |
| NN104 | ZZ-3K3A-201: Safety evaluation of 3K3A-APC in ischemic stroke (Rhapsody) | Acute stroke | 18-90 | Interventional | biologic | Industry/ academic | 110 | 14 | 10/1/2014 | 6/1/2017 | Publication Link |
| NN105 | Tolerability of SRX246 in Huntingtons Disease Patients (STAIR) | Huntington's disease | 18+ | Interventional | small molecule | Industry | 106 | 22 | 5/1/2016 | 12/1/2018 | Publication Link |
| NN106 | Cytochrome C Oxidase: Biomarker In Newly Diagnosed Glioblastoma Multiforme (Cyto-C) | Glioblastoma multiforme | 21+ | Observational (biomarker) | N/A | Academic | 152 | 19 | 11/1/2016 | analysis ongoing | |
| NN107 | Effects of AFQ056 on Language Learning in Young Children with Fragile X Syndrome (FXS) (FX-LEARN) | Fragile X syndrome | 32 mos - 6 yrs | Interventional | small molecule | Academic | 99 | 15 | 8/1/2017 | ongoing | |
| NN108 | Topiramate as a Disease Altering Therapy for CSPN (TopCSPN) | Cryptogenic sensory peripheral neuropathy | 18-80 | Interventional | small molecule | Academic | 132 | 20 | 2/1/2018 | ongoing | |
| NN109 | A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy of ManNAc in Subjects with GNE Myopathy (MAGiNE) | GNE myopathy | 18-70 | Interventional | small molecule | Academic | 51 (expected) | 10 (expected) | 2/1/2020 | ongoing | |
| NN110 | A Dose Selection Trial of Light Therapy for Impaired Sleep in Parkinsons Disease (EnlitePD) | Parkinson's disease | 45+ | Interventional | device (light box) | Academic | 144 (expected) | 25 (expected) | 9/1/2020 | ongoing | |

## Appendix 3: U.S. population race and ethnicity distribution from 2020 U.S. Census

**Source:** https://www.census.gov/library/stories/2021/08/improved-race-ethnicity-measures-reveal-united-states-population-much-more-multiracial.html

Figure 5.

**Percentage Distribution of Race and Hispanic Origin by Age Group: 2010 and 2020**




Note: Data users should use caution when comparing 2010 Census and 2020 Census race data because of improvements to the question design, data processing, and coding procedures for the 2020 Census.

Information on confidentiality protection, nonsampling error, and definitions is available at <https://www2.census.gov/programs-surveys/decennial/2020/technical-documentation/complete-tech-docs/summary-file/>.

Source: U.S. Census Bureau, 2010 Census Redistricting Data (Public Law 94-171) Summary File; 2020 Census Redistricting Data (Public Law 94-171) Summary File.

## Appendix 4: Working Group Charge

**National Advisory Neurological Disorders and Stroke (NANDS) Council Clinical Networks Evaluation Working Group (StrokeNet and NeuroNEXT)**

**CHARGE and ROSTER**
**April 21, 2021**

**Charge:** NINDS supports clinical research networks to facilitate efficient, high-quality clinical trials and research studies. This NANDS Council Clinical Networks Working Group will assess processes and outcomes to date for two NINDS-supported clinical research networks, StrokeNet and NeuroNEXT, and identify areas for improvement in the design of the next iterations of these programs. The Working Group will consider: (1) the extent to which the programs are meeting their goals; (2) the programs' outcomes and impacts; (3) the extent to which the networks collaborate with and benefit the research community; and (4) what improvements to program components and operations could allow the networks to better address current or new goals. The Working Group will evaluate these programs jointly using a common framework to assess overall goals, with separate attention to features unique to each network.

### Program Descriptions

**StrokeNet:** Launched in September 2013, StrokeNet consists of a clinical research network of 27 regional coordinating centers, involving approximately 500 hospitals across the United States and is designed to serve as the infrastructure and pipeline for new potential stroke treatments. The network includes a coordinating center, data management and statistical center, central IRB, research pharmacy, and an education core. The 2nd renewal of StrokeNet is planned for FY 2023-27, with FOAs to be published in mid-2022.

***Program Goals*:** The primary goal of the NIH StrokeNet network is to maximize efficiencies to develop, promote and conduct a balanced portfolio of high-quality, multi-site exploratory phase 1, 2 and confirmatory phase 3 clinical trials in stroke prevention, treatment, and recovery. Such trials focus on key interventions, as well as on biomarker-validation studies that are immediately preparatory to trials and ancillary studies to existing NIH StrokeNet trials. An additional goal of the StrokeNet is to educate future stroke researchers.

**NeuroNEXT:** The Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) develops and conducts exploratory clinical trials evaluating promising therapies for neurological disorders other than stroke, whether from academic, foundation, or industry discoveries. Examples include Phase 2 clinical trials and clinical studies to validate biomarkers and clinical outcomes in preparation for clinical trials. The network consists of a Clinical Coordinating Center (CCC), a Data Coordinating Center (DCC), and 25 clinical sites throughout the US. NeuroNEXT was established in 2011 and first renewed in 2018. The 2nd renewal of NeuroNEXT is planned for FY 2023-27, with FOAs to be published in mid-2022.

***Program Goals:*** Through NeuroNEXT, NINDS aims to support exploratory trials and biomarker validation studies that can provide more rapid preliminary testing of new treatments to help identify those that merit further testing, such as through Phase 3 trials. NeuroNEXT is designed to increase the efficiency of clinical trials, facilitate patient recruitment and retention, increase the quality of neuroscience clinical trials, and enable public-private partnerships between NINDS and industry, foundations, or academia. The renewal of the program in 2018 strengthened emphasis on training and career development activities.

### Working Group Composition

The Working Group will include one or more members of the NANDS Council, investigators with expertise in clinical trial execution and network coordination, investigators with expertise in research areas addressed by the networks, and representatives from industry and patient organizations. A roster of members and their relevant affiliations is attached at the end of this document.

### Working Group Activities and Deliverables

The Working Group will finalize a plan for evaluating StrokeNet and NeuroNEXT and assess information provided about both networks. The Working Group will meet as a single group to allow benefits of discussing both networks together, but subsets of the group will be assigned to focus more closely on a single network or on individual aspects of both networks. Recommendations for changes to the programs may be developed initially by subsets of the group before consolidation by the full Working Group, which may include consideration of lessons and practices that the networks could learn from each other. The Working Group will prepare a final report of their findings and recommendations to present to the NANDS Council in open session on February 2, 2022 (written report due to Council ~January 20, 2022).

The NINDS Office of Science Policy and Planning (OSPP) will provide support to the Working Group to include coordinating meetings and helping to prepare the group's report to the NANDS Council. OSPP also will lead an internal group of NINDS staff to prepare data and other materials for the evaluation, as requested by the Working Group and with the participation of network investigators and personnel as needed. All Working Group meetings will be held virtually, and summaries of all Working Group meetings will be filed with NANDS Council records. NINDS will set up a shared workspace for the Working Group to house files, meeting information, and allow online discussion.

### Working Group Meetings

Working Group meetings will be scheduled for 2 hours each in May 2021, July 2021, and monthly from September 2021-January 2022 (up to 7 meetings). Information about the networks will be organized progressively across the meetings to allow for a full understanding of the networks and consideration of the evaluation questions. Working Group members will receive meeting materials in advance and should review these materials prior to the meetings to maximize time for informed discussion. Specific assignments for some or all Working Group members may be given to gather input in advance of each meeting.

### Roster

| First Name | Last Name | Degree(s) | Affiliation |
|---|---|---|---|
| *Barbara* | *Vickrey (Co-chair)* | *MD, MPH* | *Icahn School of Medicine at Mt. Sinai* |
| *Richard* | *Rudick (Co-chair)* | *MD* | *Optimal Brain Health Consultants* |
| Ed | Trevathan | MD, MPH | Vanderbilt University |
| Erika | Augustine | MD, MS | Kennedy Krieger Institute |
| Rebecca | Gottesman | MD, PhD | NINDS Division of Intramural Research |
| Bernard | Ravina | MD | Praxis Precision Medicines |
| Janet | Hieshetter | | Dystonia Medical Research Foundation |
| Traci | Clemons | PhD | The Emmes Corporation |
| Issam | Awad | MD | University of Chicago |
| Adrian | Hernandez | MD | Duke University School of Medicine |
| E. Ray | Dorsey | MD, MBA | University of Rochester |