Title

Seven-Year Experience From the National Institute of Neurological Disorders and Stroke–Supported Network for Excellence in Neuroscience Clinical Trials

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Seven-Year Experience From the National Institute of Neurological Disorders and Stroke–Supported Network for Excellence in Neuroscience Clinical Trials

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Abstract

IMPORTANCE—One major advantage of developing large, federally funded networks for clinical research in neurology is the ability to have a trial-ready network that can efficiently conduct scientifically rigorous projects to improve the health of people with neurologic disorders.

OBSERVATIONS—National Institute of Neurological Disorders and Stroke Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) was established in 2011 and renewed in 2018 with the goal of being an efficient network to test between 5 and 7 promising new agents in phase II clinical trials. A clinical coordinating center, data coordinating center, and 25 sites were competitively chosen. Common infrastructure was developed to accelerate timelines for clinical trials, including central institutional review board (a first for the National Institute of Neurological Disorders and Stroke), master clinical trial agreements, the use of common data elements, and experienced research sites and coordination centers. During the first 7 years, the network exceeded the goal of conducting 5 to 7 studies, with 9 funded. High interest was evident by receipt of 148 initial applications for potential studies in various neurologic disorders. Across the first 8 studies (the ninth study was funded at end of initial funding period), the central institutional review board approved the initial protocol in a mean (SD) of 59 (21) days, and additional sites were added a mean (SD) of 22 (18) days after submission. The median time from central institutional review board approval to first site activation was 47.5 days (mean, 102.1; range, 1–282) and from first site

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activation to first participant consent was 27 days (mean, 37.5; range, 0–96). The median time for database readiness was 3.5 months (mean, 4.0; range, 0–8) from funding receipt. In the 4 completed studies, enrollment met or exceeded expectations with 96% overall data accuracy across all sites. Nine peer-reviewed manuscripts were published, and 22 oral presentations or posters and 9 invited presentations were given at regional, national, and international meetings.

CONCLUSIONS AND RELEVANCE—NeuroNEXT initiated 8 studies, successfully enrolled participants at or ahead of schedule, collected high-quality data, published primary results in high-impact journals, and provided mentorship, expert statistical, and trial management support to several new investigators. Partnerships were successfully created between government, academia, industry, foundations, and patient advocacy groups. Clinical trial consortia can efficiently and successfully address a range of important neurologic research and therapeutic questions.

Neurologic disorders impose a substantial burden on patients and society.[1] Potential exists to change this if recent discoveries in basic neuroscience can be capitalized on. Challenges to efficient development of treatments include recruiting capable study sites, regulatory approval delays, recruit-mentbarriers,[2] and a paucity of suitable biomarkers for nervous system disorders and of individuals trained to design and lead multicenter trials.[3] Interest in novel trial designs is increasing,[4, 5] and the National Institute of Neurological Disorders and Stroke (NINDS) Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) may provide clinical trialists with a unique opportunity to use such designs.

By facilitating collaboration, capacity, and training, trial networks can expedite therapy development.[6] A successful federally supported network, Neurological Emergencies Treatment Trials, conducting phase III randomized clinical trials began in 2007.[7] Master clinical trial agreements (MCTA) were used, but the environment was not ripe for central institutional review boards (cIRB).[8] NeuroNEXT was uniquely positioned in 2011 to expand the capabilities and achievements of networks.[9, 10] StrokeNet, developed in 2013, focused on stroke prevention, intervention, and rehabilitation/recovery.[11] In 2017, NINDS and the National Heart, Lung, and Blood Institute cofounded a new emergency network, Strategies to Innovate Emergency Care Clinical Trials Network, for emergencies in neurology, hematology, and cardiopulmonary medicine.

NeuroNEXT demonstrates that innovative technologies and experienced trial staff can speed start-up, accelerate enrollment, and ensure high-quality studies. The goal to conduct 5 to 7 studies during a 7-year funding period was exceeded, with 9 studies funded. NeuroNEXT infrastructure and metrics based on the first 7 years are described with suggestions for future networks and approaches for therapy development.

Methods

NeuroNEXT comprises a clinical coordinating center (CCC), a data coordinating center (DCC), and 25 clinical sites (some of which comprise more than 1 institution)(Figure 1).ANINDS-supported data and safety monitoring board[12] oversees funded studies, and an external scientific advisory board provides oversight. Sites were chosen based on experience in clinical trial recruitment and conduct, breadth of clinical expertise, and access to relevant populations; they are led by experienced clinical trialists and have a dedicated coordinator.

The CCC provides clinical design advice, regulatory, project, and budget management and manages site contracts, cIRB, central laboratory, and central pharmacy, while the DCC provides statistical and trial design support, data management and analysis, and study monitoring.

Leadership and policy development are provided through the NeuroNEXT executive committee and other network committees listed in Figure 1. The NeuroNEXT executive committee provides guidance, reviews study proposals for feasibility, and selects sites for each study. The number of sites per study is recommended in each grant application and selection is based on detailed feasibility questionnaires completed by each network site after funding is awarded. The foundation of network operations was defined in the first 6 months of funding with the development of standard operating procedures, a network website, and execution of reliance agreements with each site by a newly established cIRB. The cIRB model developed was previously described.[9] In collaboration with NINDS, the CCC developed an MCTA, tied to each site's infrastructure grant with NINDS, which covers all studies conducted within the network.

Results

Nine studies were funded through NeuroNEXT grant mechanisms (Table). All available grant mechanisms were used within the first setoffundedproposals:1 small business innovation research (U44), 1 industry (X01), and the remaining, academic (U01). Results from 3 studies have been published.[13–15] A fourth study completed with the results presented and the primary manuscript drafted. The remaining studies are currently active.

Three of 9 funded protocol principal investigators are new clinical trial researchers, including1PhDinvestigator.Inaddition, the CCC and DCC assisted 25 investigators, including 12 who were writing a National Institutes of Health (NIH) grant for the first time to submit initial grant applications and 14 resubmissions. Nine peer-reviewed manuscripts were published,[9, 13–16, 21–24]22oralpresentationsorposters, and 9 invited presentations have been given at regional, national, or international meetings.

Preaward

The preaward process and data from the 9 studies funded are detailed in Figure 2. The CCC and DCC staff work with investigators on study design, operational logistics, and preparation of a study budget. The DCC uses a team of faculty biostatisticians who partner with CCC clinical trialists (leads) to provide the appropriate design and outcome measures for a successful phase II trial. Per NIH policy, all studies anticipated to cost more than $500 000 in any grant year undergo review by the NINDS extramural science committee, which must grant approval for an applicant to proceed.

Grants are submitted by the protocol principal investigators with assistance from the CCC and DCC. In the first 7 years, the NeuroNEXT executive committee reviewed 148 proposals for a wide variety of neurologic diseases, 70 (47%) of which were deemed feasible based on data collected from sites to assess interest, availability of patient population, and resources to conduct the study. Of these, 17 were declined by the NINDS extramural science committee

after NeuroNEXT executive committee approval (2 of those 17 were funded elsewhere), 3 were pending review by the extramural science committee, 25 were withdrawn (2 transferred to StrokeNet, 10 withdrew owing to inactivity, 13 withdrew owing to principal investigator choice), and 25 initial grant applications were submitted (the NN101 study was funded based on request for application issued prior to the network formation). One grant received a fundable score on initial review (NN107 study), 14 responded to critiques of initial review in a resubmission, and of those, 7 (50%) were funded. The timeline for preaward activities for each of the 8 funded grants are provided in Figure 3A. The median time from proposal submission to initial grant submission was 10 months, from initial proposal to grant resubmission was 19 months, and from initial proposal to funding was 27.5 months. The most frequent proposals received were in areas of neuromuscular diseases (34 [23%]), movement disorders (27 [18%]), demyelinating disease (14 [9.5%]), and epilepsy-related disorders (14 [9.5%]) (eTable in the Supplement).

Postaward

Executing an MCTA that covers all studies across the network eliminated the need for contract negotiation, bringing time for contract execution to 0 for all studies. Establishing a cIRB decreased the time required to add sites to a trial once the first site is approved. The time required for initial review still depends on factors including Food and Drug Administration clearance and drug supply. In the first 7 years, the cIRB reviewed and approved 8 protocols, 133 site submissions, 18 continuing reviews, and 579 other amendments (eg, protocols, safety reports, deviations, staff changes). Across the first 8 studies, protocols were approved in a mean (SD)of59 (21) days and sites in a mean (SD) of 22 (18) days after submission to the cIRB. The median time from cIRB approval to first site activation was 47.5 days (mean, 102.1; range, 1–282) and from first site activation to first participant consent was 27 days (mean, 37.5; range, 0–96). The time-line for postaward study start-up activities for each of the 8 studies are provided in Figure 3B.

The efficiencies of a cIRB go beyond the study initiation phase. The median time from annual renewal review to approval was 16 days (range, 0–33days). Moreover, having protocol amendments and annual renewals occur for all sites simultaneously creates efficiency by allowing seamless implementation of study protocol changes at a single time point. Thus, when a protocol amendment affects data collection, cIRB approval for all sites can be coordinated to occur simultaneouslyandbesynchronizedwithrequiredchangestotheelectronic data capture system. Additionally, having 1 IRB review adverse events at all study sites facilitates a higher level of safety oversight for each trial. It should be noted that the NeuroNEXT cIRB has invited ad hoc members to ensure the appropriate level of expertise in their review of specific protocols and related safety reviews.

Electronic Data Capture Development Metrics

The DCC leverages the use of NINDS common data elements, 8 network core case report forms, and 5 core database modules (adverse event reporting system, drug dispensing module, manage case report form module, query system, and monitoring module) to more efficiently bring the electronic data capture system into production and ready for first

enrollment. To facilitate this, the DCC hosts a case report form development meeting to ensure efficient, complete, and accurate data collection for the trials. With these tools and methods, the DCC achieved database readiness within 3.5 months (mean, 4.0; range, 0–8) of funding receipt for the first 8 studies (NN101throughNN108), comparedwith8.6monthsforrecentnon-network trials (data not published). In collaboration with the University of Rochester Clinical Materials Services Unit, the DCC developed a blinded, site-based kit drug distribution system and an in-house interactive web response system. This resulted in a reduction in total drug supply waste from an industry standard of 30% (Patrick Bolger, RPh, MBA; University of Rochester Clinical Materials Services Unit, written communication, December 6, 2019) to 5% in the NN102 SPRINT-MS study, and 21% in the NN105 STAIR study.

Enrollment

High-performing sites share best practices to enhance recruitment. The recruitment, retention, and diversity committee is brought in early to evaluate and advise on recruitment techniques within the disease population and to assist with participant retention. Screening information is actively reviewed for reasons that participants might choose not to enroll in a study.

Recruitment was completed for the first 6 studies, is underway in the NN107 and NN108 studies and scheduled to start soon for NN109 study. We report here data on the first 4 trials that have completed data analysis of the primary outcome. Enrollment met or exceeded expectations and norms within disease-specific clinical trials (Figure 4). The NN101 study met the timeline for recruitment, despite the requirement for enrolling infants with spinal muscular atrophy as well as healthy controls. Recruitment strategies used in this study were reported by Bartlett et al[16] in 2018. In the NN102 study, theaverageenrollmentratewas0.51persitepermonth, about twice as fast as enrollment in other NIH[17, 18] and industry-sponsored trials in multiple sclerosis (estimated from ClinicalTrial.gov EXPAND (NCT01665144), ORATORIO (NCT01194570), and ASCEND(NCT01416181)trials[Robert Fox, MD, Cleveland Clinic, oral and written communication, December 2016). The enrollment rate(0.1/site/mo) for the NN103 study was twice as fast as that reported for another myasthenia gravis trial.[19] The NN104 trial completed enrollment on schedule, which is superior to the general experience inacutestrokeclinicaltrials.[20]Anextensivesearchofalltrialsinthese disorders was not conducted and could be the focus for separate manuscript. Two additional studies completed enrollment. One was delayed by approximately 8 months owing to a drug manufacturing delay that required a 3-month pause in enrollment, and the other completed enrollment within 3 months of target.

Data Quality

NeuroNEXT sites consistently provided timely and accurate data. The DCC develops the electronic data capture with the user in mind but also with attention to collecting clean, accurate, and analyzable data. Site performance report cards are issued to sites biannually to provide an overall view of performance across network studies. Each site receives data on their performance in enrollment, retention, data accuracy, and data quality, compared with

all other performance sites in a blinded fashion. These reports provide an opportunity for sites to track performance and identify potential areas for improvement. Report card data demonstrates that the overall retention rate across all studies is high, with an average of 89% of participants retained; the average data accuracy (percentage of case report forms requiring no data changes)across all sites was96%.Moreover, across all studies, the sites entered on average 81% of the required forms within 7 days of the visit, 94% within 30 days, and 82% of participants had no major protocol deviations.

Discussion

NeuroNEXT, established in 2011 and renewed in 2018, developed processes to increase efficiency and quality of randomized clinical trials, promote participant recruitment and retention, and increase the number of clinical investigators and research staff trained to lead and conduct multicenter trials. Challenges faced during the initiation of the network included establishing a cIRB and terms for the MCTA that were acceptable to all institutions and facilitating communication and collaboration between senior investigators from diverse areas of neurology. The network alleviates bottlenecks in the development of new treatments including allowing any investigator with a phase II question to apply and providing expert advice on trial design/conduct. Rigor of the basic science and design is mandatory for all proposals so that adequate justification, blinding, and replication are ensured; thus, the time to prepare, submit, and receive NIH funding for a clinical trial is still long. However, once funded, the cIRB and MCTA speed study start-up and streamline regulatory oversight, and the network provides expertise in recruitment and retention, thereby ensuring high quality data in a timely manner.[25] Rigorous studies answering phase II trial questions promote efficient and cost-effective conduct of pivotal randomized clinical trials and reduce the likelihood of costly failures.

The coordination of efforts between NINDS personnel and NeuroNEXT facilitates research results of high quality. Project vetting within NINDS and the network are closely aligned. This process was formalized and standardized but flexible enough to engage academic partners as well as industry partners.

Several features ensure protection of study participants. Having a cIRB that sees cumulative safety data allows for comprehensive oversight rather than a distributed model where site IRBs only see events that occur at their sites. The data and safety monitoring board ensured a consistent approach for data presentation and review across studies. Similarly, having a common system for safety reporting and monitoring of studies streamlined processes and ensured good oversight of study safety.

Efficiency and performance of a network is based on several factors. The initiative with the largest positive effect on study start-up was the MCTA requirement. In contrast, others have reported that execution of contracts, typically done individually for each study at a site without an MCTA framework in place, is the most significant contributor to delay in study initiation.[26]

Efficiency was achieved in drug distribution by developing novel randomization and drug distribution systems for trials with limited drug supply. This system led to a low level of drug supply waste in the NN102 SPRINT-MS (NCT01982942) (5%) and NN105 STAIR (NCT02507284) (21%) studies.

Recruitment of participants, including under represented populations, and retention of participants are considered challenges in most fields[6] but can be particularly complex in neurologic disorders. Slow enrollment can increase study costs or lead to inconclusive results if there is incomplete accrual. Loss of follow-up can result in challenges to interpretation of study results.[27, 28] NeuroNEXT studies have enrolled on or ahead of schedule. Retention was high in all studies. The combination of experienced sites, with infrastructure support and an engaged recruitment, retention and diversity committee helped ensure trial success. NeuroNEXT was also designed to lower the barriers for investigators with good ideas for a phase II trial or biomarker study to lead their study. Three of the 9 study principal investigators had not led a multicenter study previously. Several first-time investigators submitted grant applications to use the network, benefitting from mentorship and training in randomized clinical trials design from network principal investigators as well as CCC and DCC lead investigators.

There are several other ways that success or return on investment can be assessed for NeuroNEXT. One is the training of young investigators to lead multicenter trials. Several of the NeuroNEXT trials were led by first-time clinical trial investigators. While the number of papers from the network is currently small, this is largely because it is typical for most publications from clinical trials to be published after the study has ended. Our productivity from a manuscript perspective reflects that we did not close out several trials until late in the initial 7-year cycle of the network. Several of the studies published design and baseline data articles, and we expect this approach to continue. In addition, the data sets from closed studies are now publicly available through the NINDS,[30] and several secondary papers are in preparation. Another metric of return on investment is clear decisions on whether to proceed or not to additional studies. This has been clear in all completed studies to date. Moreover, one of the overarching goals for the network was to provide an opportunity for productive collaboration between different disciplines within neurology, and while unmeasurable, NINDS has seen this come to fruition.

Lessons Learned

Two key lessons that were learned in the first 7 years of NeuroNEXT are that engagement and collaboration across all disciplines is essential to develop and continuation of the network and that ongoing training must be established to foster the next generation of clinical neuroscience researchers. After the initial 7-year funding period, modifications were made to further enhance ongoing training, including the addition of clinical research fellows at each funded site, additional initiatives by the education committee to provide ongoing training, and additional partnership with the NINDS clinical trials methodology course, which is part of a larger training program across all of the NINDS-funded networks and the field of neurology as a whole.

Many networks are formed around a disease theme, such as stroke[11] or Alzheimer disease.[29] NeuroNEXT is unique in that it covers a wide variety of neurologic disorders. Therefore, it did bring together various experts, which promotes sharing of knowledge across disciplines. It posed a challenge initially because the investigators did not know each other well. It also meant that the investigators needed to know the members of their faculty well to know who to tap into for site investigators or to complete feasibility requests across a large range of pediatric and adult disorders.

Developing a rigorously designed trial with a clear phase II question, in an appropriate patient population, using relevant outcome measures, is an iterative process requiring input from both clinicians and statisticians. The median time for the initial development process leading to submission of a grant application in NeuroNEXT is 10 months. The network was not designed to change the peer review process and rigor at NIH. As such, many grants require changes after initial review and resubmission for rereview, which results in a longer timeline from initial proposal to receipt of funding (median of 27.5 months).

In the initial funding period, the network established policies on publication and data sharing. As the complexity and importance of data sharing continues to evolve, the network is well positioned to lead in the area and as such has developed a separate data sharing committee to oversee these activities.

What is needed for the future in the NeuroNEXT network? Education and training of future trialists has already been initiated with a training course as well as principal investigator and site investigator webinars. Increasing the number of trainees and impact of this education and training will be important for the next generation of clinical neuroscience researchers.

In the future, NeuroNEXT studies in amyotrophic lateral sclerosis, Parkinson disease, epilepsy, neuroimmunology, additional pediatric diseases, and other neurologic disorders may be considered. Increased engagement with disease foundations will continue to bring in the most exciting targets and treatments for testing in NeuroNEXT. There is a strong relationship between the NINDS clinical trials methodology course with lectures and small group instructors from the NeuroNEXT coordinating centers and clinical sites, as well as from 2 other NINDS-supported networks: StrokeNet and Neurological Emergencies Treatment Trials/Strategies to Innovate Emergency Care Clinical Trials Network. NeuroNEXT was recently renewed for an additional 5 years. In the renewal period, additional fellowship and other training opportunities will be implemented, and opportunities for collaboration with broader networks, including the Clinical and Translational Science Awards Program, will be explored. The networks must provide a conduit to the future with new investigators in all the clinical neurosciences and related fields to add to the current cohort of seasoned and successful investigators.

Conclusions

The network metrics of success have shown rapid study start-up of 8studies, efficient enrollment, high-quality data, and optimized central monitoring, as well as efficient use of a central pharmacy and laboratory and sharing of standard operating procedures. Overall, this

is a cohesive, well-functioning network. Feasibility assessments ensure that a trial can be completed in a timely fashion within the network. The key to success appears to be engagement of the entire network, neurologists, statisticians, neurosurgeons, PhD scientists, coordinators and others.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Murray CJ, Atkinson C, Bhalla K, et al.; U.S. Burden of Disease Collaborators. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. JAMA. 2013;310(6):591–608. doi:10.1001/jama.2013.13805 [PubMed: 23842577]
2. Bedlack RS, Wicks P, Heywood J, Kasarskis E. Modifiable barriers to enrollment in American ALS research studies. Amyotroph Lateral Scler. 2010; 11(6):502–507. doi:10.3109/17482968.2010.484494 [PubMed: 20446890]
3. Dilts DM, Sandler A, Cheng S, et al. Development of clinical trials in a cooperative group setting: the eastern cooperative oncology group. Clin Cancer Res. 2008;14(11):3427–3433. doi:10.1158/1078-0432.CCR-07-5060 [PubMed: 18519773]
4. Cerqueira FP, Jesus AMC, Cotrim MD. Adaptive design: a review of the technical, statistical, and regulatory aspects of implementation in a clinical trial. Ther Innov Regul Sci. 2019:2168479019831240. doi:10.1177/2168479019831240
5. Morgan CC, Huyck S, Jenkins M, et al. Adaptive design: results of 2012 survey on perception and use. Ther Innov Regul Sci. 2014;48(4):473–481. doi:10.1177/2168479014522468 [PubMed: 30235570]
6. Rosas SR, Cope MT, Villa C, Motevalli M, Utech J, Schouten JT. Assessing the challenges of multi-scope clinical research sites: an example from NIH HIV/AIDS clinical trials networks. J Eval Clin Pract. 2014;20(2):149–157. doi:10.1111/jep.12100 [PubMed: 24219425]
7. Barsan WG, Pancioli AM, Conwit RA. Executive summary of the National Institute of Neurological Disorders and Stroke conference on Emergency Neurologic Clinical Trials Network. Ann Emerg Med. 2004;44(4):407–412. doi:10.1016/j.annemergmed.2004.06.024 [PubMed: 15459625]
8. Ravina B, Deuel L, Siderowf A, Dorsey ER. Local institutional review board (IRB) review of a multicenter trial: local costs without local context. Ann Neurol. 2010;67(2):258–260. doi:10.1002/ana.21831 [PubMed: 20225291]

9. Kaufmann P, O'Rourke PP. Central institutional review board review for an academic trial network. Acad Med. 2015;90(3):321–323. doi:10.1097/ACM.0000000000000562 [PubMed: 25406606]
10. Ullman K A burst of speed for neurological research: NeuroNEXT streamlines research processes to encourage collaboration and make rapid advances. Ann Neurol. 2013;74(2):A7–A8. doi:10.1002/ana.23983
11. Broderick JP, Palesch YY, Janis LS; National Institutes of Health StrokeNet Investigators. The National Institutes of Health StrokeNet: a user's guide. Stroke. 2016;47(2):301–303. doi:10.1161/STROKEAHA.115.011743 [PubMed: 26715457]
12. Conwit RA, Hart RG, Moy CS, Marler JR. Data and safety monitoring in clinical research:a National Institute of Neurologic Disorders and Stroke perspective. Ann Emerg Med. 2005;45(4):388–392. doi:10.1016/j.annemergmed.2004.08.006 [PubMed: 15795717]
13. Fox RJ, Coffey CS, Conwit R, et al.; NN102/SPRINT-MS Trial Investigators. Phase 2 trial of ibudilast in progressive multiple sclerosis. N Engl J Med. 2018;379(9):846–855. doi:10.1056/NEJMoa1803583 [PubMed: 30157388]
14. Kolb SJ, Coffey CS, Yankey JW, et al.; NeuroNEXT Clinical Trial Network on behalf of the NN101 SMA Biomarker Investigators. Natural history of infantile-onset spinal muscular atrophy. Ann Neurol. 2017;82(6):883–891. doi:10.1002/ana.25101 [PubMed: 29149772]
15. Lyden P, Pryor KE, Coffey CS, et al.; NeuroNEXT Clinical Trials Network NN104 Investigators. Final results of the RHAPSODY trial: a multi-center, phase 2 trial using a continual reassessment method to determine the safety and tolerability of 3K3A-APC, a recombinant variant of human activated protein C, in combination with tissue plasminogen activator, mechanical thrombectomy or both in moderate to severe acute ischemic stroke. Ann Neurol. 2019;85(1):125–136. doi:10.1002/ana.25383 [PubMed: 30450637]
16. Bartlett A, Kolb SJ, Kingsley A, et al.; NeuroNEXT Clinical Trial Network and on behalf of the NN101 SMA Biomarker Investigators. Recruitment & retention program for the NeuroNEXT SMA Biomarker Study: super babies for SMA! Contemp Clin Trials Commun. 2018;11:113–119. doi:10.1016/j.conctc.2018.07.002 [PubMed: 30094386]
17. Bhanushali MJ, Gustafson T, Powell S, et al. Recruitment of participants to a multiple sclerosis trial: the CombiRx experience. Clin Trials. 2014;11(2): 159–166. doi:10.1177/1740774513517184 [PubMed: 24686106]
18. Waubant E, Pelletier D, Mass M, et al.; ITN STAyCIS Study Group; ITN020AI Study Management Team. Randomized controlled trial of atorvastatin in clinically isolated syndrome: the STAyCIS study. Neurology. 2012;78(15):1171–1178. doi:10.1212/WNL.0b013e31824f7fdd [PubMed: 22459680]
19. Pasnoor M, He J, Herbelin L, et al.; Methotrexate in MG Investigators of the Muscle Study Group. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. Neurology. 2016;87(1):57–64. doi:10.1212/WNL.0000000000002795 [PubMed: 27306628]
20. Feldman WB, Kim AS, Chiong W. trends in recruitment rates for acute stroke trials, 1990–2014. Stroke. 2017;48(3):799–801. doi:10.1161/STROKEAHA.116.014458 [PubMed: 28104835]
21. Fox RJ, Coffey CS, Cudkowicz ME, et al. Design, rationale, and baseline characteristics of the randomized double-blind phase II clinical trial of ibudilast in progressive multiple sclerosis. Contemp Clin Trials. 2016;50:166–177. doi:10.1016/j.cct.2016.08.009 [PubMed: 27521810]
22. Kolb SJ, Coffey CS, Yankey JW, et al.; NeuroNEXT Clinical Trial Network and on behalf of the NN101 SMA Biomarker Investigators. Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. Ann Clin Transl Neurol. 2016;3(2):132–145. doi:10.1002/acn3.283 [PubMed: 26900585]
23. Lyden P, Weymer S, Coffey C, et al. Selecting patients for intra-arterial therapy in the context of a clinical trial for neuroprotection. Stroke. 2016;47(12):2979–2985. doi:10.1161/STROKEAHA.116.013881 [PubMed: 27803392]
24. Krosschell KJ, Bosch M, Nelson L, et al.; NeuroNEXT Clinical Trial Network and on behalf of the NN101 SMA Biomarker Investigators. Motor function test reliability during the NeuroNEXT spinal muscular atrophy infant biomarker study. J Neuromuscul Dis. 2018;5(4):509–521. doi:10.3233/JND-180327 [PubMed: 30223401]

25. Neuro NEXT; The Lancet Neurology. NeuroNEXT: accelerating drug development in neurology. Lancet Neurol. 2012;11(2):119. doi:10.1016/S1474-4422(12)70008-X [PubMed: 22265207]

26. Mascette AM, Bernard GR, Dimichele D, et al. Are central institutional review boards the solution? the National Heart, Lung, and Blood Institute Working Group's report on optimizing the IRB process. Acad Med. 2012;87(12):1710–1714. doi:10.1097/ACM.0b013e3182720859 [PubMed: 23095928]

27. Bedlack RS, Pastula DM, Welsh E, Pulley D, Cudkowicz ME. Scrutinizing enrollment in ALS clinical trials: room for improvement? Amyotroph Lateral Scler. 2008;9(5):257–265. doi:10.1080/17482960802195913 [PubMed: 18608092]

28. Grill JD, Karlawish J. Addressing the challenges to successful recruitment and retention in Alzheimer's disease clinical trials. Alzheimers Res Ther. 2010;2(6):34. doi:10.1186/alzrt58 [PubMed: 21172069]

29. Morris JC, Aisen PS, Bateman RJ, et al. Developing an international network for Alzheimer research: the Dominantly Inherited Alzheimer Network. Clin Investig (Lond). 2012;2(10):975–984. doi:10.4155/cli.12.93

30. National Institute of Neurological Disorders and STroke. Archived clinical research datasets. Updated January 30, 2020. Accessed February 20, 2020 https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets

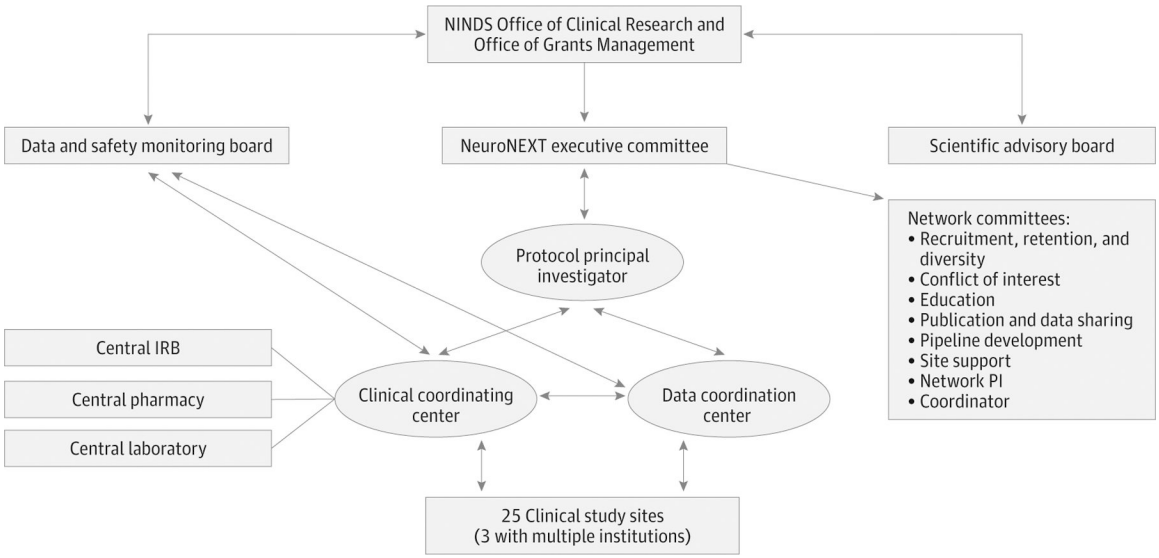


Figure 1.

Network Organization

IRB indicates institutional review board; NINDS, National Institute of Neurologic Diseases and Stroke; PI, principal investigator.

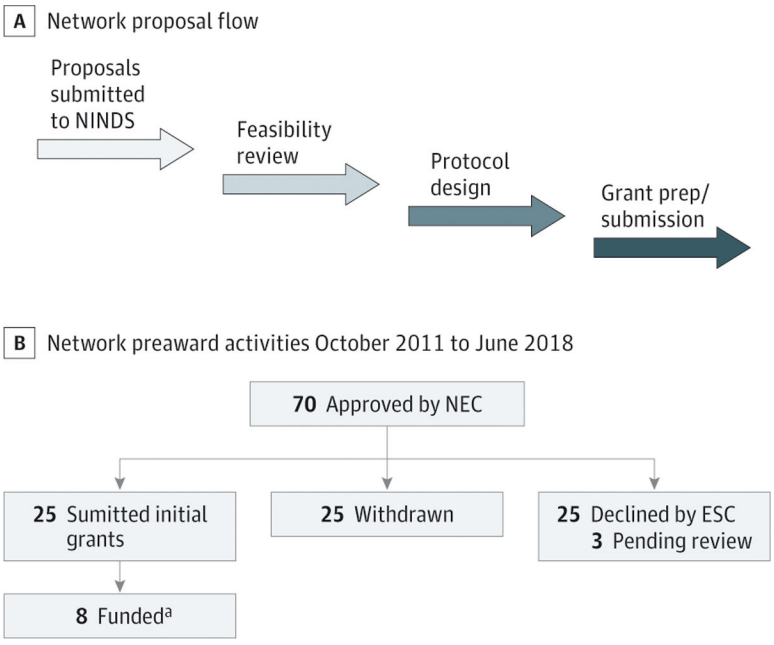


Figure 2.

Preaward Process

ESC indicates extramural science committee; NEC, National Institute of Neurological Disorders and Stroke Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) executive committee; NINDS, National Institute of Neurologic Diseases and Stroke.

[a] First study funded prior to NeuroNEXT formation.

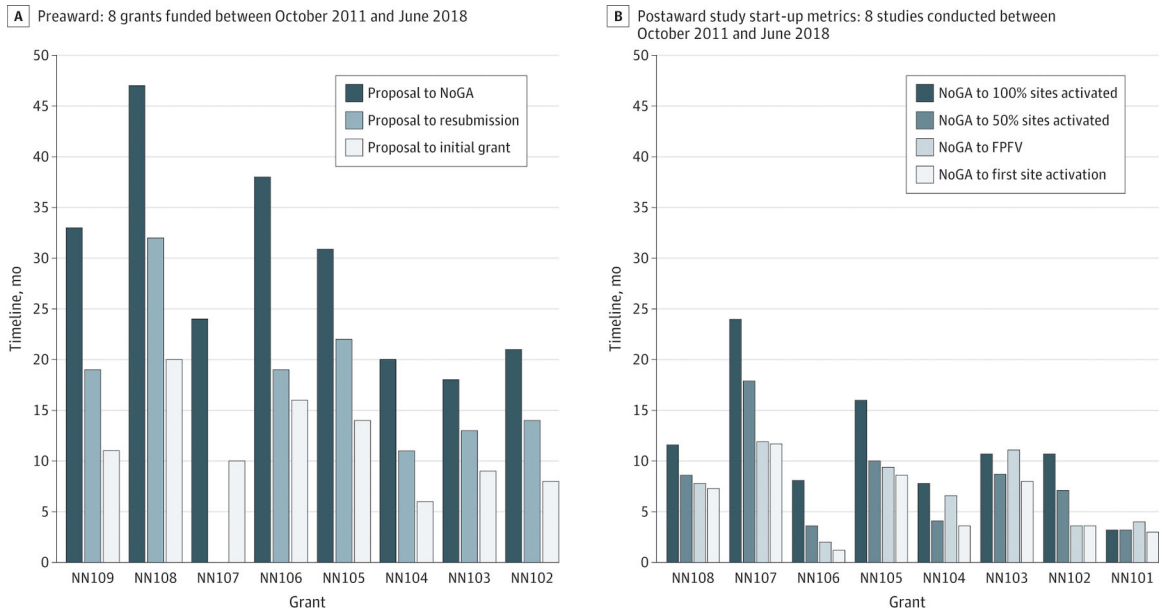
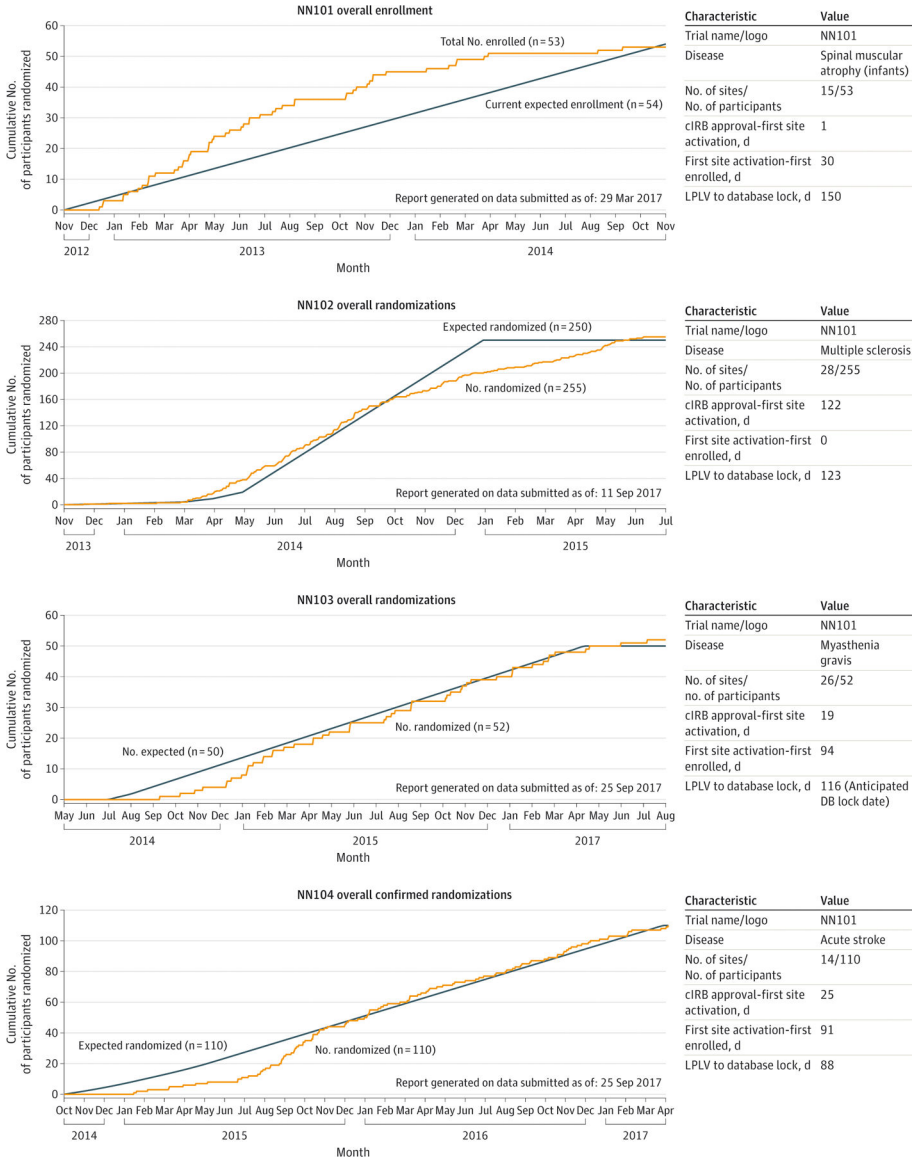


Figure 3.

Funded Studies: Preaward and Postaward Timeline

FPFV indicates first patient, first visit; NoGA, notice of grant award.



Characteristic	Value
Trial name/logo	NN101
Disease	Spinal muscular atrophy (infants)
No. of sites/ No. of participants	15/53
cIRB approval-first site activation, d	1
First site activation-first enrolled, d	30
LPLV to database lock, d	150

Characteristic	Value
Trial name/logo	NN101
Disease	Multiple sclerosis
No. of sites/ No. of participants	28/255
cIRB approval-first site activation, d	122
First site activation-first enrolled, d	0
LPLV to database lock, d	123

Characteristic	Value
Trial name/logo	NN101
Disease	Myasthenia gravis
No. of sites/ no. of participants	26/52
cIRB approval-first site activation, d	19
First site activation-first enrolled, d	94
LPLV to database lock, d	116 (Anticipated DB lock date)

Characteristic	Value
Trial name/logo	NN101
Disease	Acute stroke
No. of sites/ No. of participants	14/110
cIRB approval-first site activation, d	25
First site activation-first enrolled, d	91
LPLV to database lock, d	88

Figure 4.

Network Metrics and Recruitment Curves for NN101 to NN104

cIRB indicates central institutional review board; LPLV, last patient, last visit.

Table.

Funded National Institute of Neurological Disorders and Stroke Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) Studies

Study No.	Study name	Disease	NCT number	Grant mechanism (award date)	Type of study	Submitting institution	No. of individuals enrolled		No.of sites
							Projected	Actual	
NN101	Super Baby[14,16,22,24]	Spinal muscular atrophy	NCT01736553	U01 (August 2012)	Observational	Ohio State University	54	53	15
NN102	SprintMS[13,21]	Progressive multiple sclerosis	NCT01982942	U01 (July 2013)	Interventional	Cleveland Clinic	250	255	28
NN103	BeatMG	Myasthenia gravis	NCT02110706	U01 (September 2013)	Interventional	Yale University	50	52	15
NN104	Rhapsody[15,23]	Acute stroke	NCT02222714	X01/U01 (June 2014)	Interventional	ZZ Biotech/Cedars-Sinai Medical Center	100	110	15
NN105	STAIR	Huntington disease	NCT02507284	U44 (August 2015)	Interventional	Azevan Pharmaceuticals	108	106	20
NN106	Cyto-C	Glioblastoma multiforme	NCT02997423	U01 (September 2016)	Observational	University of Alabama at Birmingham	245	259	19
NN107	FX-LEARN	Fragile × syndrome	NCT02920892	U01 (September 2016)	Interventional	Rush University	100	NA[a]	14
NN108	Top-CSPN	Cryptogenic sensory peripheral neuropathy	NCT02878798	U01 (June 2017)	Interventional	University of Utah	125	NA[a]	15
NN109	MAGiNE	GNE myopathy	Not yet posted	U01 (August 2017)	Interventional	Brigham and Women's Hospital	50	NA[a]	12

[a]This study is ongoing.