NeuroNEXT Is at Your Service

Conducting clinical trials in neurology is a tough business. Many of the diseases we deal with are rare, slowly progressive, debilitating, and only modestly responsive to therapy. Organizing an infrastructure to help accelerate and facilitate the testing of promising agents in the neurological diseases was the underlying premise for the creation of the National Institutes of Health (NIH) Network of Excellence in Neuroscience Clinical Trials, NeuroNEXT, which puts the investigator in the driver's seat. The researcher from academia or industry proposes a study, and NeuroNEXT is there to help make it a reality.

Organized after an initial request for applications in 2010, NeuroNEXT was the brainchild of researchers at NIH and several experienced academic investigators. The goal of NeuroNEXT is to streamline clinical therapeutic trials in neurology by organizing academic research sites across the United States. NeuroNEXT includes a Clinical Coordinating Center that manages the participating sites and projects, and a Data Coordinating Center responsible for overseeing data collection, data management, and analysis. Perhaps most importantly, NeuroNEXT also includes a central institutional review board (cIRB) that all participating sites use for approval via a reliance agreement; essentially, the local IRBs cede authority to the cIRB. Having all of these components in place and ready for implementation means that clinical studies can be initiated and performed more quickly and efficiently than would be possible if such an effort were attempted de novo.

At the time of its initial organization, all clinical sites proposing to participate in NeuroNEXT had to prove their worth via a competitive grant application process, explaining what each institution had to offer in terms of clinical trial readiness, the population of patients available for study across the neurological spectrum, past clinical trials experience (both industry and federally sponsored), facilities, and equipment. In addition, institutional support for the idea needed to be demonstrated. In the end, 25 sites across the country were selected to participate, each receiving funds for 5 years to maintain clinical trials readiness. A renewal of the NeuroNEXT site participation is currently underway.

The way in which a new NeuroNEXT study is initiated is fairly straightforward and can be found on the website https://www.neuronext.org. Typically, a researcher proposes to study a specific therapy in a neurological disease and puts together a detailed outline of an experimental plan (termed a "synopsis"); this is reviewed sequentially by a combination of individuals from the National Institute of Neurological Disorders and Stroke and the NeuroNEXT executive committee. If it is considered appropriate for NeuroNEXT, of sufficient priority, and feasible, it is then handed off to a protocol working group that will work with the principal investigator to further refine the idea and help prepare a formal grant application. The grant application is then submitted in the usual fashion to NIH, and undergoes peer and council review to determine eligibility for funding. If it is successful, NeuroNEXT will then assist the investigator in the implementation of the trial.

This issue of *Annals of Neurology* contains the first completed study from NeuroNEXT, "Natural History of Infantile Onset Spinal Muscular Atrophy."[1] Stephen J. Kolb from the Ohio State University Wexner Medical Center was the principal investigator, and the study was proposed in response to a request for applications issued in 2011 specifically to develop better biomarkers in spinal muscular atrophy (SMA). The study included 15 NeuroNEXT sites and focused on infants with the most severe forms of the disease presenting before 6 months of age. A group of healthy infants were also enrolled and followed for 2 years. All children underwent a number of assessments at baseline and every 6 months for 2 years. Assessments included 2 standard SMA scales, electrophysiologic tests, and blood-based molecular biomarkers. The study demonstrated marked divergence in all clinical functional and electrophysiologic parameters over time in the SMA children as compared to the healthy children; the molecular biomarkers were different at baseline and remained relatively stable in both groups.

Perhaps the most remarkable aspect of this study is that it is already serving as the gold standard for the natural history of untreated infantile SMA. In the short time since the study was completed, the first effective therapy, nusinersen (Spinraza), was approved by the U.S.

Food and Drug Administration; this approval was likely based in part on the data obtained in this NeuroNEXT-supported study. A gene therapy, currently in clinical trials, may soon follow; if approval is granted, it will be thanks in part to this natural history data. Finally and most importantly, in light of these new therapies, a nationwide newborn screening for SMA may soon be instituted, such that all children can begin effective therapy before the disease even becomes clinically manifest.

A final and easily overlooked aspect of this study is the healthy infant data that were collected along with the patient data. This unique dataset actually documents the anticipated normal motor developmental changes in children from infancy until 2 years of age. Any clinical investigator who deals with pediatric data understands the monumental challenges associated with obtaining such normative longitudinal values. Not only do these values serve a critical role in this SMA-specific study, they may serve as foundational comparative data for clinical studies in a variety of disorders, ranging from muscular dystrophy to cerebral palsy.

Whereas the landscape around the therapy of SMA may have changed dramatically almost overnight, most other neurological diseases remain stubbornly resistant to therapy. Accordingly, NeuroNEXT has undertaken a variety of other studies, including the Sprint-MS study (ibudilast in progressive multiple sclerosis), the BeatMG study (rituximab in myasthenia gravis), the Rhapsody study of a cytoprotectant (3K3A-APC) in acute stroke, the STAIR study of SRX246 to help control neuropsychiatric symptoms in Huntington disease, and the Cyto-C study, evaluating the role of cytochrome oxidase activity in patients with glioblastoma. A study of AFQ056 for the enhancement of neural plasticity in fragile X syndrome is also soon to begin. With the exception of only the STAIR study, all of these were investigator initiated.

What this quick survey of NeuroNEXT projects demonstrates is the wide swath of diseases and therapies being assessed. NeuroNEXT is clearly trying to change the landscape of clinical trials in neurology, helping to empower the academic investigator to pursue research efforts that would otherwise be impossible.

What is next for NeuroNEXT? That is up to you.

Potential Conflicts of Interest

Nothing to report.

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Reference

1. Kolb SJ. Natural history of infantile onset spinal muscular atrophy. Ann Neurol 2017;82:931–939.