NeuroNEXT: New Neuroscience Network Aims to Speed Up Phase 2 Trials

BY GINA SHAW

If you've ever played a role in conducting a federally funded clinical trial, you know that one of the biggest challenges often isn't the science — it's the paperwork.

Moving a phase 2 exploratory clinical trial forward so that it can answer the necessary questions about a new therapy and — hopefully — lead to testing that therapy in a larger phase 3 trial, nearly always involves cumbersome approval processes that are exponentially multiplied by the number of sites involved in the trial. Have 10 trial sites? That requires 10 institutional review boards (IRBs) and 10 contracts with the NIH that need to be reviewed and reapproved annually.

"I have a trial with over 60 sites," said Merit Cudkowicz, MD, the Julieanne Dorn Professor of Neurology at Harvard Medical School and director of the Neurology Clinical Trials Unit at Massachusetts General Hospital. "It can often take the entire year to get that trial's contract renegotiated at all 60 sites. And then the next year you have to amend it and do it all over again."

In an effort to turn the cumbersome elephant of today's phase 2 neuroscience trials into a sleek and efficient cheetah, the NINDS has recently announced the establishment of an innovative new trials network: NeuroNEXT, a Network for Excellence in Neuroscience Clinical Trials.

NINDS will invest more than $84 million over the next seven years in supporting the NeuroNEXT infrastructure, which brings together a group of 25 neuroscience clinical trials sites plus one coordinating center (Massachusetts General) and one data center (the University of Iowa). The aim: to facilitate the rapid, efficient advancement of phase 2 exploratory trials in neuroscience.

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A CENTRAL IRB

There are a number of unique aspects to NeuroNEXT, according to Dr. Cudkowicz, who leads the NeuroNEXT Clinical Coordinating Center at Mass General. First, the entire network will use a central IRB.

"Each protocol will have one review rather than 25," she said. "That will ensure the safety of the participants while at the same time significantly cutting down on the time factor. Last year, Bernard Ravina published a paper [in the *Annals of Neurology*] examining the costs of having multiple institutions reviewing the same protocol. It added more than $100,000 to the process while no substantive changes were made by any institutions that had any impact on safety."

The Mass General Hospital will establish and run the central IRB. "After the first year, we'll convene a meeting with people who are involved with central IRBs for other disease groups, and talk about what worked and what didn't, so we can keep improving the system," Dr. Cudkowicz said.

The central IRB will be accompanied by a master site agreement for all of the 25 NeuroNEXT trial sites — so there will be none of those cumbersome multisite renegotiation battles. "We've revamped the whole process," said Dr. Cudkowicz. "There's one master agreement for all sites and all studies run through the network that will last the duration of NeuroNEXT, which for the moment is seven years."

NON-DISEASE SPECIFIC

In addition to the infrastructure improvements, NeuroNEXT is also innovative in philosophy. It's far from the first neuroscience clinical trial network, but it may be one of the first to be entirely non-disease-specific.

"If you're looking for the best therapies to bring forward in neuroscience, you have a very short list, so a disease-specific network is limited," said NINDS Deputy Director Walter Koroshetz, MD. "Since NeuroNEXT is not limited to a specific disease, we have a lot more potential to bring forward the most promising therapies."

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Dyskinesia

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"One important question is whether drugs acting on mTORC1 signaling might have the same anti-dyskinetic effect of rapamycin without causing immune suppression," he said. "Another question is whether rapamycin or analogues to it can counteract dyskinesia once it has been established. In our initial study, we only showed that the development of dyskinesia is reduced when you give rapamycin at the same time you begin L-DOPA therapy."

Whereas the drugs already in clinical trials for dyskinesia act upon neurotransmitter receptors, all three of the approaches presented at the symposium target defects occurring within the striatal neurons themselves, Dr. Fisone said.

DR. GILBERTO FISONE: "This concept of targeting intracellular signaling molecules is already being used in the treatment of cancer, but it has lagged behind in the treatment of disorders of the nervous system. We think that acting at the level of intracellular signaling represents an alternative treatment approach for neuropsychiatric and neurodegenerative disorders."

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That ecumenical approach was clearly evident at the inaugural meeting of all the NeuroNEXT sites, held Nov. 18 at NINDS.

"It's a unique opportunity to work with all types of neuroscientists in every field: neurology and psychiatry, neurosurgery, and rehab medicine. I've never been in a group with this kind of representation, that allows us to span every type of neurologic disorder across the lifespan," said Karen Marder, MD, MPH, Sally Kerlin Professor of Neurology at the Columbia University College of Physicians and Surgeons and chief of the Division of Aging and Dementia in the department of neurology.

The first NeuroNEXT trial was chosen very specifically to underscore another unique element of the network: its emphasis on pediatric neurology alongside adult neurology.

"Our first trial will be a biomarker study in spinal muscular atrophy," said Dr. Koroshetz. "We wanted the first trial to be a pediatric trial. The leading neuroscience research networks are primarily in adult disorders, and we want NeuroNEXT to be strong in both adult and pediatric conditions."

Interested in proposing a biomarker trial or clinical trial on a promising idea to NeuroNEXT? You needn't be on the faculty at a member site to do it. You don't have to be an experienced clinical trialist.

"We want to lower the barriers for people who have good ideas, but who aren't necessarily trialists or study designers," Dr. Cudkowicz said. "Say you're in the lab and you've discovered something you think is ready to bring to patients. You can submit the concept in short form to the NINDS, and if it's within the mission of the network, it will come to the NeuroNEXT executive committee. If we think it's feasible for the network, the staff at the Clinical Coordinating Center and Data Coordinating Center will help the person design the trial and apply for funding." (More information is available here: http://1.usa.gov/uZ31ZG.)

At Columbia, Dr. Marder is already working with a junior faculty member who has an exciting research idea related to subarachnoid hemorrhage. "NeuroNEXT has had seven protocols submitted just since Nov. 1, and there are apparently a lot more coming our way," she said.

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SUBMISSIONS FROM INDUSTRY

Some may be coming from outside

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academic health centers. NeuroNEXT also offers mechanisms for industry and small business to apply for cooperative agreement grants — or simply to request expedited access to the network's resources. "They can use the network and benefit from all its efficiencies,

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while funding the per-subject fee and drug costs," said Dr. Cudkowicz.

These relationships will work because of the adoption of a National Cancer Institute-modeled agreement that allows for the testing of therapies coming from industry while assuring that their intellectual property will be respected.

"In the past we've had real difficulty engaging with industry partners, and many

of the really exciting neuroscience discoveries are patented," said Dr. Koroshetz. "The *Bayh-Dole Act* states that if someone makes a discovery as part of a government-sponsored trial, the researcher files the patent. Companies have feared coming into arrangements like that. But using a Cooperative Research and Development Agreement allows us to protect the intellectual property of industry partners who work with us in NeuroNEXT."

A final key aim of the program, said Dr. Cudkowicz, is education. "We want to train all the staff at all the sites how to be really good clinical trial centers. Most of them are, but just because the PI [principal investigator] is good doesn't mean that everyone in the department is knowledgeable about how to conduct trials. We will offer site management and good clinical practice training, and also train investigators at these sites to be leaders of multicenter trials in order to grow the pool of academic trialists."

"Only the NINDS has the clout to get something like this done," said Dr. Marder. "We've wanted to do something like this for a long time, but it took NINDS to do it. If it works as we hope it will, it will be a fantastic model, and I think we'll see more and more of the NeuroNEXT approach across institutes." •

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