Stroke Progress Review Group

Use of Recruitment Networks in Randomized Trials
North American versus Global

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There is growing recognition among investigators, funding agencies, and other constituencies that the clinical trial enterprise in the United States is not keeping pace with our health system’s need for more and better information to guide clinical decision making. The need for better information is largely driven by the rapid pace of discovery in biology, technology, and health services delivery, which has yielded new medical capabilities that require testing before rationale clinical dissemination. The need for better information is also driven by an alarming rise in the cost of health care. Better research can help policymakers select services on the basis of value.

The randomized clinical trial is the best source for unbiased information about the effectiveness of new therapies, diagnostic strategies, and health delivery innovations. Trials, however, have become expensive and inefficient in the United States, resulting in fewer investigators, unanswered questions, and more of the work shifting to other countries. It is not uncommon, furthermore, for randomized clinical trials to fail after initiation, resulting in unanswered questions, loss of initial investment, and unnecessary risk to participants. The causes of this failed enterprise include regulatory burden, lack of infrastructure, and a clinical culture that does not uniformly view research as a core mission in patient care.

Funding agencies and investigators are keenly interested in strategies to revive the clinical trial enterprise. Established methods include pretrial planning with attention to feasibility, inclusion of patients and advocacy groups to vet the research question, funding mechanisms that direct funds to sites with better performances, and oversight that allows early redesign or termination. A relatively new method is the clinical research network. This method and its variations are still in development but may expand our capacity to conduct highly efficient clinical trials in many areas of biomedical science. In this article, I elaborate on a recent taxonomy of clinical research networks to describe their cardinal features.

Four Network Models

Multicenter clinical trials by definition comprise networks of participating sites. Newer network models are distinguished by features that improve control over process and allow multiple trials to operate simultaneously and sequentially. The following taxonomy of networks includes the conventional system that defines most large commercial trials and 3 more novel networks established by various funding agencies.

Model 1: The Convenience Network

This is the network used in most large trials, particularly large commercial trials (Figure 1). The convenience network is constructed for a specific trial and disbands when the trial is completed. Each network comprises a Clinical Coordinating Center that relates directly to the funding agency and the Data Center, and indirectly to the Data and Safety Monitoring Board. The Clinical Coordinating Center recruits, trains, and supports practices or hospital sites that do the actual work of participant recruitment and follow-up. Contract research organizations provide data- and site-management services in a common variation of this model. Convenience networks often comprise large numbers of sites that each enroll only a small number of participants but complete the research quickly.

Model 2: Local Identification and Outreach Network

Single research sites can expand their recruitment capability by collaborating with regional practices and hospitals. In the process, patients from smaller, less academically oriented centers have access to clinical trial research. One model for regional collaboration is the local identification and outreach network (LION) model that was described in 2009 and validated in 2011 by investigators in the state of Connecticut and several major US metropolitan areas. A LION comprises a LION Coordinating Center, located at an academic health center, and several regional practices or hospitals. Research coordinators from the LION Coordinating Center travel to the regional practices or hospitals to recruit participants, gather data, and arrange follow-up visits. The LION Coordinating Center builds the network and handles data collection, regulatory approval, and site management. Like the convenience model, a LION may be constructed to support a singular trial and dissolve on its completion. One distinct advantage of the LION model is that research is conducted by experienced coordinators who are familiar with the research protocol. This facilitates tight control over data quality.
Model 3: The Gateway Network

The essential feature of a gateway model is a group of experienced site investigators who agree to conduct clinical trials that have been approved by an agency working on its behalf. Many gateway networks are disease specific.

Access to a gateway network begins when a principal investigator applies to the network. An agency, often a subcommittee of investigators, reviews the application, considering such features as scientific merit, overlap with other protocols, and financial support. Once approved, the principal investigator may invite individual members of the gateway network to participate. Approval, therefore, gives the principal investigator access to a potentially large number of experienced investigators and their research sites. Principal investigators who gain access to a gateway network must bring their own Clinical Coordinating Center, data management, statistical analysis capability, and site monitoring.

Many gateway networks exist. In neurology, examples include the Canadian Stroke Consortium, the Australasian Stroke Trials Network, and the Stroke Research Network (SRN) of the National Institute for Health Research (NIHR) in England (Figure 2). The NIHR SRN is 1 of 8 research networks sponsored by the NIHR and illustrates essential features of the gateway model. The SRN comprises a Coordinating Center at the University of Newcastle and 8 local hubs. Each hub is staffed by a manager and lead clinician to support research infrastructure at several participating hospitals. The support can be instrumental to facilitate contracts and adherence with good clinical practice. NIHR provides funding to the Coordinating Center and each hub. Other research costs (eg, study design, laboratory testing, and data management, site monitoring) are covered by funds obtained by principal investigators. Most trials in the SRN are proposed by network investigators who have obtained funding in the United Kingdom during competitive peer-review, but foreign-funded studies may be adopted if they address a question relevant to stroke patients in the United Kingdom. Once a study is adopted into the SRN portfolio, the principal investigators enter into discussion with managers at the hubs to identify suitable hospitals to participate in the work. The principal investigator, not the SRN, is responsible for complying with the United Kingdom federal regulations, obtaining central ethics approval, and implementing the protocol. Once a trial is accepted, however, the SRN typically sets recruitment targets and works with each hub to stay on schedule. The SRN is accountable to the NIHR for its productivity and research quality. At any time, the SRN supports slightly more than 100 studies.

Model 4: The Fully Managed Network

This is the full-service model. Like the gateway model, the fully managed network model comprises sites that are preselected to conduct research. Trial proposals may come from...
investigators within the network or from outside. Going beyond the gateway model, however, fully managed networks also include a Clinical Coordinating Center that is responsible for trial coordination, administration, and monitoring and a Data Coordinating Center that is responsible for data management and statistical analysis.

Access to a fully managed network begins when a principal investigator applies to the network, usually during the design phase before funding is secured. A committee established by the network or its funding agency reviews the application just as in the gateway model. Once approved, the principal investigator collaborates with the network to finalize the protocol and grant application. If funded, the principal investigator stays involved providing scientific leadership, but day-to-day management of the trial falls to the network.

Fully managed networks are established by funding agencies typically to support clinical trials in 1 specialty area. These networks support multiple trials simultaneously and sequentially by means of secure, long-term funding. Their purpose is to increase national capacity for clinical trial research, improve patient access to trials, and reduce the time from funding to result. Examples in neurology include the Neurological Emergencies Treatment Trials network for phase III trials of emergency interventions9 and the Network for Excellence in Neuroscience Clinical Trials for clinical studies and phase II trials. Consistent with the fully managed model, each of these networks comprises research sites, a Clinical Coordinating Center, and a Statistical and Data Management Center. Each of these structures receives some secure funding, which can lower the cost of adapted trials. The efficiency in these networks, however, is largely gained through reuse of infrastructure for successive and cotemporaneous trials and management engineering that includes central storage of personnel certifications (eg, National Institutes of Health Stroke Scale, human subjects research, medical license) for easy redeployment to regulatory agencies and institutional review boards (IRBs). These are experienced systems that are primed for quick activation.

Comment
The LION, gateway, and fully managed models demonstrate a progressive investment in clinical trial infrastructure. Each of the 3 models accomplish improved efficiency and quality using experienced, professional researchers, and holding them accountable for their performance in ways that were less possible in older models of trial research. The gateway and fully managed models go further to establish a reusable research infrastructure to support multiple trials simultaneously and sequentially. These 2 models promise to expedite the cycle between early scientific discovery and clinical application.

Clinical research network models are evolving more effectively to meet the needs of clinical trial stakeholders. Two important improvements include the central IRB and new systems for financial accountability. In health systems and research networks that use a central IRB, the IRB is responsible for the only ethics review of a trial protocol; this review is accepted by other participating sites. Any subsequent local review is typically only for financial and administrative planning. In parts of Europe, and the United Kingdom in particular, use of a central IRB has streamlined ethics management and reduced the administrative burden for investigators; it may also reduce errors that can occur in a duplicative process.10

In the United States, Network for Excellence in Neuroscience Clinical Trials has adopted the central IRB model and requires the US sites to sign on to this arrangement. Financial management, too, is evolving. In clinical trial research, there is often a tension between minimizing financial risk to the funders, which can be partially accomplished by paying researchers only for work delivered, and assuring fiscal predictability for researchers, which can be achieved with guaranteed funding. Networks may be able to negotiate this tension by supporting researchers with predictable funding that is linked to long-term, measurable, performance.

There is broad agreement that the clinical trial enterprise needs to improve to meet growing needs for better research to inform clinical care. Networks will be an important part of this improvement.

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References


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