

NIH Centers of Excellence

Rare Diseases Clinical Research Network

Overview

Why the RDCRN Was Established

The need for Centers of Excellence for rare diseases research has been voiced since the mid-1980s. A disease is defined as rare if it has a prevalence of fewer than 200,000 people in the United States. There are almost 7,000 rare diseases known today. Approximately 80 percent of rare diseases are thought to have a genetic origin.

In 1989, the National Commission on Orphan (or rare) Diseases considered the lack of specialized centers for the diagnosis and treatment of rare diseases to be a serious barrier to the advancement of research on rare diseases. The commission found that 15 percent of patients with rare diseases did not obtain a correct diagnosis until after 5 years or more. An additional 30 percent of patients waited from 1 to 5 years before obtaining a diagnosis.

In 1999, the NIH Special Emphasis Panel on the Coordination of Rare Diseases Research endorsed the need for Centers of Excellence. The panel recommended funding for Specialized Research and Diagnostic Centers of Excellence for Rare Diseases for major categories of rare diseases. The proposal in 1999 was to establish Centers of Excellence on a graduated basis, starting with 10 regional centers in the first year and followed by incremental increases of 10 centers per year until 40 research Centers of Excellence were established. The panel also emphasized that centers should work closely with patient advocacy groups.

Some of the panel's recommendations were realized when President George W. Bush signed the Rare Diseases Act of 2002, Pub. L. No. 107-280, and when NIH established the Rare Diseases Clinical Research Network (RDCRN).

How the RDCRN Functions Within the NIH Framework

The RDCRN involves collaboration among the NIH Office of Rare Diseases (ORD), NCRR, NICHD, NINDS, NIAMS, NIDDK, and NHLBI. In 2003, the original RDCRN, funded through a U54 cooperative agreement, consisted of seven Centers of Excellence (consortia) and a Data and Technology Coordinating Center (DTCC). In 2004, three additional consortia were funded (see Table 4-5). During the first 2 years of operation, each consortium focused on developing clinical protocols for a subset of related rare diseases. RDCRN incorporated standards across consortia and developed and instituted an adverse event reporting system.

The RDCRN contains more than 70 sites distributed across the United States and in other countries. The goals of the sites are to make investigational studies and treatments more accessible to patients with rare diseases and to facilitate the recruitment of patients for clinical trials.

The RDCRN Steering Committee consists of the principal investigator of each consortium, NIH representatives, and a patient advocacy representative. The committee meets on a monthly basis via teleconferencing and two times per year in person.

Other cross-network committees ensure collaboration, cooperation, efficiency, and quality for RDCRN research.

They include the Human Subjects Committee, the Participant/Community Liaison Committee, the Standards Committee, the Web Site Committee, the Training Committee, a project managers committee, and the Coalition of Patient Advocacy Groups. Since 2006, 17 training modules on individual protocols and important issues of common interest have been developed and are available to RDCRN participants through the Network Media Center.

Description of Disease or Condition

Rare diseases affect many tissues, organs, and organ systems. Researchers affiliated with the RDCRN study more than 40 rare diseases. These include Angelman, Rett, and Prader-Willi syndromes; myelodysplastic syndrome and other bone marrow failure conditions; lymphangioleiomyomatosis, rare genetic disorders of the airways, and other rare lung diseases; episodic ataxia, Andersen-Tawil syndrome, and nondystrophic myotonias; several vasculitides; urea cycle disorders; antiphospholipid syndrome and other rare thrombotic diseases; rare pediatric liver diseases; and rare genetic steroid defects.

Burden of Illness

The burden of illness for rare diseases is difficult to estimate because of the large number of these disorders and the limited availability of prevalence and incidence statistics for each disease. Estimates of prevalence or incidence exist for only a minority of rare diseases, and the burden of illness and associated costs are complex. Occasionally, estimates have been produced by patient advocacy organizations or principal investigators applying for funding either to NIH or the U.S. Food and Drug Administration's Office of Orphan Products Development. The National Organization for Rare Disorders estimates that 20-25 million people are affected by a rare disease.

Overall, rare diseases are devastating because of their severity and because diagnosis may take a long time, well after symptoms have appeared. Additionally, there may be no available treatment once the disease is diagnosed.

Scope of NIH Activities: Research and Programmatic

The RDCRN brings together health care researchers who are skilled in diagnosing and treating particular groups of rare diseases. Additionally, the consortia gather groups of patients with similar or related disorders, foster basic scientific investigation, encourage synergy in translational research, and enhance opportunities for collaborative clinical investigation.

The DTCC is designed to enable sharing of study results nationally and internationally in a timely and uniform way. Although data and technology coordination is primarily the responsibility of the DTCC, each center as well as NIH IC program officers also participate in overall coordination.

More than 30 patient advocacy groups are affiliated with the RDCRN and have formed the Coalition of Patient Advocacy Groups to support outreach efforts to patients with rare diseases, their families, and the public. A representative of the group serves on the RDCRN Steering Committee and acts as a liaison between the committee and participating advocacy groups.

NIH Funding for FY 2006 and FY 2007

As the Rare Diseases Act of 2002 stipulated, each consortium award has been made for 5 years. Total funding in FY 2006 was \$14.1 million and \$9.4 million in FY 2007.

Outcomes: FY 2006 and FY 2007 Progress Report

Programmatic and Research Accomplishments

To date, the network has produced 25 publications, posters, and abstracts. In 2006, NIH launched the first [clinical studies of the RDCRN](#), and, by September 20, 2007, 26 clinical protocols had been approved, of which 24 were recruiting patients. Twenty more protocols are under development. To date, 2,357 subjects have been enrolled in research studies.

Many consortia participating in the RDCRN have developed longitudinal studies as well as clinical trials to test the safety and efficacy of new therapeutic agents. The consortia have established training programs for clinical investigators who are interested in rare diseases and have developed a [Web site](#) to inform the public, physicians, patients, and investigators about rare diseases.

The DTCC has developed and enabled new technology, tools, and services for the RDCRN, including electronic data entry, remote direct laboratory transfer, vocabulary and laboratory standards, statistical support, Web site development and maintenance, and database querying tools. The DTCC, in collaboration with each consortium, has also implemented a patient contact registry that allows individuals to register to receive information about new or ongoing clinical studies in addition to periodic educational updates.

To facilitate patients' transportation needs, Angel Flight NIH has widened its services to include the RDCRN. Volunteer pilots donate their time, planes, fuel, and operating expenses to transport patients and family members free of charge to and from medical and research facilities in the RDCRN so that no patient is denied medical access to ongoing research projects because of lack of air transportation.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the RDCRN

In anticipation of the completion of the first 5 years of the network, ORD and the participating NIH ICs assessed the current design of the RDCRN and published a [Notice of Intent](#) to announce that an RFA would be published. The new [RFA](#) will be open to the current participating centers as well as to new applicants and builds on lessons learned during the initial 5 years. With the completion of the first 5 years of the network, the re-issuance of the RFA, and a probable increase in the number of participating NIH ICs, NIH continues to respond to the needs of the rare diseases community and the legislative mandate of the Rare Diseases Act of 2002.

Evaluation Plans

Because the RDCRN was established so recently, it has not been formally evaluated. The ORD estimates that it takes approximately 3 years for a clinical study on a rare disease to be developed, fulfill requirements for approval, and enroll patients. Another 10 years are required to assess the overall impact of the research conducted within the RDCRN.

Eventually, the contribution of the RDCRN to rare diseases research will be determined by the following criteria:

- Completion and outcomes of the 45-50 studies
- Successful recruitment of adequate patient populations
- Number of trainees who complete their training programs
- Seminal impact of scientific publications on future rare diseases research
- Contribution of the DTCC to research in terms of a coordinated data management system, the ability to

capture and integrate many different forms of data, and the development and broad acceptance of novel technological approaches to distributed computing, federated databases, and data mining.

Although no formal evaluation of the RDCRN is planned soon, a review of the consortia and the DTCC will occur in 2008/2009, when applications of currently participating consortia are peer reviewed along with those of new applicants. New awards will be made in 2009.

Future Directions

ORD and the partner ICs will continue to coordinate the network's clinical research and encourage the training of new rare diseases researchers. Depending on IC interest in applications, the RDCRN may be expanded to comprise more than the current 10 consortia, thereby encompassing a larger number of rare sites across the United States and in other countries with additional research protocols as well as rare diseases under study.