

A model for collaborative clinical research in rare diseases: experience from the Rare Disease Clinical Research Network program

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To overcome a lack of interest in research of rare diseases and an insufficient number of patients who can be recruited into clinical studies of rare diseases and potential diagnostics and treatments, the Rare Diseases Clinical Research Network (RDCRN) was established with the services of a centralized Data Management and Coordinating Center. The RDCRN has been very successful at recruiting patients, initiating clinical studies and trials, meeting patient recruitment milestones, training the next generation of research investigators and developing an active role for patient advocacy groups as research partners. The RDCRN has fostered international collaborations at multiple research sites that have led to regulatory approval of several drug products and expanded the knowledgebase for diseases included in the RDCRN. Rare disease research continues to evolve and considerable emphasis is placed on the translational research of discoveries from basic and clinical research activities, leading to the possible development of orphan products.

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Statistics state that approximately 25 million people in the USA are affected by an estimated total of 7000 rare diseases or conditions that lead to significant morbidity and mortality. The term 'rare disease' is defined through an Amendment to the Orphan Drug Act of 1983 as being "a condition affecting fewer than 200,000 Americans or a disease with a greater prevalence but for which no reasonable expectation exists that the costs of developing or distributing a drug can be recovered from the sale of the drug in the USA"^[1,2].

The NIH is the primary provider of research resources and support for basic, clinical and translational research in the USA. Rare diseases research provides unique challenges to the research community, the biopharmaceutical and medical device and diagnostics industries, the academic and public sector researchers, government funding agencies, regulatory agencies, Patient Advocacy Groups (PAGs) and private foundations.

The challenges presented to the rare diseases community include small patient populations distributed over a wide geographic area, difficult recruitment of subjects to clinical studies, few expert centers for diagnosis, management and research and a scarcity of research investigators with an interest in rare diseases. As these issues continue to be resolved, we are observing an industry with renewed interest in orphan product development and rare diseases research.

Despite the advances and opportunities for research in rare diseases, difficulties remain in clinical diagnosis, clinical trials methodology and clinical management. Obtaining a correct diagnosis may be straightforward due to well-described phenotypes or due to the availability of diagnostics tests. Conversely, the diagnosis may be

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challenged by a lack of well-defined diagnostic criteria or the absence of differential symptoms. For most rare diseases, there exist insufficient characterizations of the natural history of the diseases. Treatment can be equally challenging with many questions raised concerning clinical management and a lack of therapeutic options. There are special and unique challenges to address in coordinating and identifying disease expertise and resources for the small patient population of rare diseases who are geographically dispersed around several research sites. Rigorous characterization and longitudinal assessment is needed to facilitate discovery of clinical end points and biomarkers of disease risk, disease activity and response to therapy. In addition, systematic assessment may potentially help to improve and develop an evidence base for current treatment strategies. In order to bring promising therapies to the clinic, well-described patient populations are required.

For several rare diseases there are defects in only one gene. Many rare diseases are complex and result from the interaction of multiple genes or due to the impact of environmental and genetic factors. Studies by investigators of these abnormalities in genes or proteins may provide useful information about normal biologic function of these genes. These will help in the scientific advancement of the rare diseases field. Understanding the pathogenesis of rare diseases may also advance our understanding of the more common medical disorders.

To respond to these needs the NIH Office of Rare Diseases Research (ORDR), now located in the National Center for Advancing Translational Sciences (NCATS), established the Rare Diseases Clinical Research Network (RDCRN) in 2003 with assistance and program support from six NIH institutes and centers (ICs) and established ten rare disease clinical research consortia (RDCRC) and a data management and coordinating center (DMCC). The RDCRN currently consists of 17 research consortia with the guidance and program support from eight research ICs. Each RDCRC (consortium) is required to focus on a group of at least three related disorders, multiple investigators and collaborate with PAGs or research partners. Each consortium receives 5 years of support from a cooperative agreement award (U54); [Figure 1](#) provides the current list of 17 consortia, the participating NIH ICs and the collaborating research partners in the RDCRN.

The RDCRN is unique in its approach to addressing rare diseases as a group. Previously, the NIH's ICs funded research on individual rare diseases in their respective disease-type or organ domains. The RDCRN aims to create a multisite specialized infrastructure including academic investigators, PAGs and NIH to support rare diseases clinical research. It is

serving as a model of collaboration for clinical research in rare diseases. Each consortium within the RDCRN consists of a group of clinical investigators, multiple institutions and relevant organizations, including PAGs, and focuses on at least three related rare diseases, disorders, conditions or syndromes that are relevant to the interests of the participating NIH ICs.

One of the important features of the RDCRN is the involvement of PAGs as consortia members and research partners. There are 97 PAGs and collectively they have formed the Coalition of PAG (CPAG). In each RDCRN consortium, relevant PAGs are involved in attending consortium meetings, helping in recruitment of patients to clinical studies and various other activities. Several PAGs also provide financial support for training of young investigators. The CPAG members meet monthly via telephone conference call and attend at least one face-to-face meeting. The CPAG chairperson also attends a steering committee of the RDCRC and is a full voting member.

The RDCRN brings together experts who are skilled in basic and clinical sciences and who are experts in diagnosing and treating groups of several rare diseases. They show interest in and train junior clinicians, faculty members and fellows to increase the pool of investigators in rare diseases research. Creation of multisite consortia on groups of related rare diseases has increased collaborations among clinical researchers and facilitated longitudinal studies (natural history studies), epidemiological studies and clinical trials. This creates synergy in translational research and increases opportunities for collaborations in clinical research. The DMCC enables sharing of study results nationally and internationally in a timely and uniform way.

RDCRN background

In 1999, the NIH office of rare diseases, later referred to as ORDR, (now located in NCATS) at the request of congressional appropriations to NIH convened a special emphasis panel, comprised of academic scientists, representatives of voluntary patient support groups, pharmaceutical, biotechnology and device industries and other federal agencies [101]. This panel made recommendations to Congress regarding the special research opportunities and healthcare issues posed by rare diseases. These recommendations are contained within the department of health and human services NIH 'Report on Steps to Coordinate Rare Diseases Research Programs,' January 2001 [101].

The Rare Diseases Act of 2002 (Public Law 107–280) directed ORDR at NIH to support regional centers of excellence for clinical research into, training in, and demonstration of diagnostic, prevention, control and treatment methods for rare diseases. This

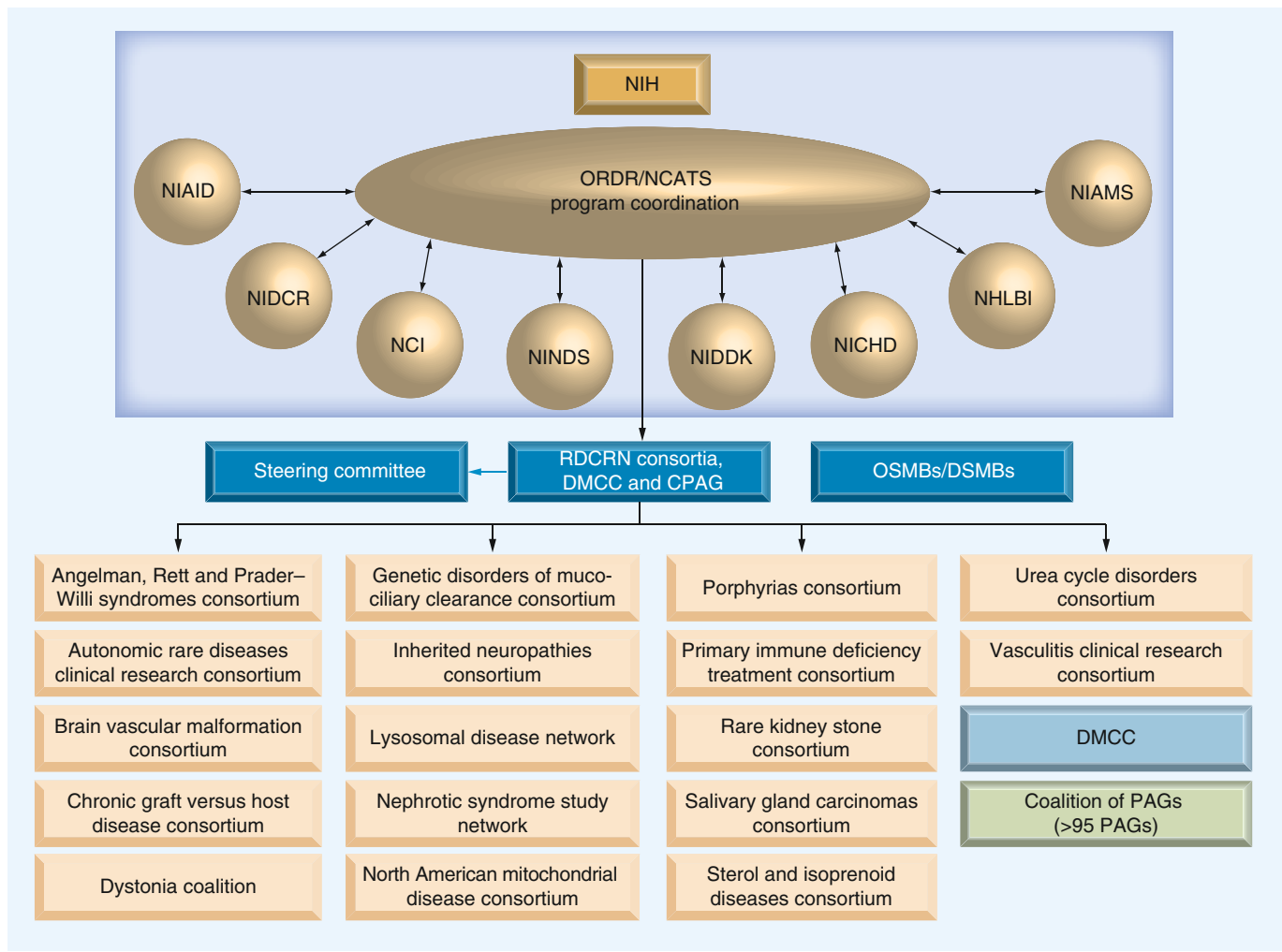


Figure 1. Rare Diseases Clinical Research Network. The network shows the current list of 17 consortia, the participating NIH Institutes and centers and the collaborating research partners in the RDCRN.

CPAG: Coalition of Patient Advocacy Group; DMCC: Data management and coordinating center; DSMBs: Data and safety monitoring boards; NCATS: National Center for Advancing Translational Sciences; NCI: National Cancer Institute; NHLBI: National Heart, Lung and Blood Institute; NIAID: National Institute of Allergy and Infectious Diseases; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NICHD: National Institute of Child Health and Human Development; NIDCR: National Institute of Dental and Craniofacial Research; NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases; NINDS: National Institute of Neurological Disorders and Stroke; ORDR: Office of Rare Diseases Research; OSMBs: Observational study monitoring boards; PAG: Patient Advocacy Group; RDCRN: Rare Diseases Clinical Research Network.

law provided the legislative mandate for the funding opportunity announcement to address the needs of rare disease clinical research [3].

In 2003, ORDR released a Request for Applications (RFA) for an RDCRN together with several NIH ICs and initially funded ten RDCRCs and one Data and Technology Coordinating Center. In 2009, the ORDR, in collaboration with ten NIH Institutes, reissued RDCRN RFAs (one for the consortia and the other for DMCC). The purpose of the RDCRN RFA was to invite new and renewal cooperative agreement applications for RDCRCs that individually focus on a subset of related rare diseases.

A separate RFA was published to invite new and renewal cooperative agreement applications for DMCC. Through an open competition, initially 19 rare diseases clinical research consortia and one DMCC were funded.

Goals & purpose of the RDCRN program

The goal of the RDCRN is to advance clinical research in rare diseases involving multiple institutions and PAGs. This is accomplished through collaborative efforts of clinical researchers at multiple sites, PAGs and NIH. These clinical studies include longitudinal studies and Phase I, II and III clinical trials. Through this

program, training is also provided primarily to young clinicians. It also supports pilot projects and provides clinical data management and data sharing across the RDCRN. In addition, through the RDCRN website, it provides access to information related to rare diseases for basic and clinical researchers, academic and practicing physicians, patients and the public.

Individual consortia involve collaborating investigators at multiple different research sites and institutions. This program helps facilitate identification of biomarkers for disease risk and disease severity/activity, and measures of clinical outcome applicable to clinical trials. It also encourages development of new approaches for diagnosis, prevention and treatment of rare diseases [4].

Structure of the RDCRN (partners & PAGs)

The RDCRN consists of all funded consortia and a single DMCC. This program supports a collaborative and coordinated RDCRN of consortia comprised of investigators at multiple institutions/sites and PAGs committed to investigation of rare diseases working in partnership to enhance communication and sharing of resources in a multidisciplinary approach. The consortia and DMCC are supported by cooperative agreement awards from ORDR, NCATS and other participating ICs. Project scientists from NIH ICs also collaborate as scientific partners with each consortium. Currently more than 90 PAGs, as members of RDCRN, are involved in identifying cohorts of patients with a range of phenotypic expression, recruiting patients for the clinical studies and educating patients, public, media and healthcare providers. All participating PAGs of RDCRN have formed a group called the CPAG. Individual PAGs associated with consortia work collaborate with DMCC to provide information on rare diseases for patients and family through the RDCRN website and provide input in developing informed consent statements, recruitment strategies and protocols. Through RDCRN, emphasis is placed on collecting clinical information for the development of biomarkers. The RDCRN also promotes and supports new approaches for preventing, diagnosing and treating rare diseases, as well as providing training opportunities to young and new clinical investigators through consortia. The DMCC supports RDCRN consortia by providing technologies and tools to collect standardized clinical research data. It also provides support for clinical study design for several consortia. The RDCRN also provides an online protocol management system for web-based patient enrollment and adverse event reporting for multisite studies. The DMCC for RDCRN is responsible for monitoring network protocol adherence, clinical data collection (along with imaging, pathologic and laboratory data) and data submission. The DMCC has

utilized novel approaches to distribute computing and federated databases.

The RDCRN Steering Committee guides the network and consists of the principal investigator of each consortium, ORDR, NCATS program coordinator, NIH ICs project scientists and the CPAG chairperson. There are subcommittees including training, operations, registry and strategic planning. These subcommittees have been created to foster enhanced communications and collaborations within and across consortia. The RDCRN requires cooperation among the NCATS, the ORDR program coordinator for RDCRN, the participating IC project scientists, directors of the consortia and their collaborators, and the director of the DMCC to maximize their effectiveness.

RDCRN DMCC

To foster collaborative research efforts, the RDCRN utilizes a centralized DMCC. The DMCC supports the RDCRN by providing technologies, tools and support of study design and data analyses. The RDCRN utilizes an online protocol management system for patient enrollment and randomization of study participants. The management system provides electronic data entry and collection with data vocabulary and laboratory standards and adverse event reporting capabilities. Protocol training is provided for multiple investigators involved in the investigation under a common study protocol. The DMCC also provides an investigators-only website to provide access to study evaluation databases and documentation of study participation. The DMCC takes on active roles in developing the required forms for the studies, a biospecimen recording and distribution system and a pharmacy distribution system for clinical trials. There is also a DMCC website for patient contact registry, to stimulate patient recruitment and community engagement through internet services available to the public. The patient contact registry is a service that allows individuals to register to and receive information in regards to new or ongoing clinical studies, in addition to periodic educational updates, as well as allowing consideration of participating in clinical studies.

The DMCC, in conjunction with the NIH, provides logistical and administrative assistance for RDCRN activities. DMCC produces and maintains RDCRN operating policy and procedures, documents, worksheets and data collection forms; and monitors RDCRN compliance while addressing privacy and confidentiality issues related to database management and multilevel data sharing. All consortia collaborate with the DMCC throughout the course of their studies in order to assure compatibility and standardization of data management approaches.

The data from RDCRN studies are made available for sharing with the scientific community to the largest possible number of qualified investigators for the purposes of scientific research. To accomplish this, ORDR-governed data repository (through dbGaP, a database for genotype and phenotype information available from the national library of medicine) has been created and is utilized for the repository for data generated in the clinical studies of the RDCRN.

Activities of the RDCRN

Collectively, the RDCRN is studying more than 200 diseases at 225 research sites around the world, with 86 active protocols and 37 additional protocols in development. There have been 134 trainees in the current cycle of RDCRN, with a total 174 trainees in both 5-year periods. More than 15,000 patients have enrolled in studies in the second 5-year period and a total of 21,836 people have been enrolled in RDCRN clinical studies since 2003. More than 95 PAGs are active participants in the RDCRN. A total of 119 studies have been activated since inception and there are currently 76 activated studies thus far in RDCRN 2.

■ International collaboration

The RDCRN has 17 consortia, each of which conducts multisite clinical studies. Most consortia have formed collaborations with international sites in 14 countries other than the USA including Australia, Austria, Belgium, Canada, England, France, Germany, Iceland, India, Italy, Netherlands, Scotland, Spain and Switzerland. The RDCRN Contact Registry that enhances participation in clinical trials and disseminates information has approximately 11,000 registrants from 90 countries for more than 200 rare diseases.

Studies conducted in the RDCRN

The RDCRN was created to provide the infrastructure to conduct different types of studies. The majority of studies are longitudinal or natural history studies followed by pilot studies and Phase I, II and III studies. Industry sponsorship of studies is encouraged and endorsement of the study as an RDCRN study is possible. Currently there are 13 protocols that involve collaborations with the pharmaceutical industry (Table 1).

Training of young investigators

To respond to the need for the training of the next generation of rare disease research investigators, each consortium requires a training or career development component. More than 170 trainees have completed the training program. Collaboration with PAGs represents community-engaged research partnerships. Many of these research partnerships are global activities. The

Table 1. NIH management of the Rare Diseases Clinical Research Network.

Study type	Protocols (n)
Pilot	9
Longitudinal	69
Phase I	2
Phase II	7
Phase III	5
Investigational new drug	5
Industry sponsored	13
Case control	2
Chart review	1

RDCRN has established a comprehensive training program for clinical investigators and developed a network-wide website to inform the public, physicians, patients, and investigators about the rare diseases under study. Through the training program in each consortium, trainees receive experience in designing and performing patient-oriented clinical research studies in rare diseases under the mentorship of senior investigators (clinician researchers and biostatisticians). They also learn how to analyze and report the results of clinical studies. The trainees can attend several academic courses including basic science, ethics, experimental therapeutics, epidemiology, computer science and biostatistics. Several of these trainees have gained relevant experience through RDCRN and become independent investigators to pursue an academic career in clinical research in rare diseases. In addition, the RDCRN investigators in collaboration with NIH ICs organize conferences on clinical research in rare diseases focused on the needs of young investigators advising them about career development through interactive educational sessions and lectures from experts (including clinicians and biostatisticians) on logistics of conducting rare diseases research.

Value of PAGs as research partners

Since 2004, all PAGs within the RDCRN are involved in expanded roles as research partners. They help in recruiting patients for clinical studies, encouraging participation in natural history studies, identifying cohorts of patients with a range of phenotypic expression and educating patients, public, media and healthcare providers. Several of these PAGs provide financial support for research and training programs of consortia and patient registries. In addition, they identify research efforts and translate research results to communities, organize and fund research-based scientific conferences and meetings for patients/families/caregivers and establish

global partnership. A few PAGs also provide financial support for travel clinics to facilitate patient access to investigators and studies.

Selected scientific accomplishments & tools

■ Efficacy & safety of sirolimus in lymphangioliomyomatosis

Lymphangioliomyomatosis (LAM) is a cystic lung disease that occurs mostly in women. It is progressive and is associated with inappropriate activation of the mammalian target of rapamycin signaling, which regulates cellular growth and lymphangiogenesis. Sirolimus (also known as rapamycin) inhibits mTOR and has shown promise in Phase I–II trials involving patients diagnosed with LAM.

The Rare Lung Diseases Consortium conducted a two-stage trial of sirolimus involving 89 patients with LAM who had moderate lung impairment – a 12-month randomized, double-blind comparison of sirolimus with placebo, followed by a 12-month observation period. The primary end point was the difference between the groups in the rate of change (slope) in forced expiratory volume in 1 s. Through this study they concluded that in patients with LAM, sirolimus stabilized lung function, reduced serum VEGF-D levels, and was associated with a reduction in symptoms and improvement in quality of life. Therapy with sirolimus may be useful in selected patients with LAM [5].

■ Mexiletine improves symptoms & signs of myotonia in nondystrophic myotonia: secondary outcomes from a Phase II trial

The objective of this trial was to determine if mexiletine is effective therapy for myotonia in patients with nondystrophic myotonia (NDM). NDM results from rare mutations of muscle sodium and chloride channels. Patients experience delayed muscle relaxation following contraction, functionally limiting stiffness and pain. Mexiletine, a class 1B antiarrhythmic medication with a high affinity for muscle sodium channels, may reduce myotonia in NDM.

The Clinical Investigation of Neurologic Channelopathies Consortium conducted a randomized, double-blind, placebo-controlled, crossover trial of mexiletine 200 mg three-times daily in 59 patients with NDM. Each treatment period was 4 weeks, separated by a 1-week washout. The primary outcome was patient reported stiffness on an interactive voice response diary (IVR). Secondary end points included changes in pain, weakness and tiredness on the IVR, SF-36, INQoL, clinical myotonia assessment, electrophysiological short- and long-exercise testing, quantitative grip myotonia and needle electromyography. Earlier they had reported that mexiletine provides major

benefit for all symptoms of myotonia on the IVR and SF-36 quality of life measures, without study-related serious adverse events. Through this Phase II trial they concluded that mexiletine at a dose of 200 mg three-times daily is effective therapy for symptoms and signs of myotonia in patients with NDM [6,7].

■ *N*-carbamyglutamate augments ureagenesis & reduces ammonia & glutamine levels in patients with propionic acidemia

To determine whether *N*-carbamyglutamate reduces plasma levels of ammonia and glutamine and increases ureagenesis rate in patients with propionic acidemia, identical 4 h studies were performed before and immediately after a 3-day trial of oral *N*-carbamyglutamate in seven patients with propionic acidemia. An oral bolus of [¹³C]-sodium acetate was administered at the start of each study, and sequential blood samples were obtained to measure [¹³C]-urea, ammonia, urea and amino acids. The investigators concluded that the *N*-carbamyglutamate augments ureagenesis and decreases plasma ammonia and glutamine in patients with propionic acidemia. The drug may serve as an important therapeutic adjunct in the treatment of acute hyperammonemia in this disorder [8].

The Urea Cycle Disorders (UCD) Consortium has also been an active research partner with studies for three compounds approved by the US FDA:

- Ucylyd Pharma (AZ, USA): Ammonul (sodium phenylacetate and sodium benzoate) for acute hyperammonemia of UCD;
- Recordati (Milan, Italy): Carbaglu (Carglumic acid, *N*-carbamyglutamate) for hyperammonemia due to *N*-acetylglutamate synthase deficiency;
- Hyperion (NY, USA): Ravicti (glycerol phenylbutyrate) for UCD.

■ Sturge–Weber syndrome & port-wine stains caused by somatic mutation in *GNAQ*

Sturge–Weber syndrome is a skin and neurological disorder. Affected individuals have a classic symptom of port-wine-stain on the face. Other symptoms may include seizures, angiomas, glaucoma, weakness on one or both sides of body and developmental delays. The investigators from Brain Vascular Malformation Consortium were successful in identifying a nonsynonymous single nucleotide variant in *GNAQ* gene through wholegenome sequencing studies. The brain vascular malformation consortium investigators concluded that both port-wine stain birthmarks and Sturge–Weber syndrome are caused by a somatic mutation in the *GNAQ* gene. This discovery will eventually help studies for investigating drug development for Sturge–Weber syndrome [9].

■ Patient contact registry

Since there is generally a lack of a sufficient number of patients in any single location, the RDCRN utilizes the patient contact registry to increase patient participation in the clinical studies in the RDCRN. The RDCRN contact registry was developed in 2004 by the DMCC as a tool to facilitate participant recruitment in clinical studies. Through this contact registry patients and their family members can register and receive information about relevant clinical studies and clinical research projects. The contact registry can also be used by the investigators to facilitate the rapid enrollment of subjects in study protocols. The contact registry is not limited to information on an individual rare disease. Patients can select more than one diagnosis in their enrollment process. The contact registry has an enhanced capability to collect treatment information from multiple diseases. There is also an option to share information with all investigators and the PAGs. The contact registry has an open enrollment process to patients with diseases for individual studies by the consortia. The contact registry provides an international online system for communication, recruitment and research studies in 90 countries.

A significant challenge

Despite many accomplishments in the field of rare diseases there is a significant challenge for the approval of multisite studies. There are various options for streamlining approval of multisite protocols: Investigators can consider models that facilitate 'shared review' such as central institutional review board (IRB) of record or IRB share for multisite trials. A central IRB of record for multisite trials is a preference. It may even approve trial efficacy as well as improve patient safety and scientific validity. The central IRB can reside at the lead institution and other member institutions can agree to either accept the findings of the central IRB or accept the central IRB findings with modifications.

Future perspective

Rare diseases research continues to evolve and addresses the needs of translating research discoveries into diagnostics and treatments. To maintain this momentum, expanded emphasis on translational research activities is needed in the investigator training programs. As more resources become available in new and evolving translational research programs supported by NIH ICs, academic centers will continue to expand the emphasis to meet the scientific opportunities presented in these programs. Research consortia and networks such as the RDCRN will be utilized more extensively on a global basis as training ground for new investigators and as research sites to conduct the studies required in the research continuum progressing to the development of products for rare diseases. The RDCRN has proven to be an effective research model to maximize research investigator participation, initiating clinical trials, facilitating patient recruitment with established research partnerships with PAGs at multiple research sites around the world and enabling pharmaceutical industry and government sponsored research clinical studies to proceed with a supportive infrastructure to complete the clinical studies in a timely fashion.

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