

CONCEPT CLEARANCE RECORD
FY 2019 RESEARCH INITIATIVE — NCATS
September 2017, Concept 1

CONCEPT TITLE: Rare Diseases Clinical Research Network (RDCRN) Program

CONCEPT TYPE: Reissuance

[RFA-TR-13-002](#): Rare Diseases Clinical Research Consortia (RDCRC) for Rare Diseases Clinical Research Network (U54)

ASSIGNED DISCUSSANTS: Bartek, O'Boyle, Shekhar

OBJECTIVE(S): The purpose of this cooperative agreement research program is to facilitate clinical research in rare diseases through support for the establishment or continuation of the Rare Diseases Clinical Research Consortia (RDCRC) and a central Data Management and Coordinating Center (DMCC). Each RDCRC will perform collaborative, multisite clinical research in rare diseases, train new investigators in rare diseases research, and provide content for an internet resource site on rare diseases. Each RDCRC will consist of a consortium of clinical investigators, institutions and relevant organizations, including patient advocacy group organizations, and will focus on at least three related rare diseases, disorders or syndromes. The focus of each RDCRC can be on particular defects (e.g., lysosomal storage diseases, amino acid metabolism defects), particular organ systems (e.g., primary immune deficiencies, neurodevelopmental delay and intellectual disability syndromes) or other groupings. Since rare diseases are diverse, the nature of clinical research that is feasible will vary. Clinical data management for efficient data collection as well as data mining and data sharing across rare diseases will be addressed by the DMCC of the RDCRN program.

It is advantageous for clinical studies of diseases in small populations to use a multicenter approach. There are an estimated 6,000-7,000 rare diseases, almost all of which have substantial unmet medical needs. Because of their rarity, there are few disease experts, treating physicians and experienced centers for patient care for each of the individual rare diseases, and collaboration across clinical research centers is necessary to facilitate, support and accelerate the development of treatments for patients with rare diseases. Additionally, given the large number of rare diseases, there is a pressing need for better approaches that investigate mechanisms that are applicable to multiple diseases. Therefore, a substantial need remains for the continuation of existing or development of new collaborative rare disease consortia for rare disease clinical research.

DESCRIPTION: This initiative will continue to facilitate identification of biomarkers for disease risk and disease severity/activity and measures of clinical outcome applicable to clinical trials. It also will encourage development of new approaches to diagnosis, prevention and treatment of rare diseases.

The RDCRN will consist of all funded RDCRC and a single DMCC. It will support the continuation of a collaborative and coordinated network of RDCRCs composed of investigators at multiple institutions/sites and patient advocacy groups committed to investigation of rare diseases working in partnership to enhance communication and sharing of resources in a multidisciplinary approach. The reissuance of the funding opportunity announcement (FOA) will be open to new as well as existing RDCRCs and a DMCC.

The purpose of this initiative is to solicit applications to establish clinical research consortia and a central DMCC to promote the clinical study of rare diseases. This initiative will serve the following critical functions: Provide support for (1) collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies and/or clinical trials; (2) training of clinical investigators in rare diseases research; (3) pilot/demonstration (proof of concept) clinical research projects; (4) clinical data management that incorporates novel approaches and technologies for data management, data mining, and data sharing across rare diseases, data types, and platforms; and (5) access to information related to rare diseases for basic and clinical researchers, academic and practicing physicians, patients, and the lay public. The DMCC will focus on innovative ways to provide the infrastructure and support to the individual sites in their activities relevant to items 1-3 as well as a focus on issues relevant to items 4 and 5.

IMPORTANCE: Approximately 25 million people in the United States are affected by an estimated 7,000 rare diseases or conditions leading to significant morbidity and mortality. "Rare disease" is defined through an Amendment to the Orphan Drug Act of 1983 (Orphan Drug Act, P.L. 97-414; Health Promotion and Disease Prevention Amendments, P.L. 98-551) as 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 United States.

Investigations into rare diseases offer promising leads for scientific advancement. Many rare diseases represent single gene defects whose abnormalities in specific genes or proteins offer insight into normal biologic function. Other rare diseases are complex, resulting from the interaction of two or more genes. Understanding the pathogenesis of rare diseases may advance our understanding of more common medical disorders.

Despite the advances and opportunities for research in rare diseases, difficulties remain in clinical diagnosis, clinical trials methodology and clinical management. Diagnoses may be straightforward as a result of well-described phenotypes or due to the availability of diagnostics tests, or conversely, they may be challenged by a lack of well-defined diagnostic criteria. Furthermore, there are insufficient characterizations of the natural history of many rare diseases. Determining effective treatment options can be equally challenging due to challenges in clinical trial design and interpretation, and a lack of proven therapeutic options. Rare diseases pose unique challenges to identification and coordination of resources and expertise for small populations dispersed over wide geographic areas. Rare diseases research often requires collaboration of scientists from multiple disciplines sharing research resources and patient populations. Rigorous characterization and longitudinal assessment are needed to facilitate discovery of biomarkers of disease risk, disease activity and response to therapy. In addition, systematic assessment could help to improve and develop an evidence base for current treatment strategies. Well-described patient populations will be important to bring promising therapies to the clinic.

HISTORY: In November 2002, the Rare Diseases Act of 2002 (Public Law 107-280) directed Office of Rare Diseases Research (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 law provides the legislated mandate for this FOA to address the needs of rare disease clinical research.

The RDCRN program was established in late 2003, with expansion and renewal occurring in 2009 and 2014. The present RDCRN leverages collective knowledge of investigators in 21 RDCRCs, at 439 clinical

sites in the United States and more than 20 countries worldwide. More than 95 clinical studies are ongoing or have been completed in rare diseases since the RDCRN's inception, which have contributed to shared data resources for rare diseases through a data management coordinating center and have contributed substantial work to the advancement and acceleration of rare disease clinical research. There is now an increasing momentum among rare disease stakeholders (funders, regulators, biopharma, academia, health systems and patient groups) to build upon this body of knowledge and to develop strategies to accelerate the translation of rare disease knowledge into effective treatments for rare diseases.

CONCEPT CLEARANCE DATE:

Sept. 7, 2017

COUNCIL RECOMMENDATION:

Council approved as recommended by staff.

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