Rare Diseases Clinical Research Network (RDCRN): A Model for Collaboration to Facilitate Research Efforts

INTERNATIONAL CONFERENCE ON RARE DISEASES AND ORPHAN DRUGS
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Conflict of Interest

No COI to disclose
Office of Rare Diseases Research (ORDR), NCATS Collaborative Programs/Initiatives

Stimulates and coordinates research on rare diseases

- **Rare Diseases Clinical Research Network (RDCRN) Program**
  - Genetic and Rare Diseases Information Center (GARD)
  - Scientific Conferences - Identify Research Opportunities and Establish Research Agenda (>1200 Conferences)

- Global Rare Diseases Registry and Repository (GRDR)
- NIH Clinical Center’s Bench to Bedside Research Program
Rare Diseases: Background

- Prevalence < 200,000 people in the USA
- ~ 7000 Genetic and Acquired Rare Diseases
- Estimated 6%-8% of Population has a Rare Disease
- ~ 18-25 million people in the United States are affected
Challenges for Rare Diseases Research

• Disease often not well characterized or defined
• Rarity means:
  ➢ Recruitment for trials is usually quite difficult
  ➢ Study populations become widely dispersed
  ➢ Few expert centers for diagnosis, management, and research
• Often little high-quality evidence available to guide treatment
Rare Clinical Diseases Research Network

Initiative of the National Center for Advancing Translational Sciences (NCATS)
RDCRN: Objective

The overall objective of RDCRN is to contribute to the clinical research and treatment for rare diseases by

- working collaboratively to identify biomarkers for disease risk, disease severity and activity, and clinical outcome
- while encouraging the development of new approaches to diagnosis, prevention, and treatment.
RDCRN: Led by ORDR (NCATS), Collaboration with 10 NIH Institutes

Office of NIH Director
Deputy and Associate Directors
Administrative Offices

Advisory Committee to the Director

National Cancer Institute
National Eye Institute
National Heart Lung and Blood Institute
National Institute on Aging
Clinical Center
Center for Information Technology
Center for Scientific Review
John E. Fogarty Center for Advanced Study in the Health Sciences

National Institute of Alcohol Abuse and Alcoholism
National Institute of Allergy and Infectious Disease
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Child Health and Human Development
National Center for Complementary and Alternative Medicine
National Center for Minority Health and Health Disparities
National Center for Advancing Translational Sciences, Office of Rare Diseases Research
National Human Genome Research Institute

National Institute of Drug Abuse
National Institute of Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Child Health and Human Development
National Center for Complementary and Alternative Medicine
National Center for Minority Health and Health Disparities
National Center for Advancing Translational Sciences, Office of Rare Diseases Research
National Human Genome Research Institute

National Institute of Mental Health
National Institute of Neurological Disorders and Stroke
National Library of Medicine

Office of Research on Women’s Health
Office of AIDS Research, Office of Dietary Supplements, Office of Behavioral and Social Sciences Research, Office of Disease Prevention, Office of AIDS Research, Office of Dietary Supplements, Office of Behavioral and Social Sciences Research, Office of Disease Prevention,
RDCRN: Background Information

- Established (in 2003 by ORDR) in response to a Request for Application (RFA). Ten consortia a central Data Management and Coordinating Center (DMCC).
- Expanded in 2009 to 17 consortia and a DMCC (Reissuance of RFA).
- Each RDCRN Consortium: multiple diseases/investigators/sites, collaborative clinical research involving Patient Advocacy Groups (PAGs) as research partners.
RDCRN: Background Information

- These are cooperative agreement (U54) awards for 5 years. Scientific collaborators from ORDR, NCATS and NIH Institutes/Centers (ICs)
- Each awardee (Consortium) receives no more than $1.25 M Total Cost/year for multi site studies
- RDCRN 3rd cycle (Renewed - 2014), an ORDR, NCATS Initiative
  22 distinct multi-site Consortia and a DMCC
  A Network of Network!
Goals of the RDCRN

• Facilitate clinical research by:
  ➢ Creating multi-site Consortia focused on a group of minimum three related diseases
  ➢ Making meaningful large-scale clinical studies possible
    ▪ Longitudinal studies, Clinical Trials, Natural History Studies (NHS) are required
    ▪ Establishing uniform protocols for data collection
    ▪ Cost sharing infrastructure
    ▪ Centralized data repository and data sharing for rare diseases

• Directly engage patient advocacy groups (PAGs) and their advocates as research partners
• Provide training for new investigators
• Support Pilot Projects Program
• Provide Website resource for education and research in rare diseases
Special Features of NCATS RDCRN

• **The RDCRN is unique in its approach to addressing rare diseases as a group.** Each consortium studies a group of *minimum three related rare diseases.*

• **The direct involvement of PAGs as research partners is a major feature and requirement of this network.**

• Collaboration of ORDR, NCATS with 10 NIH ICs
About RDCRN

• Collectively, the RDCRN is studying 282 rare diseases in natural history and clinical trials at 253 clinical sites located in the US and in 17 countries.

• There are more than 90 active protocols.

• 40,000 patients have enrolled in clinical studies.

• There have been 208 trainees.

• There are 2,937 collaborative members.

• There are more than 130 PAGs as research partners, collectively formed a Coalition (RDCRN-CPAG).
The Data Management and Coordinating Center

Coalition of Patient Advocacy Groups (CPAG)

Porphyria Rare Disease Clinical Research Consortium

North America Mitochondrial Diseases Consortium

Primary Immune Deficiency Treatment Consortium

Brittle Bone Disorders Consortium

Chronic Graft Versus Host Disease

The Data Management and Coordinating Center

Urea Cycle Disorders Consortium

Brain Vascular Malformation Consortium

Genetic Disorders of Mucociliary Clearance

Consortium of Eosinophilic Gastrointestinal Disease Researchers

Rett, MECP2 Duplications and Rett-Related Disorders Consortium

Clinical Research in ALS & Related Disorders for Therapeutic Development

Autonomic Disorders Consortium

Sterol and Isoprenoid Diseases Consortium

The Frontotemporal Lobar Degeneration Clinical Research Consortium

Inherited Neuropathies Consortium

Nephrotic Syndrome Study Network

Rare Kidney Stone Consortium

Vasculitis Clinical Research Consortium

Lysosomal Disease Network

Dystonia Coalition

Developmental Synaptopathies Associated with TSC, PTEN And SHANK3 Mutations

Rare Lung Diseases Consortium

Clinical Research in ALS & Related Disorders for Therapeutic Development

Autonomic Disorders Consortium

Sterol and Isoprenoid Diseases Consortium

NIH
National Center for Advancing Translational Sciences

ORDR/NCATS
(NCI, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIDDK, NIMH, NINDS, ODS)
### RDCRN Protocols

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Number of Protocols</th>
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<tbody>
<tr>
<td>Pilot</td>
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<tr>
<td>Longitudinal</td>
<td>50</td>
</tr>
<tr>
<td>Phase I</td>
<td>1</td>
</tr>
<tr>
<td>Phase II</td>
<td>6</td>
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<tr>
<td>Phase III</td>
<td>4</td>
</tr>
<tr>
<td>IND</td>
<td>5</td>
</tr>
<tr>
<td>Industry Sponsored</td>
<td>12</td>
</tr>
<tr>
<td>Case Control</td>
<td>1</td>
</tr>
<tr>
<td>Chart Review</td>
<td>2</td>
</tr>
</tbody>
</table>
Value of PAGs as Research Partners

Since 2004 PAGs within RDCRN are involved in more than one of the following roles as research partners:

- Recruit patients for clinical studies, encourage participation in NHS
- Identify cohorts of patients with range of phenotypic expression
- Educate patients, public, media and health care providers
- Identify research efforts and translate research results to communities
Value of PAGs as Research Partners

- Organize and fund research based Scientific conferences and meetings for patients/families/caregivers
- Provide financial support for research and training programs of RDCRN (consortia) and patient registries
- Provide financial support for travel clinics to facilitate patient access to investigators and studies
- Establish global partnership
RDCRN International Sites

- Australia
- Austria
- Belgium
- Canada
- England
- France
- Germany
- Iceland
- India
- Italy
- Netherlands
- Scotland
- Spain
- Switzerland
RDCRN Activated International Sites Over Time
RDCRN Steering Committee Organization

(Review, facilitate and establish all Network procedures and functions)

NIH Institutes’ Project Scientists

CPAG Chairperson

Consortia PIs

DMCC PI

NCATS Program Lead and Coordinator for RDCRN (From ORDR)

RDCRN Steering Committee
Subcommittees of RDCRN Steering Committee

1. Strategic Planning
   - PAGs-PIs manuscript

2. Operations
   - Single IRB

3. Training
   - RDCRN RD Certificate Program (launched September 30, 2015)
   - Training Conferences

4. Contact Registry
RDCRN Funding

- All consortia are co-funded by
  - ORDR, NCATS and
  - one or more collaborating NIH Institute (Brittle Bone Disease Consortium is funded by NCATS, 3 more Institutes/Center-IC)

- RDCRN-DMCC is funded by ORDR, NCATS
- Award/grant managed by other NIH IC (culture change)
Communication!

- Monthly RDCRN Steering Committee calls, two in person meetings in Washington DC area
- Monthly meeting with NIH Institutes~50 medical officer and program officers
- Biweekly meetings with RDCRN-DMCC
- Quarterly calls with RDCRN-CPAG
- Individual RDCRN-Consortium calls with PAG’s participation
RDCRN-Data Management and Coordinating Center (DMCC)

• Supports RDCRN by providing technologies, tools to collect clinical research data and support for study design and data analysis

• On-line protocol management system
  ➢ Web-based patient enrollment (recruitment and referral)
  ➢ Data entry and collection with data standards
  ➢ Adverse event reporting

• Provides protocol training for research staff
Responsibilities of RDCRN-DMCC (Cont.)

- Works with the individual NIH Institutes’ Data and Safety Monitoring Boards to establish protocols for Adverse Events notification and reporting
- Monitor Network protocol adherence, data collection and data submission
- Coordinates site visits for auditing individual consortia sites
Responsibilities of RDCRN DMCC (Cont.)

- Provides a user-friendly web resource site for the public, research scientists, and clinicians; involvement of PAGs (>2 million hits/year)
- Maintain members’ website, documentation and database
- Oversees and maintains RDCRN Patient Contact Registry
RDCRN Protocol Activation

Data as of September 24, 2015

Median time to activation from initial protocol review
N = number of activated protocols
RDCRN Contact Registry (2004)  
(U.S. Geographic Distribution of Contact Registrants)

- Enrollment open to patients with diseases under study by Consortia

- Provides international online system for communication, recruitment, research
RDCRN Contact Registry Overview
(World Geographic Distribution of Contact Registrants)
Data as of August 31, 2015

- 213 diseases represented
- 109 countries
- 16,512 total registrations
- 39% referred from PAGs
- 38% from internet
- 6% referred from med. prof.
- 260,000+ email communications

Goals: To inform registrants about RDCRN studies available; To disseminate information about RDCRN activities
Electronic Regulatory Binder (New Initiative)

- Implemented January 2015
  - DMCC added historical documents (IRB approvals, DSMB determinations, etc.) for RDCRN consortia
- **Online access** to consortium regulatory documents
- Implemented September 1, 2015: *Remote auditing* of regulatory documents for RDCRN audits
  - Smaller audit teams
  - Less time on site
  - Cost savings
Data Sharing
(ORDR, NCATS Data Repository)

• The RDCRN-DMCC also coordinates with ORDR program staff including registration with and data uploading of appropriate RDCRN studies to ORDR-governed data repository

• Through dbGaP, a database for genotypes and phenotypes (NCBI, National Library of Medicine)

• Data transfer to dbGaP occurs on regular basis

• RDCRN Data Access Committee (DAC)
## Collaboration with Industry

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Pharmaceutical Company</th>
<th>Description</th>
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<tbody>
<tr>
<td>Ucyclyd Pharma, Inc.</td>
<td>Drug</td>
<td></td>
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<tr>
<td>Orphan Europe</td>
<td>Drug</td>
<td></td>
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<tr>
<td>Orphan Europe</td>
<td>Full funding</td>
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<tr>
<td>Bristol-Myers Squibb</td>
<td>Supplemental funding and drug</td>
<td></td>
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<tr>
<td>Bristol-Myers Squibb</td>
<td>Supplemental funding and drug</td>
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<tr>
<td>Office of Orphan Products Development</td>
<td>Full funding and drug</td>
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</tr>
<tr>
<td>Roche, Genentech</td>
<td>Supplemental funding and drug</td>
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<tr>
<td>Bristol-Myers Squibb</td>
<td>Full funding and drug</td>
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<tr>
<td>Baxter</td>
<td>Drug (IVIG)</td>
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<tr>
<td>Novartis Corporation, Genentech</td>
<td>Drug</td>
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<tr>
<td>GlaxoSmithKline</td>
<td>Drug</td>
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<tr>
<td>Merck &amp; Co., Inc.</td>
<td>Drug</td>
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<tr>
<td>Genzyme Corporation, Shire HGT</td>
<td>Supplemental funding</td>
<td></td>
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<tr>
<td>Shire HGT</td>
<td>Supplemental funding</td>
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<tr>
<td>Genzyme Corporation</td>
<td>Supplemental funding</td>
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<td>Genzyme Corporation</td>
<td>Supplemental funding</td>
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<tr>
<td>Genzyme Corporation</td>
<td>Funding for processing of whole blood sample, skin fibroblasts and mutation analysis</td>
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<tr>
<td>Amicus Therapeutics, Shire HGT, Genzyme Corpor</td>
<td>Supplemental funding</td>
<td></td>
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<tr>
<td>Genzyme Corporation</td>
<td>Supplemental funding</td>
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<tr>
<td>BioMarin Pharmaceutical, Inc.</td>
<td>Supplemental funding (vials of Aldurazyme from commercial source)</td>
<td></td>
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<tr>
<td>Genentech</td>
<td>Drug</td>
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<tr>
<td>Genentech</td>
<td>Full Funding &amp; drug</td>
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## RDCRN Accomplishments

Data current as of January 14, 2015

<table>
<thead>
<tr>
<th>Category</th>
<th>1st Cycle 8/1/03-7/31/09</th>
<th>2nd Cycle 8/1/09-7/31/14</th>
<th>3rd Cycle 8/1/14-present</th>
<th>Total</th>
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<tbody>
<tr>
<td>Consortia</td>
<td>10</td>
<td>17</td>
<td>22</td>
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<tr>
<td>Activated protocols</td>
<td>38</td>
<td>98</td>
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<td>140</td>
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<td>Participants enrolled on studies</td>
<td>5,556</td>
<td>22,728</td>
<td>2,346</td>
<td>30,630</td>
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<tr>
<td>Participants joined the Contact Registry</td>
<td>5,177</td>
<td>10,705</td>
<td>846</td>
<td>16,728</td>
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<td>Journal Articles</td>
<td>257</td>
<td>907</td>
<td>35</td>
<td>1,199</td>
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<tr>
<td>Books and book chapters</td>
<td>30</td>
<td>96</td>
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<td>Conference papers</td>
<td>111</td>
<td>157</td>
<td>0</td>
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<td>Conference proceedings</td>
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<td>150</td>
<td>0</td>
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<tr>
<td>Trainees</td>
<td>48*</td>
<td>160</td>
<td>Unknown</td>
<td>208</td>
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<td>Audits</td>
<td>71</td>
<td>402</td>
<td>42</td>
<td>515</td>
</tr>
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</table>

*Do not have trainee information from all RDCRN1 consortia*
An Example of Collaboration/Scientific Advancements: The Urea Cycle Disorders Consortia at Children’s National Medical Center
Dr. Mark Batshaw (PI)

- 19 Academic Research Centers in USA and 2 International Sites
- Collaborators With European Registry And Network For Intoxication Type Metabolic Disorders (EIMD)
- Industry Partnerships - 3 Products Approved
  - Ucyclyd Pharma: Ammonul
  - Recordati: Carbaglu
  - Hyperion: Ravicti
- Patient Advocacy Group - The National Urea Cycle Disorders Foundation
- Foundations - O’Malley Family Foundation, Kettering Fund, Rotenberg Family Foundation, and Dietmar-Hopp Foundation
- ORDR/NCATS and NICHD (from NIH), providing support and scientific collaboration
Another Example: RDCRN-Rare Lung Diseases Consortium (RLDC)

- In early 2015 FDA accepted for priority review a supplemental New Drug Application for (sNDA) RAPAMUNE® for the treatment of lymphangioleiomyomatosis (LAM)
- LAM is a rare, progressive lung disease that primarily affects women of childbearing age that is often fatal. (March/2015 FDA approval)
- *This is the first drug approved for the treatment of LAM!*
- This is an accomplishment of the Multicenter International LAM Efficacy and Safety of Sirolimus (MILES) Trial (conducted by Dr. Francis McCormack of RDCRN RLDC in collaboration with LAM Foundation). The sNDA was based on results from the MILES Trial. (Wyeth)
  - *Collaborative effort!*
Genetic Disorders of Mucociliary Clearance Consortium & Primary Ciliary Diskinesia (PCD) Foundation

- Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD foundation consensus recommendations based on state of the art review.

- Pediatric Pulmonology. September 29, 2015

Through the RDCRN program......

- New diagnostic methods have been generated
- New gene identification has been facilitated and
- New therapies have been identified.

by creating collaborative multidisciplinary, multi-site research consortia consisting of PAGs, academic researchers from domestic and international sites and project scientists from NIH as collaborators, the program has demonstrated that collaborative effort can accelerate clinical research.
The RDCRN program......

Has proven to be an effective model to

- Maximize investigator participation
- Initiate clinical trials
- Facilitate patient recruitment
- Accelerate young investigator training and
- Engage patient support

*enabling pharmaceutical industry and government sponsored research clinical studies to proceed with a supportive infrastructure to complete the clinical studies in a timely fashion.*
Team Work!

- Clinical Sites
- Principal and co-investigators and the DMCC (multidisciplinary group)
- Trainees
- Study Coordinators
- Patient Advocacy Groups (PAGs)
- Pharmaceutical industry
- ORDR/NCATS and NIH Institutes staff (program officers and project scientists)
- Patients

RDCRN: Working model for collaborative, multi-site clinical studies with PAGs partnership in an inexpensive way!

RDCRN consists of 253 sites, more than 130 PAGs and conducts research on more than 282 rare diseases
RDCRN: An Effective and Working Model for Collaborative Multi-Site Rare Diseases Research Efforts

Initiative of the National Center for Advancing Translational Sciences (NCATS)
Thanks for your attention!

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