

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

INTERNATIONAL CONFERENCE ON RARE DISEASES  
AND ORPHAN DRUGS

MEXICO CITY, MEXICO  
OCTOBER 16TH, 2015

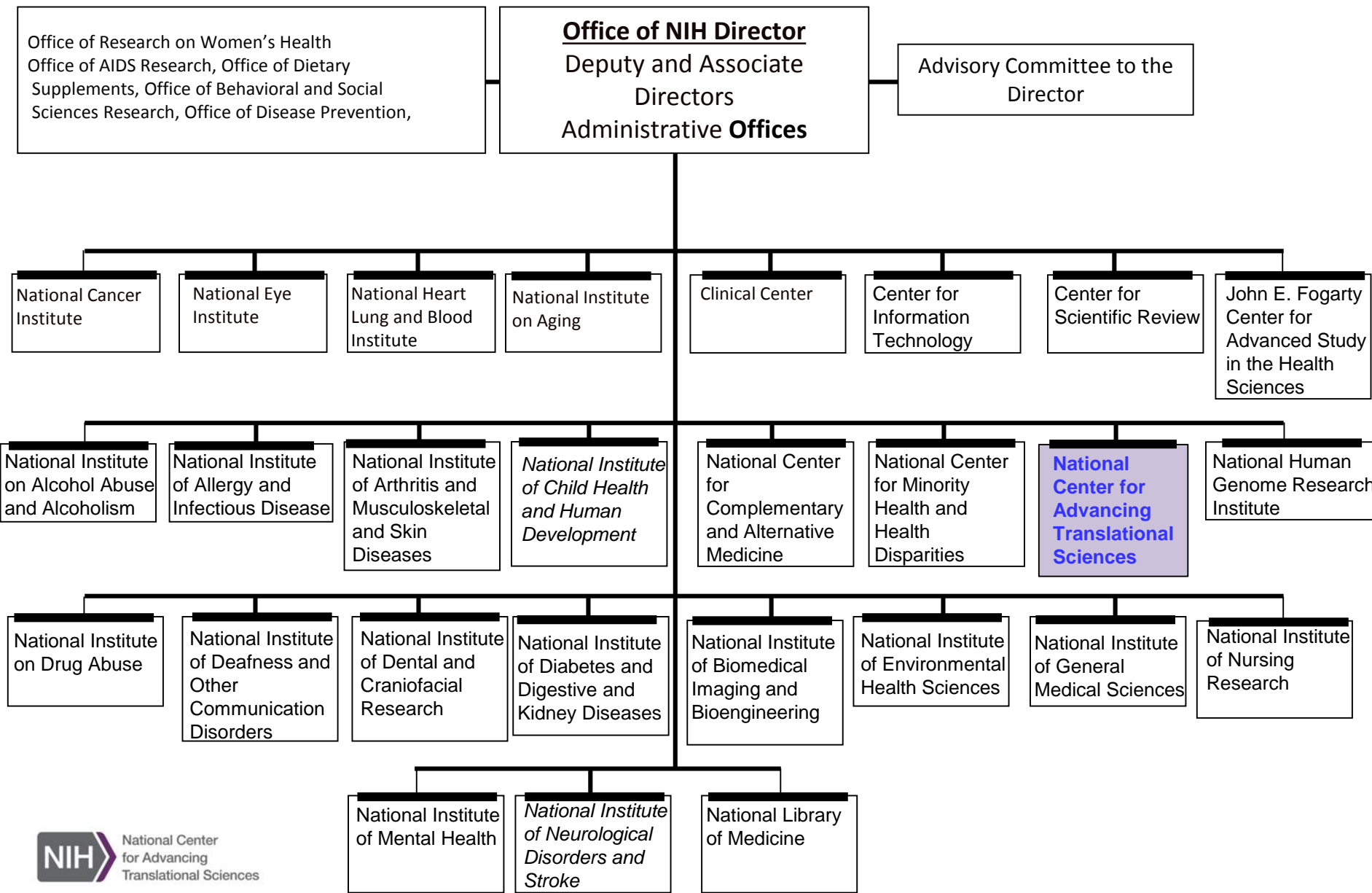
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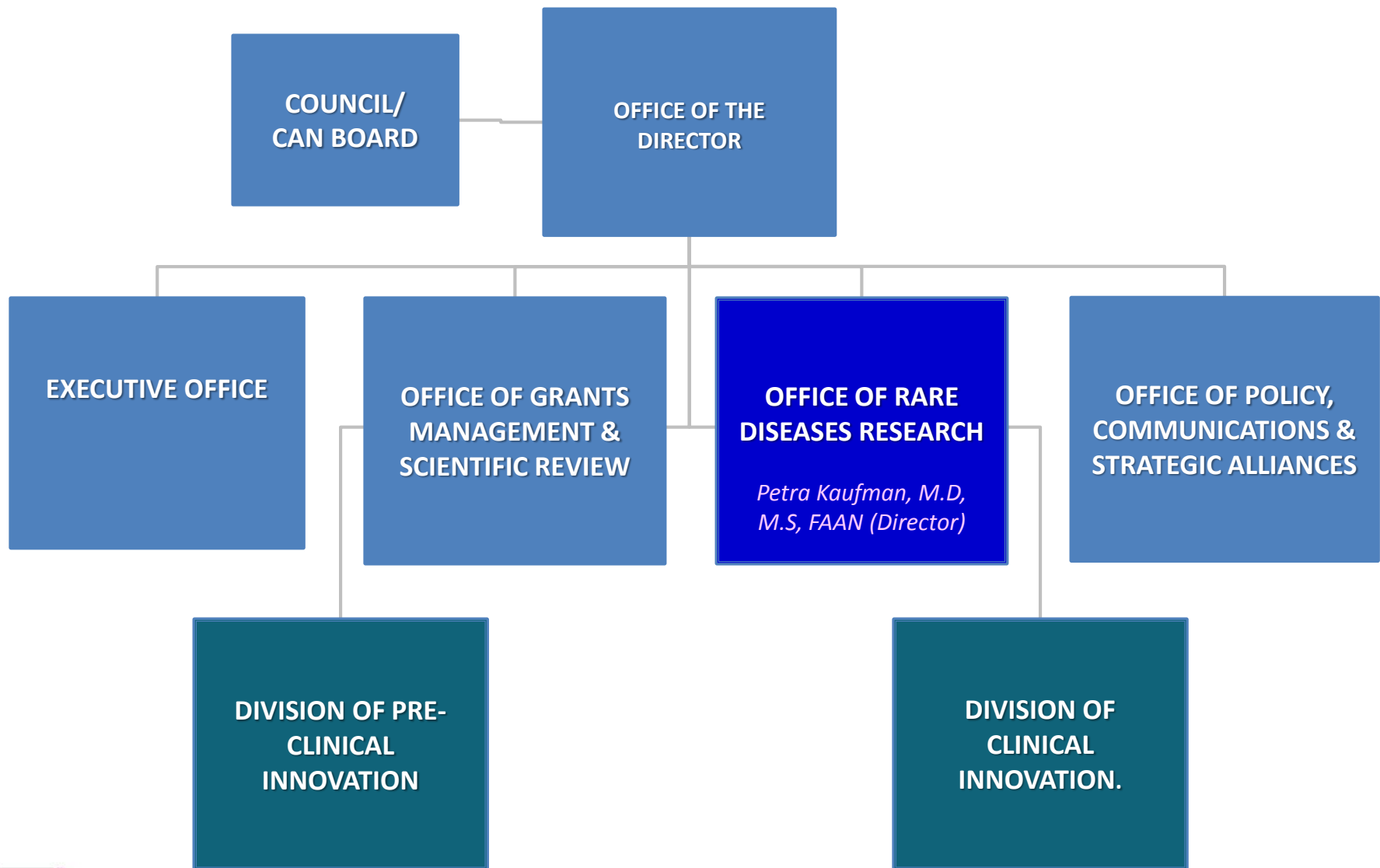
# Conflict of Interest

No COI to disclose

# A View of the National Institutes of Health (NIH), USA



# National Center for Advancing Translational Sciences (NCATS)



# 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

The logo features a stylized, overlapping circular design in shades of yellow and orange, resembling a flower or a network of interconnected nodes. The text "RARE DISEASES CLINICAL RESEARCH NETWORK" is overlaid on this design in a dark blue, serif font. The words "RARE DISEASES" and "RESEARCH NETWORK" are on the right, while "CLINICAL" is on the left, partially obscured by the circular design.

# RARE DISEASES CLINICAL RESEARCH NETWORK

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

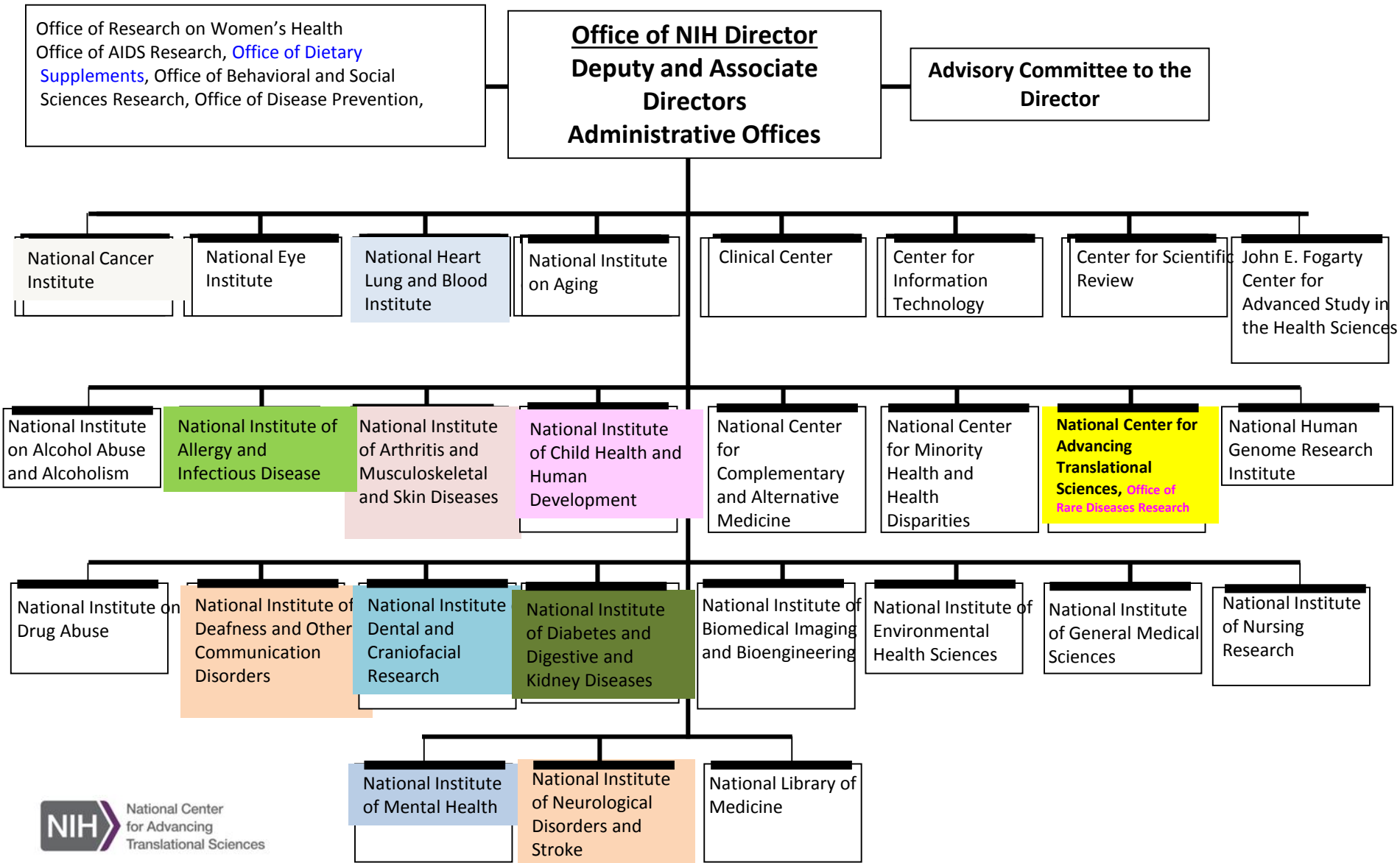


# RDCRN: Objective

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



# 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).

## ORDR/NCATS

(NCI, NHLBI, NIAID, NIAMS,  
NICHD, NIDCR, NIDDK, NIMH,  
NINDS, ODS)

Dystonia  
Coalition

Coalition of Patient  
Advocacy Groups  
(CPAG)

Porphyria Rare Disease Clinical  
Research Consortium

PAG

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

Sterol and Isoprenoid  
Diseases Consortium

Autonomic Disorders  
Consortium

Developmental Synaptopathies  
Associated with TSC, PTEN  
And SHANK3 Mutations

The Frontotemporal Lobar  
Degeneration Clinical  
Research Consortium

Inherited Neuropathies  
Consortium

Nephrotic Syndrome  
Study Network

Rare Lung Diseases  
Consortium

Lysosomal  
Disease Network

Rare Kidney  
Stone Consortium

Vasculitis Clinical  
Research Consortium

Clinical Research in ALS & Related  
Disorders for Therapeutic Development



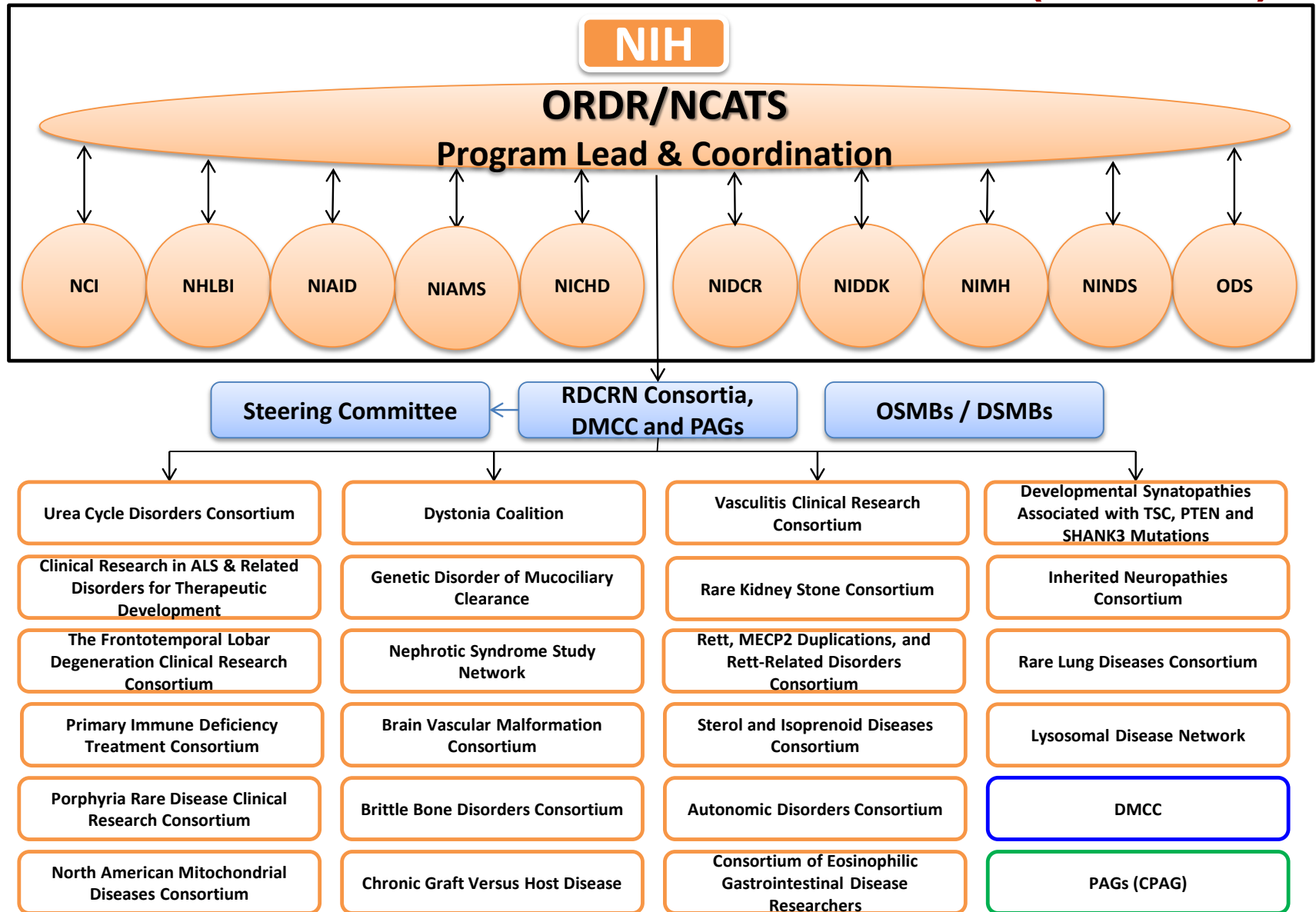
- Collaborative Clinical Research
- Centralized Data Coordination and Technology Development
- Public Resources and Education
- Training



# RDCRN Protocols

Type of Study	Number of Protocols
Pilot	17
Longitudinal	50
Phase I	1
Phase II	6
Phase III	4
IND	5
Industry Sponsored	12
Case Control	1
Chart Review	2

# Rare Disease Clinical Research Network 3 (RDCRN 3)



# 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 U.S. Sites

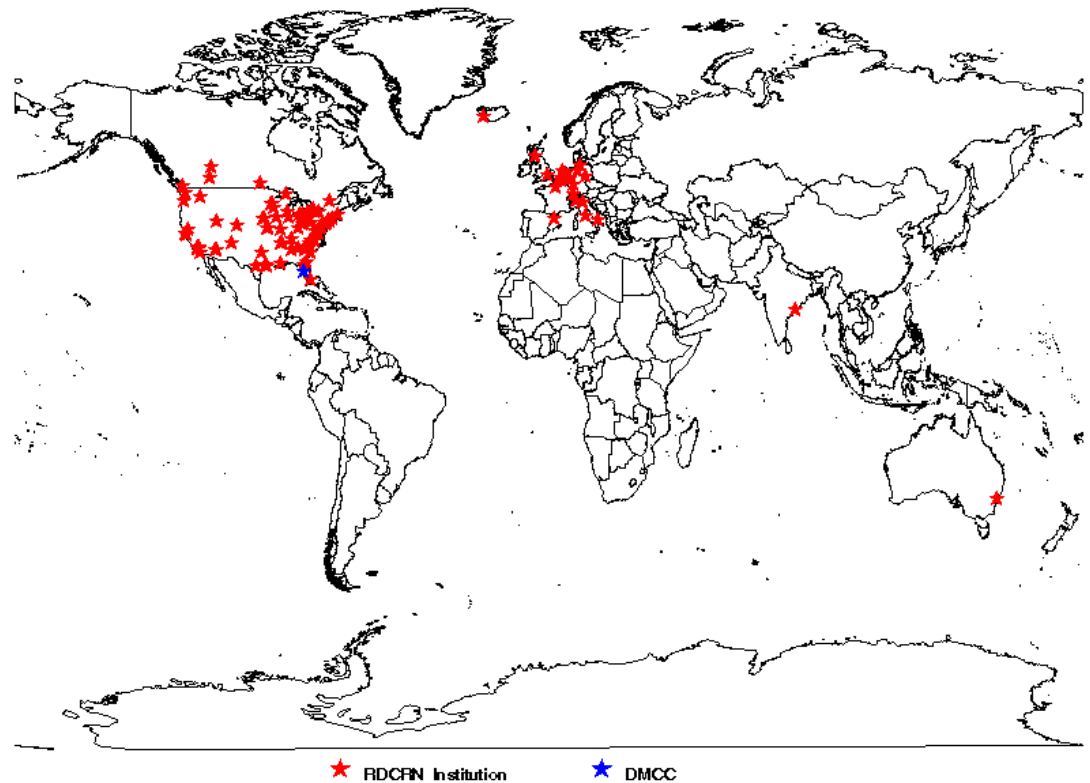


★ RDCRN Institution

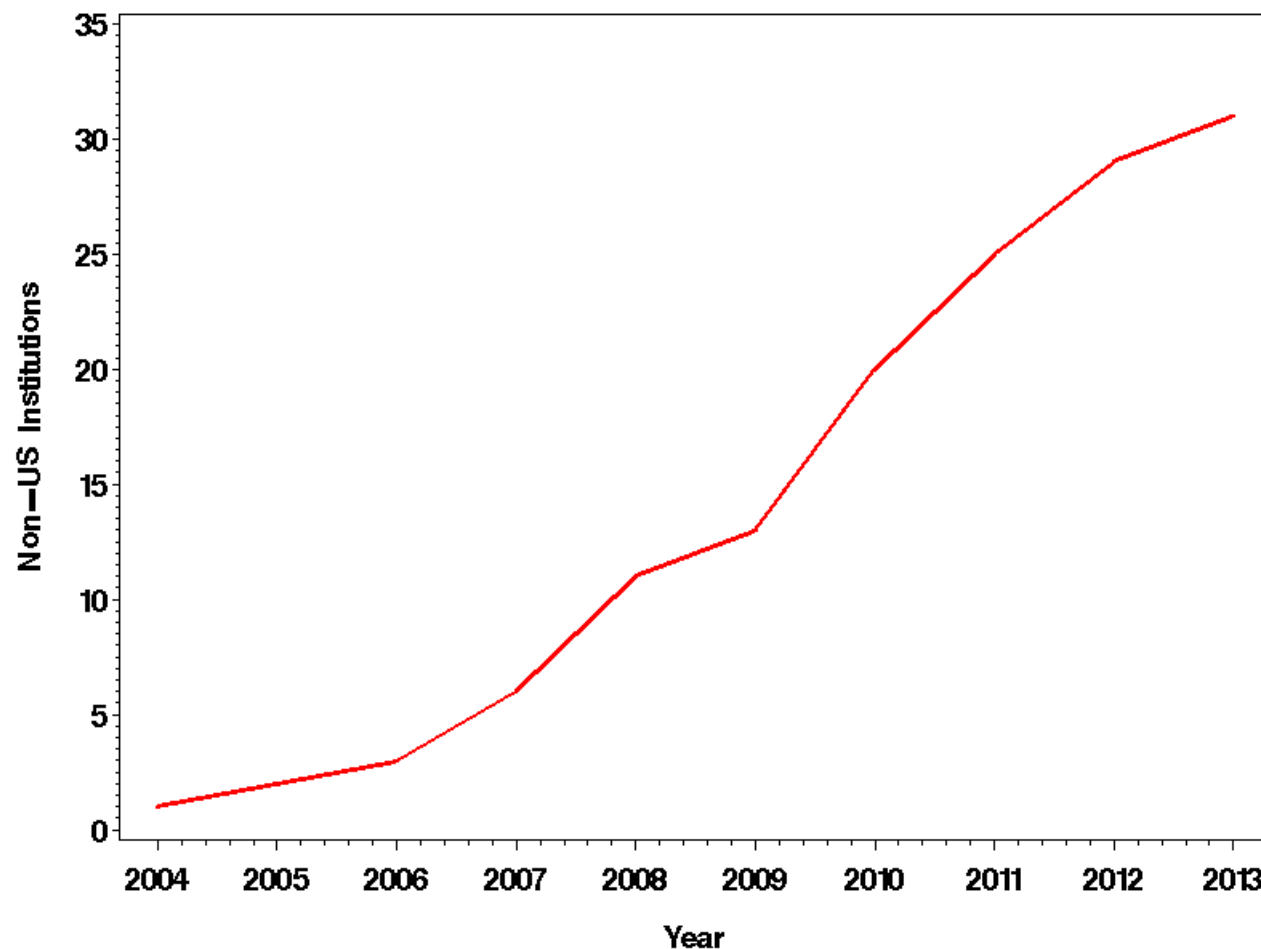
★ DMCC

# RDCRN International Sites

- Australia
- Austria
- Belgium
- Canada
- England
- France
- Germany
- Iceland
- India
- Italy
- Netherlands
- Scotland
- Spain
- Switzerland

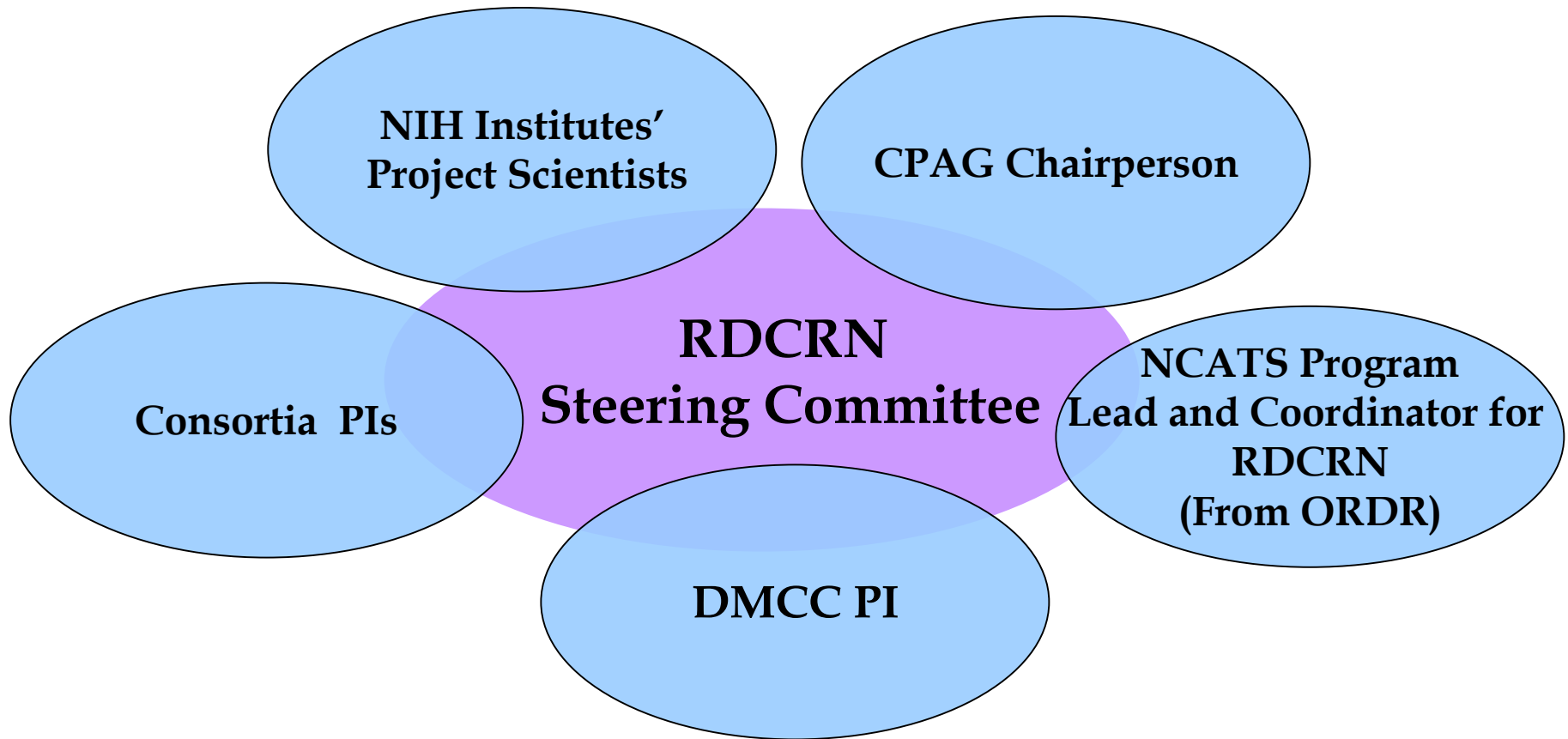


# RDCRN Activated International Sites Over Time



# RDCRN Steering Committee Organization

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





# 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.)

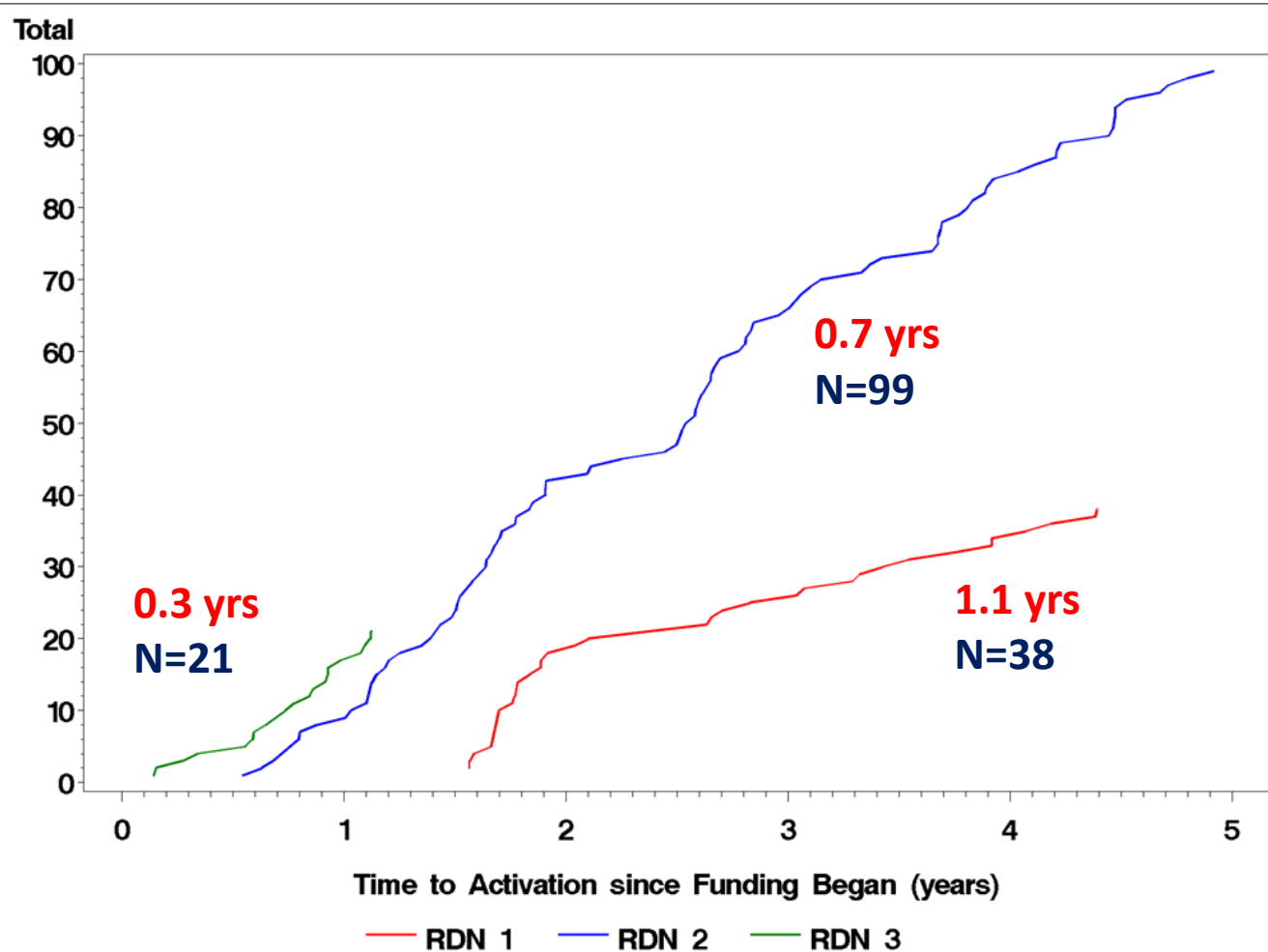
- Works with the individual NIH Institutes' Data and Safety Monitoring Boards to establish protocols for Adverse Events notification and reporting
- Monitor Network protocol adherence, data collection and data submission
- Coordinates site visits for auditing individual consortia sites

## 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

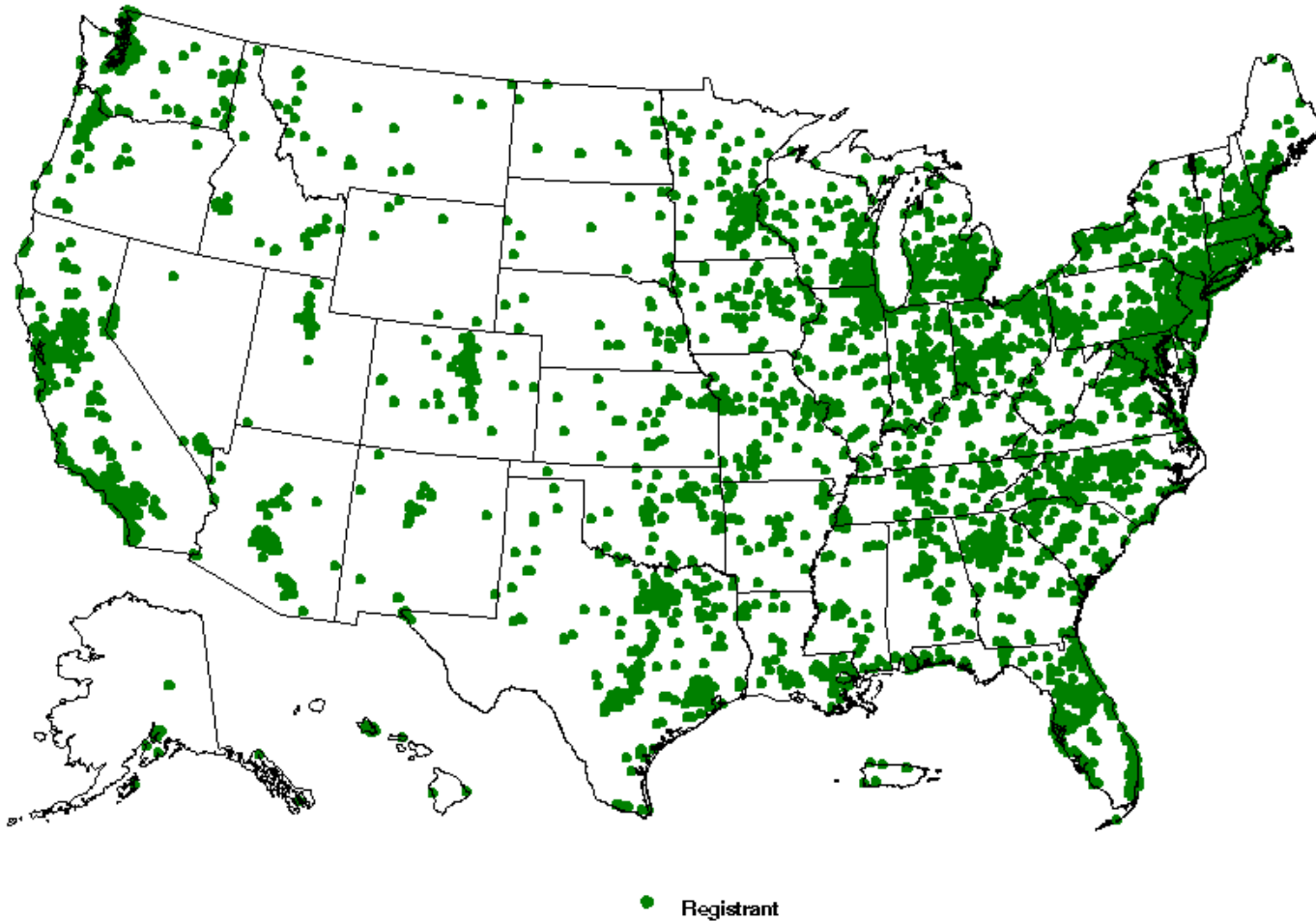
Data as of September 24, 2015



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

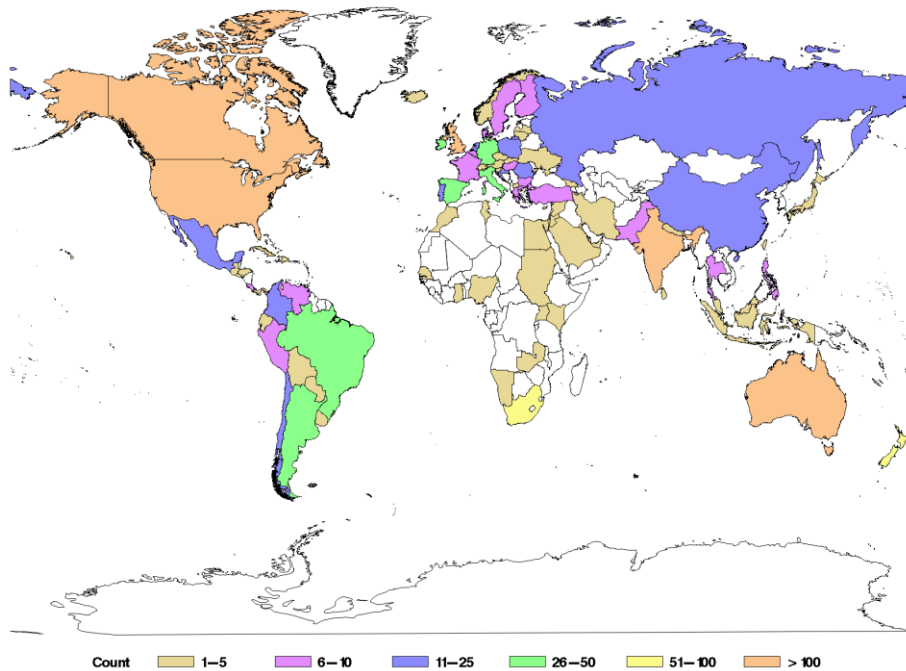
- Provides international on-line system for communication, recruitment, research



# 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

Protocol	Pharmaceutical Company	
	Ucyclyd Pharma, Inc.	Drug
	Orphan Europe	Drug
	Orphan Europe	Full funding
	Bristol-Myers Squibb	Supplemental funding and drug
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	Office of Orphan Products Development	Full funding and drug
	Roche, Genentech	Supplemental funding and drug
	Bristol-Myers Squibb	Full funding and drug
	Baxter	Drug (IVIG)
	Novartis Corporation, Genentech	Drug
	GlaxoSmithKline	Drug
	Merck & Co., Inc.	
	Genzyme Corporation, Shire HGT	Supplemental funding
	Shire HGT	Supplemental funding
	Genzyme Corporation	Supplemental funding
	Genzyme Corporation	Funding for processing of whole blood sample, skin fibroblasts and mutation analysis
	Amicus Therapeutics, Shire HGT, Genzyme Corporation	Supplemental funding
	BioMarin Pharmaceutical, Inc.	Supplemental funding (vials of Aldurazyme from commercial source)
	Genentech	Drug
	Genentech	Full Funding & drug

# RDCRN Accomplishments

Data current as of January 14, 2015

	1 <sup>st</sup> Cycle 8/1/03- 7/31/09	2 <sup>nd</sup> Cycle 8/1/09- 7/31/14	3 <sup>rd</sup> Cycle 8/1/14- present	Total
Consortia	10	17	22	
Activated protocols	38	98	4	140
Participants enrolled on studies	5,556	22,728	2,346	30,630
Participants joined the Contact Registry	5,177	10,705	846	16,728
Journal Articles	257	907	35	1,199
Books and book chapters	30	96	0	126
Conference papers	111	157	0	268
Conference proceedings	9	150	0	159
Trainees	48*	160	Unknown	208
Audits	71	402	42	515

\*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
- Shapiro AJ, Zariwala MA, Ferkol T, Davis SD, Sagel SD, Dell SD, Rosenfeld M, Olivier KN, Milla C, Daniel SJ, Kimple AJ, Manion M, Knowles MR, Leigh MW



# 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!

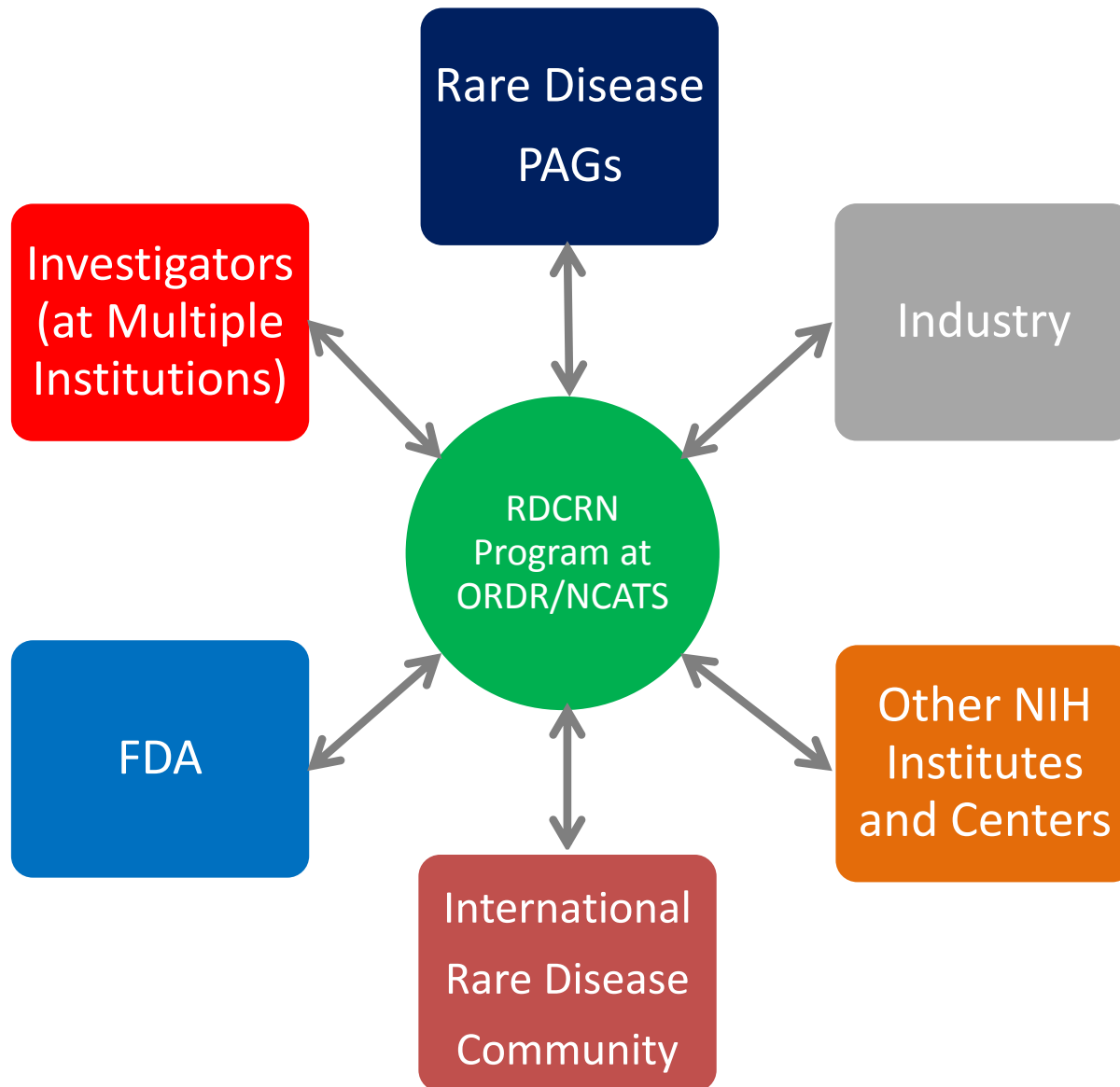
- Clinical Sites
- Principal and co-investigators and the DMCC (multidisciplinary group)
- Trainees
- Study Coordinators
- Patient Advocacy Groups (PAGs)
- Pharmaceutical industry
- ORDR/NCATS and NIH Institutes staff (program officers and project scientists)
- *Patients*

**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***





# Thanks for your attention!

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# NCATS