NCATS
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NIH National Institute of Neurological Disorders and Stroke

RARE DISEASES CLINICAL RESEARCH NETWORK

Tiina K. Urv, Ph.D.

NIH – NCATS

Office of Rare Diseases Research

NIH National Center for Advancing Translational Sciences

RARE DISEASES CLINICAL RESEARCH NETWORK

Established by Rare Diseases Act of 2002
(Public Law 107-280)

*"planning, establishing, or strengthening, and providing basic operating support for **regional centers of excellence** for clinical research into, training in, and demonstration of diagnostic, prevention, control, and treatment methods for rare diseases"*

Established 2003
Recompeted every 5 years

Division of Rare Diseases Research Innovation

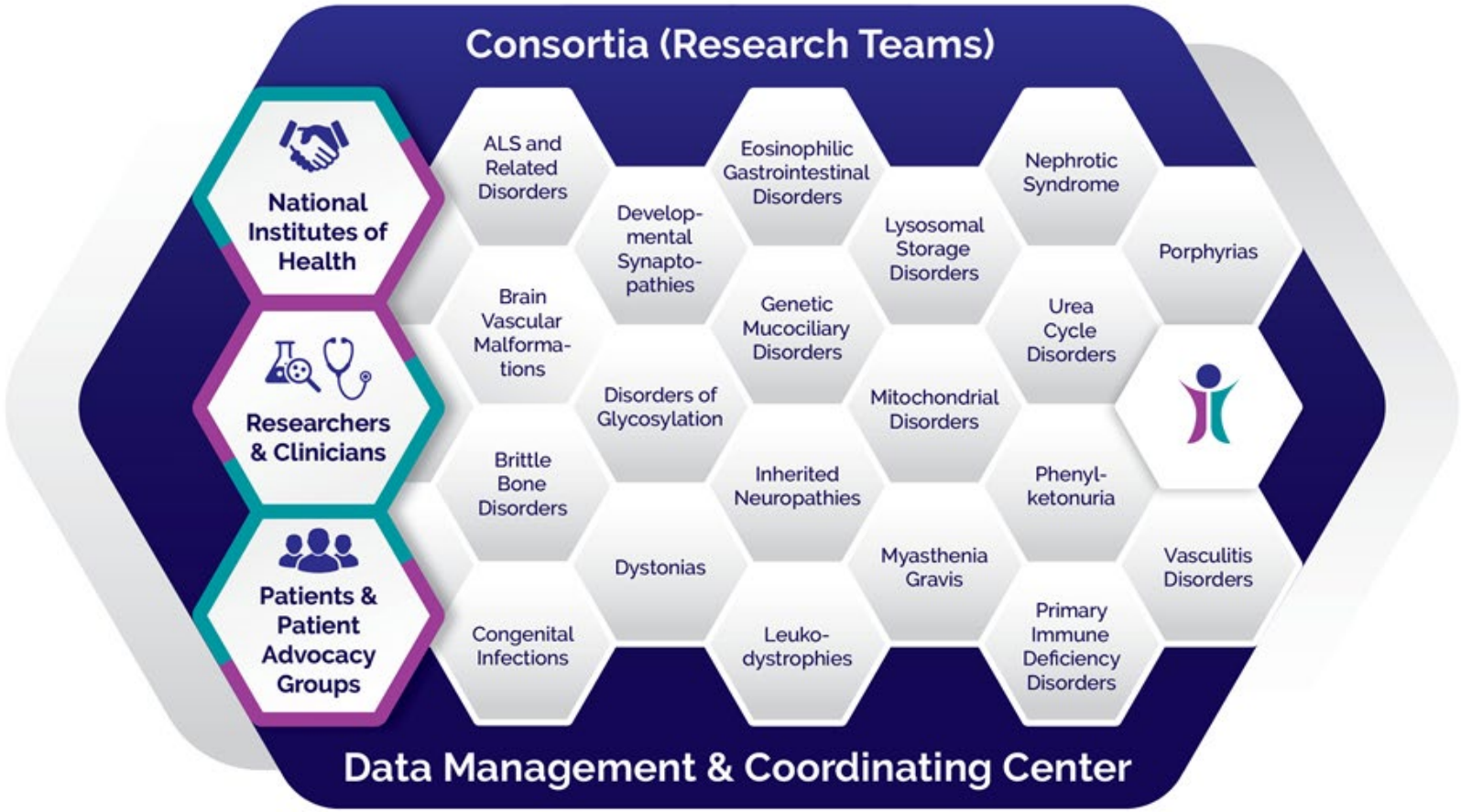
Tiina Urv, Ph.D
Program Director

Joanne Lumsden, Ph.D.
Scientific Program Manager

Consortium Acronym	Consortium Name	RDCRN1 2003-2008	RDCRN2 2009-2013	RDCRN3 2014-2018	RDCRN4 2019-2023
GDMCC	Genetic Disorders of Mucociliary Clearance Consortium	X	X	X	X
UCDC	Urea Cycle Disorders Consortium	X	X	X	X
VCRC	Vasculitis Clinical Research Consortium	X	X	X	X
PC	Porphyrias Consortium		X	X	X
NAMDC	North American Mitochondrial Disease Consortium		X	X	X
DC	Dystonia Coalition		X	X	X
BVMC	Brain Vascular Malformation Consortium		X	X	X
NEPTUNE	Nephrotic Syndrome Study Network		X	X	X
PIDTC	Primary Immune Deficiency Treatment Consortium		X	X	X
INC	Inherited Neuropathy Consortium		X	X	X
LDN	Lysosomal Disease Network		X	X	X
CReATe	Clinical Research in ALS and Related Disorders for Therapeutic Development			X	X
BBDC	Brittle Bone Disorders Consortium			X	X
CEGIR	Consortium of Eosinophilic Gastrointestinal Disease Researchers			X	X
DSC	Developmental Synaptopathies Consortium			X	X
PHEFREE	Phenylalanine Families and Researchers Exploring Evidence				X
MGNet	Myasthenia Gravis Rare Disease Network				X
CPIC	Congenital and Perinatal Infections Consortium				X
FCDGC	Frontiers in Congenital Disorders of Glycosylation				X
GLIA-CTN	Global Leukodystrophy Initiative Clinical Trials Network				X
RTT	Rett Syndrome, MECP2 Duplications, and Rett-related Disorders Consortium	X	X	X	
RKSC	Rare Kidney Stone Consortium		X	X	
STAIR	Sterol and Isoprenoid Diseases Consortium		X	X	
ADC	Autonomic Disorders Consortium		X	X	
RLDC	Rare Lung Diseases Consortium	X		X	
ARTFL	Advancing Research and Treatment for Frontotemporal Lobar Degeneration Consortium			X	
CINCH	Clinical Investigation of Neurologic Channelopathies	X	X		
SGCC	Salivary Gland Carcinomas Consortium		X		
cGVHD	Chronic Graft Versus Host Disease Consortium (cGVHD)		X		
BMFC	Bone Marrow Failure Consortium	X			
RGSDC	Rare Genetic Steroid Disorders Consortium	X			
RTDC	Rare Thrombotic Diseases Consortium	X			
CLiC	Cholestatic Liver Disease Consortium	X			

RARE DISEASES
CLINICAL RESEARCH NETWORK

A network of 20 research teams collaborating to achieve faster diagnosis and better treatments for patients with rare diseases



National Center for Advancing Translational Sciences | National Institute of Neurological Disorders and Stroke | National Institute of Allergy and Infectious Diseases | National Institute of Diabetes and Digestive and Kidney Diseases | *Eunice Kennedy Shriver* National Institute of Child Health and Human Development | National Institute of Arthritis and Musculoskeletal and Skin Diseases | National Heart, Lung, and Blood Institute | National Institute of Dental and Craniofacial Research | National Institute of Mental Health | Office of Dietary Supplements

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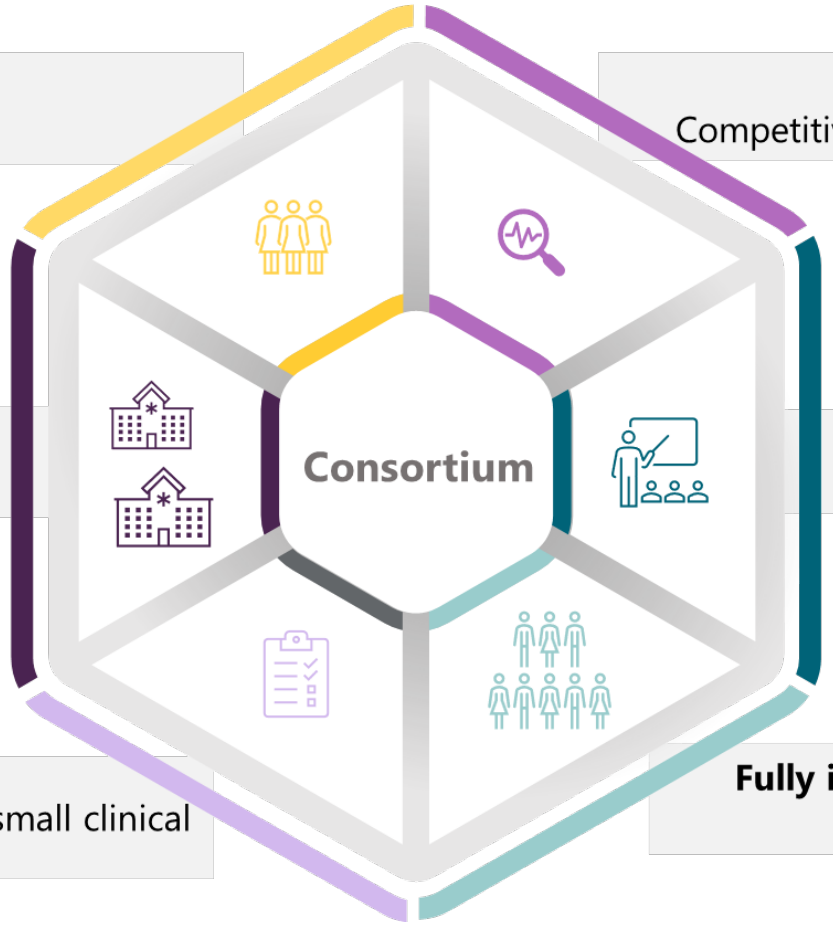
Rare Diseases Clinical Research Consortium

Three or more disorders
Mean = 9 disorders

Pilot Studies
Competitive within the consortium's discretion



Multiple sites
Mean =19 sites Range – 5 - 42

Career enhancement core.
e.g., Competitive scholar awards

Three – Five clinical studies
e.g., Natural History, biomarkers, small clinical trials, outcome measures

Fully integrated patient advocacy group
Mean = 9 Range 1-60

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RARE DISEASES CLINICAL RESEARCH NETWORK

RDCRN Clinical Sites

Active Sites	Unique Locations
358	197

Site	# of consortia
Children's Hospital of Philadelphia	9
Baylor College of Medicine	8
Mayo Clinic	8
University of Minnesota	8
University of Utah	8
Children's Hospital Colorado	7
Seattle Children's Hospital	7
Stanford University	7
Boston Children's Hospital	6
Children's National Medical Center	6
Duke University	6
Massachusetts General Hospital	6
Washington University in St. Louis	6
Cleveland Clinic	5
Johns Hopkins University	5
University of Alabama at Birmingham	5
University of California, Los Angeles	5
University of California, San Francisco	5
University of Miami	5
University of Pennsylvania	5

Country	# of sites
Australia	2
Belgium	1
Canada	18
England	13
Germany	3
India	1
Ireland	1
Italy	2
Netherlands	1
South Africa	1
Switzerland	1

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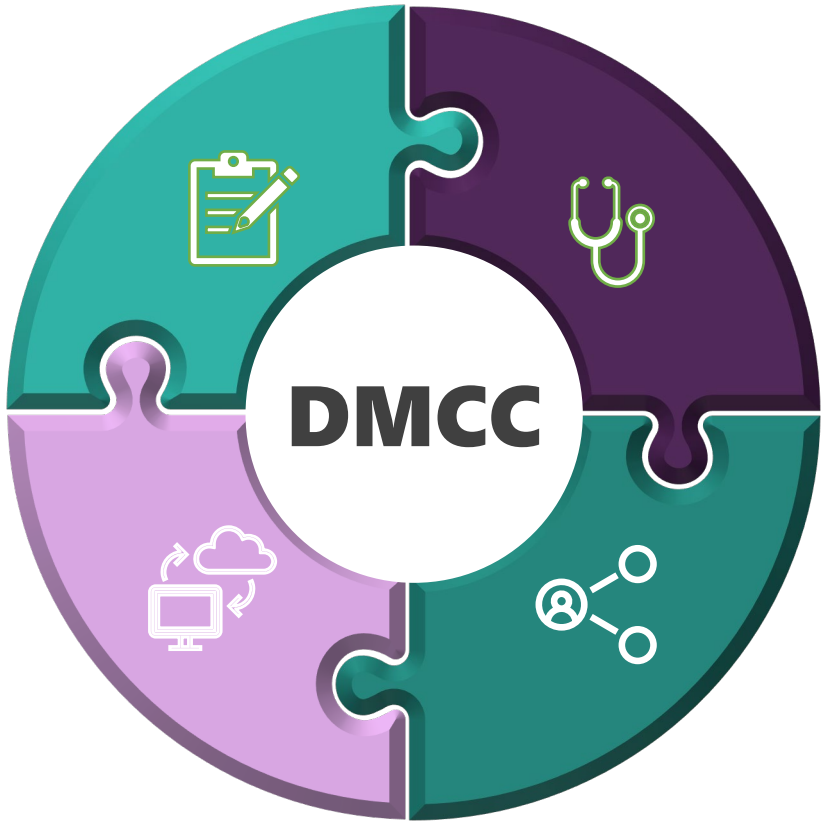
RARE DISEASES CLINICAL RESEARCH NETWORK

RDCRN Data Management and Coordinating Center

Administrative Support

Facilitates network operations, governance and communication.



Clinical Research Support

Supports best practices in clinical research, protocol development and good data practices (FAIR)

Data Management

Builds and maintains a robust, secure data infrastructure for the RDCRN working closely with NCATS

Engagement and Dissemination

Promote patient engagement and broad research dissemination

RDCRN Translational Impact

RARE DISEASES CLINICAL RESEARCH NETWORK

Clinical Trials directly funded by U54 grant

- Predominantly small **Phase 1/Phase 2**
- Currently 18 trials funded in RDCRN4
- Primarily repurposed drugs, diets, supplements, procedures, devices, some novel drugs

RDCRN-associated Clinical Trials

- Predominantly **Phase 2/Phase 3**
- Funded by industry, IC-specific grants, FDA, PAGs
- Leveraging disease phenotype, patient population, clinical sites, endpoints, biomarkers, early phase safety and efficacy data
- *No NCATS $$ involved*

11 FDA-approved treatments for rare diseases

Consortium	Drug	Other Name	Indication	Company	Approval Date
UCDC	CARBAGLU®	carglumic acid	N-acetylglutamate synthetase (**NAGS**) deficiency	Orphan Europe	March 2010
VCRC	RITUXAN®	rituximab in combination with corticosteroids	Wegener's granulomatosis (**WG**) and microscopic polyangiitis (**MPA**)	Genentech and Biogen	April 2011
UCDC	RAVICTI®	glycerol phenylbutyrate	urea cycle disorders (**UCD**)	Hyperion Therapeutics	February 2013
RLDC	RAPAMUNE®	sirolimus	lymphangioleiomyomatosis (**LAM**)	Pfizer	May 2015
PC	SCENESSE®	afamelanotide	erythropoietic protoporphyria (**EPP**)	Clinuvel	October 2019
PC	GIVLAARI®	givosiran	acute hepatic porphyria (**AHP**)	Alnylam Pharmaceuticals	November 2019
RKSC	OXLUMO®	lumasiran	primary hyperoxaluria type 1 (**PH1**)	Alnylam Pharmaceuticals	November 2020
CEGIR	DUPIXENT®	dupilumab	eosinophilic esophagitis (**EoE**)	Regeneron	May 2022 Jan 2024 (pediatric)
RTT	DAYBUE™	trofinetide	**Rett** syndrome	Acadia Pharmaceuticals	March 2023
MGNet	RYSTIGGO®	rozanolixizumab-noli	generalized myasthenia gravis (**gMG**)	UCB	June 2023
RKSC	RIVFLOZA™	nedosiran	primary hyperoxaluria type 1 (**PH1**)	Novo Nordisk	October 2023

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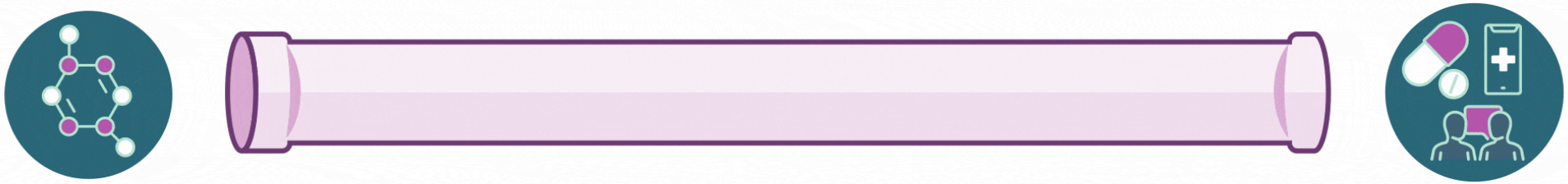
The Translational Pipeline

RDCRN addresses longstanding bottlenecks in the road to developing treatments, to accelerate progress to health solutions -- so that new treatments reach people faster



Operational **Financial/Administrative** **Scientific**

Bottlenecks:	RDCRN Solutions:
▪ Slow	▪ Consortia, Patient Advocacy Involvement, Natural History Studies, Outcome measures, Biomarkers
▪ Expensive	▪ Economies of Scale, Shared Tools, Shared Work Environment
▪ Poor quality Data	▪ Good data practices, FAIR Principles, Scientific Rigor, Reproducibility and Transparency

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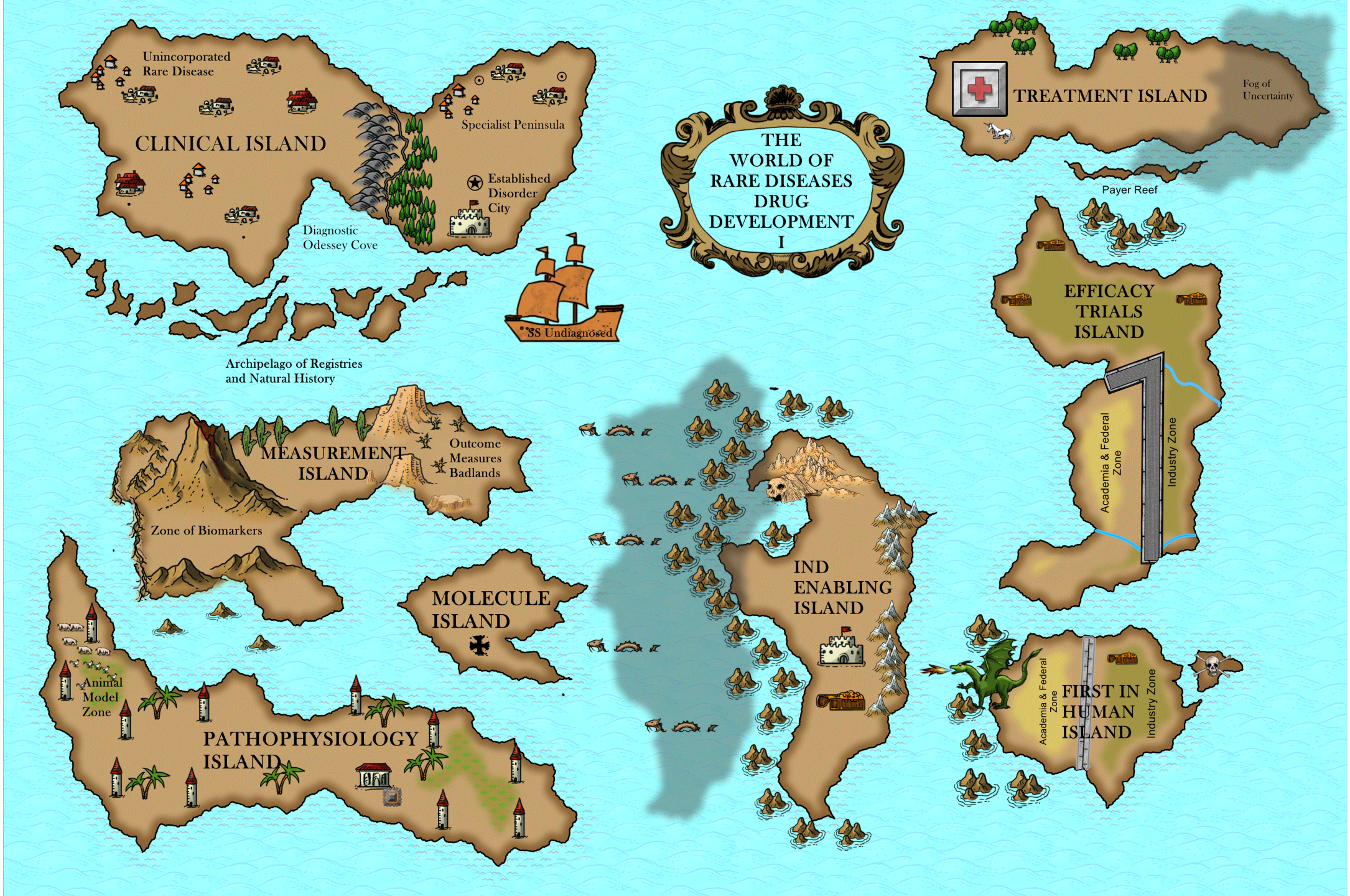
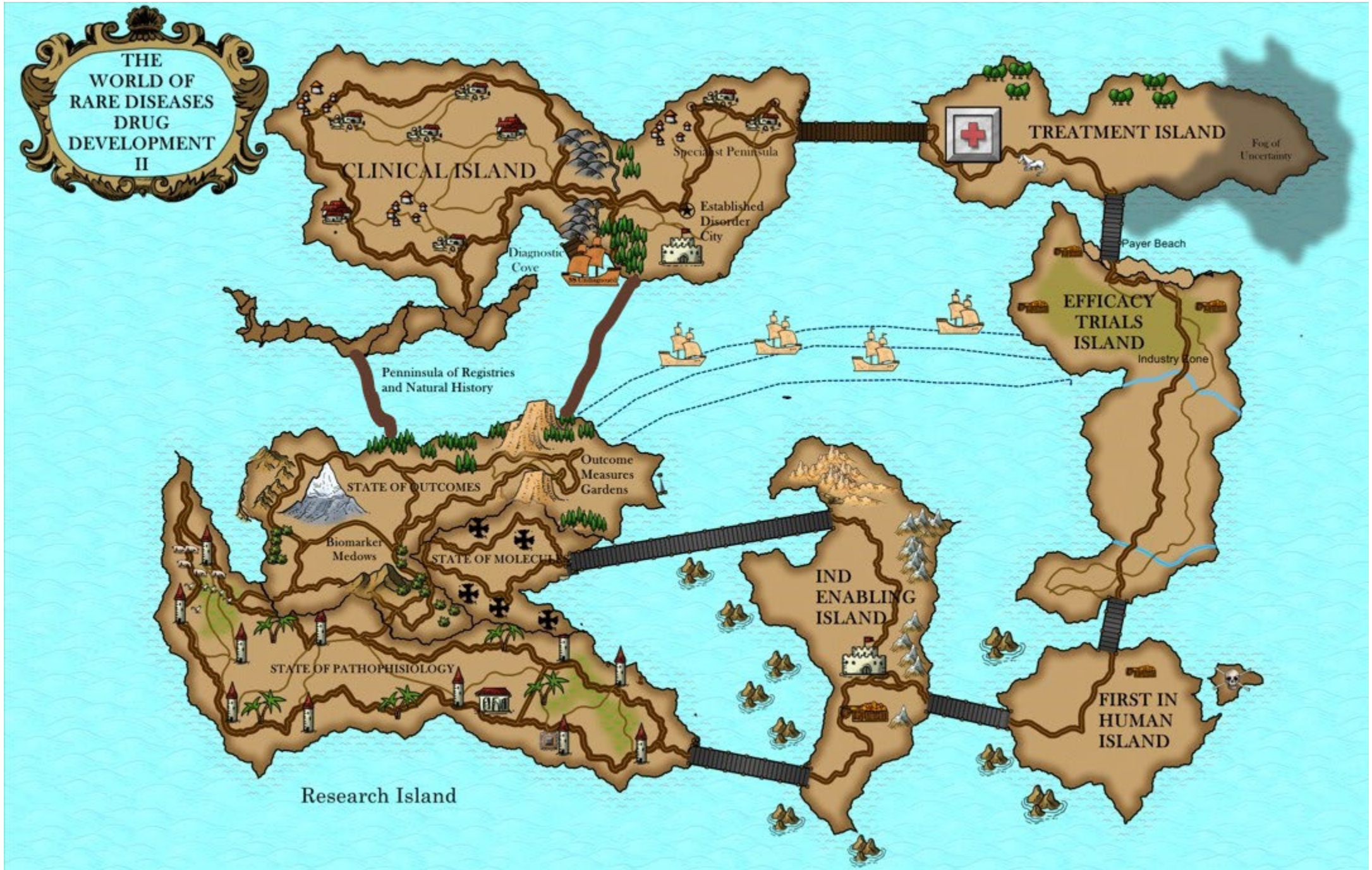

THE WORLD OF RARE DISEASES DRUG DEVELOPMENT I
CLINICAL ISLAND
Unincorporated Rare Disease
Specialist Peninsula
Established Disorder City
Diagnostic Odessey Cove
SS Undiagnosed
Archipelago of Registries and Natural History
TREATMENT ISLAND
Fog of Uncertainty
Payer Reef
EFFICACY TRIALS ISLAND
Academia & Federal Zone
Industry Zone
MEASUREMENT ISLAND
Outcome Measures Badlands
Zone of Biomarkers
MOLECULE ISLAND
IND ENABLING ISLAND
Animal Model Zone
PATHOPHYSIOLOGY ISLAND
FIRST IN HUMAN ISLAND
Academia & Federal Zone
Industry Zone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Industry Zone
Penninsula of Registries and Natural History
Outcome Measures Gardens
STATE OF OUTCOMES
Biomarker Medows
STATE OF MOLECULE
IND ENABLING ISLAND
STATE OF PATHOPHISIOLOGY
FIRST IN HUMAN ISLAND
Research Island

Challenges our RDCRN PIs have shared…more than once

- *“There was no one in the review that knew about rare diseases”*
- *“I have electronic data but the software we are using is not official CFR part 11 compliant. We have all the required information – but we can’t afford the official software. Does that mean we can’t use our data”*
- *“I wish I could just call and talk to someone at the FDA before I even start my study to make sure I don’t go down the wrong track.”*
- *“They keep telling me the evaluations are considered case by case – but I just don’t know what they will want.”*
- *“I really need help with the regulatory side of things my university does not have the bandwidth to provide the help I need.”*
- *“I am a clinician – I know the patients and I know the science, but I need more support to develop the treatments”*

2022 | FDA CDER & NIH NCATS *WORKSHOP*

Regulatory Fitness in Rare Disease Clinical Trials

Monday, May 16: 9 am – 4 pm ET | Tuesday, May 17: 9 am – 12 pm ET

- We shared what we were hearing with our colleagues at the FDA.
- A public meeting was held to respond to many of the common questions that the academic researchers had.
- More meetings are in the pipeline.

Final Agenda

Day 2 — Tuesday, May 17, 2022

9:00 a.m. ET **Welcome**

Kerry Jo Lee, M.D., Associate Director for Rare Diseases, Rare Diseases Team (RDT), Division of Rare Diseases and Medical Genetics (DRDMG), Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA)

9:05 a.m. **Session 5: The Nuts and Bolts of Investigational New Drug (IND) Applications and Additional Considerations**

This session will walk through the IND process and how to prepare for each step, including special considerations for pediatric studies and basics of preclinical packages.

Moderator: *Cynthia Welsh, M.D.*, Medical Officer, RDT, DRDMG, ORPURM, OND, CDER, FDA

Panelists:

- *Mari Suzuki, M.D.*, Medical Officer, DRDMG, ORPURM, OND, CDER, FDA
- *Margaret Kober, R.Ph., M.P.A.*, Chief, Project Management Staff, Division of Regulatory Operations for Urology, Obstetrics, and Gynecology, Office of Regulatory Operations (ORO), CDER, FDA
- *Shamir Tuchman, M.D., M.P.H.*, Medical Officer, Division of Pediatrics and Maternal Health (DPMH), ORPURM, OND, CDER, FDA
- *Arianne L. Motter, Ph.D., DABT*, Senior Toxicologist, Division of Pharmacology and Toxicology for Infectious Diseases (DPTID), Office of Infectious Diseases (OID), OND, CDER, FDA

What are some specific actions that stakeholders (e.g., regulatory agencies, sponsors, researchers) could take to better support the use of this approach for review/approval of drugs to treat rare diseases and conditions?

- Transparency of required information - including data formats and standards
- Academic researchers have the knowledge, but often do not have the resources needed to move a potential treatment forward.
  - Industry has large teams of professionals – academics do not
- Academic researchers and clinicians would benefit from earlier communication with:
  - Regulators
  - Industry