Natural History Studies and Registries in the Development of Rare Disease Treatments

Hybrid Public Workshop

May 13, 2024 | 10am-4pm *(eastern)*

The public meeting will begin shortly

A workshop prepared in collaboration with the Food and Drug Administration and the NIH National Center for Advancing Translational Sciences

REAGAN-UDALL FOUNDATION FOR THE FDA

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This activity is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an award of $97,915 in federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit FDA.gov.

REAGAN-UDALL FOUNDATION FOR THE FDA

Welcome

Susan C. Winckler, RPh, Esq.
Chief Executive Officer
Reagan-Udall Foundation for the FDA

Hybrid Meeting

REAGAN-UDALL FOUNDATION FOR THE FDA

Joining online:
Microphone and video will remain off during the meeting
Share your questions using the Zoom Q&A function

Joining in-person:
Please write your questions on the index cards provided

This public meeting is being recorded
The slides, transcript, and video will be available at www.ReaganUdall.org

Today's Agenda (Eastern Time)

REAGAN-UDALL FOUNDATION FOR THE FDA

10am	Welcome & Opening Remarks
10:15am	"What Are Registries and Natural History Studies" "Why Registries and Natural History Studies are Critical to Rare Disease Treatment Development"
10:30am	Getting Started: Developing Registries and Designing Natural History Studies
11:25am	Addressing Challenges in Registry and Natural History Data Collection
12:25pm	Funding Opportunities
12:40pm	Lunch
1:35pm	Collecting Fit for Purpose Data to Inform Regulatory Decision Making
2:35pm	Case Examples
3:45pm	Closing Remarks & Adjourn

REAGAN-UDALL FOUNDATION FOR THE FDA

Opening Remarks

Patrizia Cavazzoni, MD
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

"What Are Registries and Natural History Studies?"

Dominique Pichard, MD, MS
National Center for Advancing Translational Sciences, NIH

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NCATS

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What are registries and natural history studies?

Dominique C. Pichard, MD, MS

Director

Division of Rare Diseases Research Innovation, NCATS

NIH National Center for Advancing Translational Sciences

Definitions

- **Natural history of a disease**: the course a disease takes in the absence of intervention in individuals with the disease, from disease onset until either the disease's resolution or death.

- **Natural history study**: a preplanned observational study intended to track the course of a disease over time.

- **Registry**: a collection of information about a specified group of people
  - Ex. Contact registry, disease registry, population registry

Examples of registries

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

National Amyotrophic Lateral Sclerosis (ALS) Registry

NATIONAL CANCER INSTITUTE
Surveillance, Epidemiology, and End Results Program

Rett Syndrome Registry™

National Center for Advancing Translational Sciences

Definitions

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National Center for Advancing Translational Sciences

"What Are Registries and Natural History Studies?"

Kerry Jo Lee, MD
Center for Drug Development and Research, FDA

REAGAN-UDALL FOUNDATION FOR THE FDA

Accelerating Rare disease Cures (ARC) Program

NATURAL HISTORY STUDIES AND REGISTRIES IN THE DEVELOPMENT OF RARE DISEASE TREATMENTS

Kerry Jo Lee, M.D.

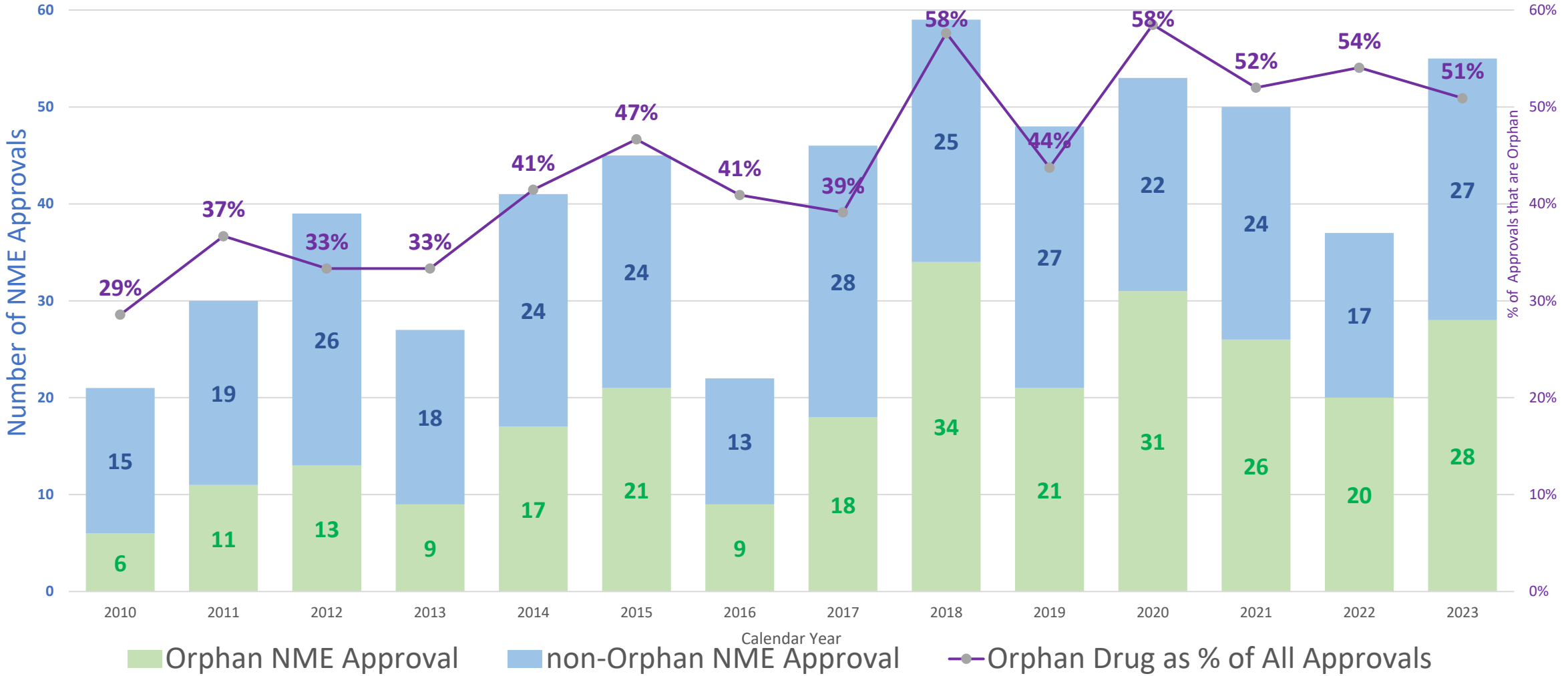
Associate Director for Rare Diseases

Rare Diseases Team

DRDMG | ORPURM | CDER | US FDA

FDA U.S. FOOD & DRUG ADMINISTRATION

Proportion of CDER Novel Drug Approvals that are Orphan



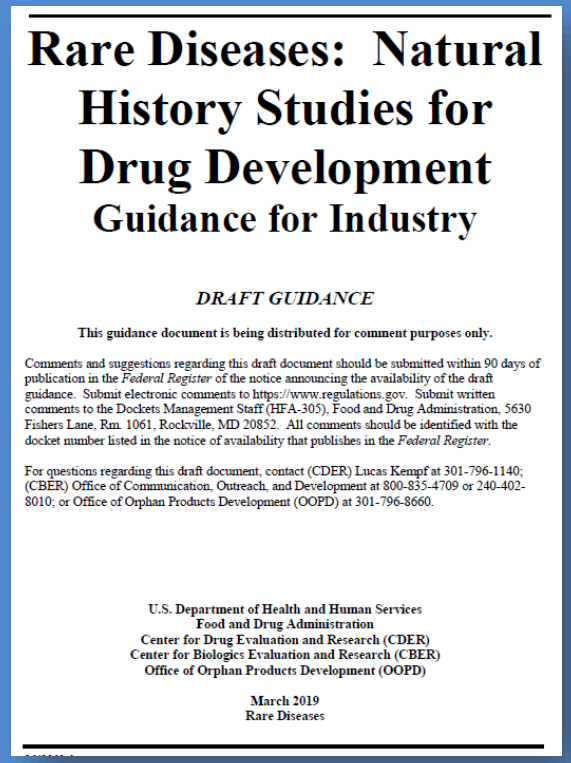
We Face Common Challenges in Rare Disease Drug Development

- **Natural history** is often poorly understood
- Diseases are progressive, **serious**, **life-limiting** *and* often lack adequate **approved therapies – urgent needs,** many have **pediatric onset**
- **Small populations** often restrict study design options
- **Phenotypic and genotypic** diversity within a disorder
- **Development programs often lack solid translational background**
- **Drug development tools** - **outcome measures** and **biomarkers** often **lacking**
- Lack of **precedent**, including **clinically meaningful endpoints**, for drug development in many rare diseases

Supporting the Design and Conduct of Clinical Trials for Rare Diseases

Search for Selected FDA Guidance Documents by Topic Relevant to Rare Disease Drug Development

https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development



Rare Diseases: Natural History Studies for Drug Development
Guidance for Industry

DRAFT GUIDANCE

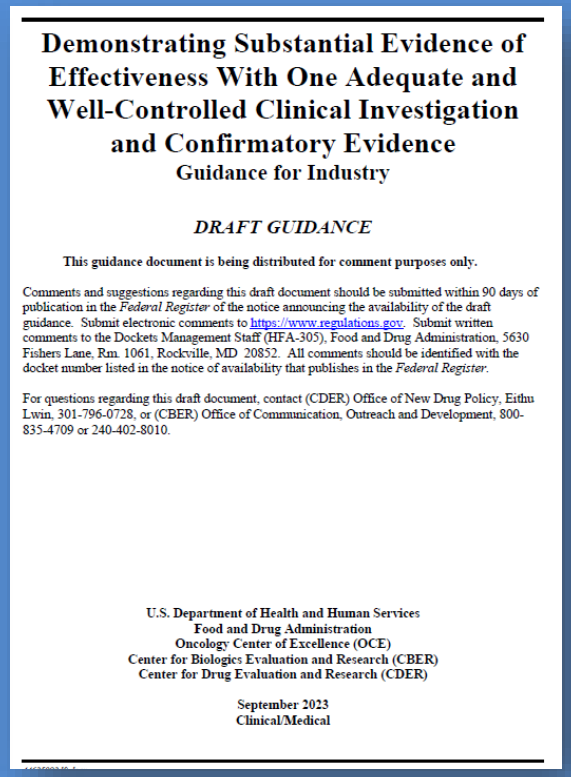
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lucas Kempf at 301-796-1140; (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010; or Office of Orphan Products Development (OOPD) at 301-796-8660.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Orphan Products Development (OOPD)

March 2019
Rare Diseases



Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence
Guidance for Industry

DRAFT GUIDANCE

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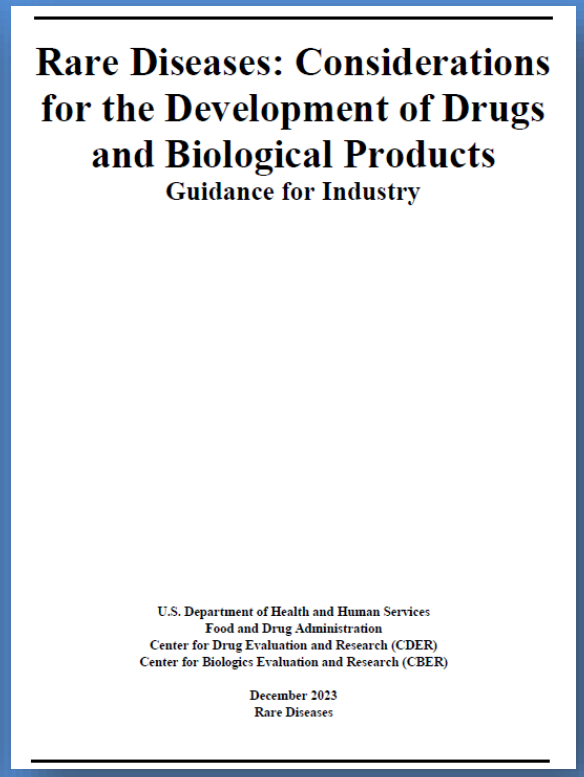
For questions regarding this draft document, contact (CDER) Office of New Drug Policy, Eithu Lwin, 301-796-0728, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)

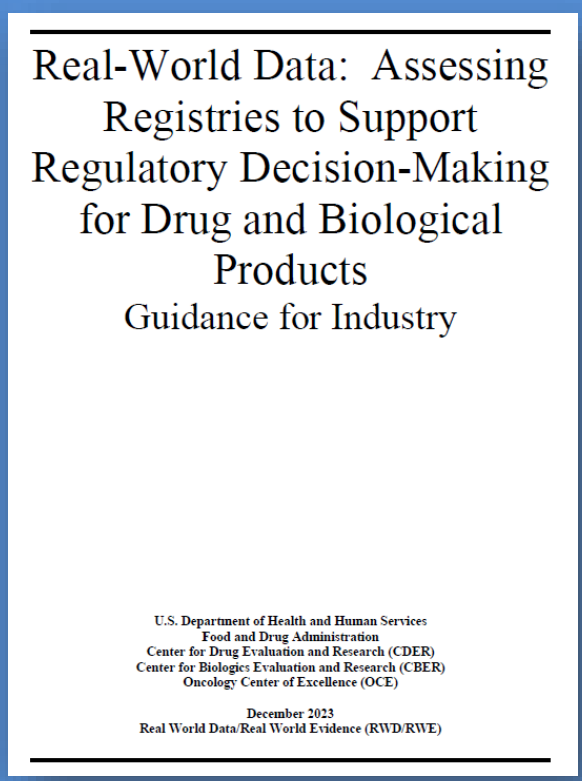
September 2023
Clinical/Medical



Rare Diseases: Considerations for the Development of Drugs and Biological Products
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2023
Rare Diseases



Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

December 2023
Real World Data/Real World Evidence (RWD/RWE)

Visit the ARC website for conference recordings and other resources

- https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program

Getting Started: Developing Registries and Designing Natural History Studies

Presenters

Leslie Gordon, MD, PhD
The Progeria Research Foundation

Eileen King, PhD
Cincinnati Children's Hospital Medical Center

Michael Wagner, PhD
University of Cincinnati College of Medicine

Kristen Wheeden, MBA
United Porphyrias Association

REAGAN-UDALL FOUNDATION FOR THE FDA

Getting Started: Developing Registries and Designing Natural History Studies

Photo Courtesy of PRF

Leslie B. Gordon, MD, PhD
The Progeria Research Foundation
Hasbro Children's Hospital & Alpert Medical School of Brown U.
Boston Children's Hospital Boston and Harvard Medical School

Reagan-Udall Foundation For The FDA

May 13, 2024

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Families sign consents for PRF to permit use of their photographs. To respect those families and children's wishes, please do not use the photos in this presentation.

Please contact The Progeria Research Foundation for image use permissions.

Thank you very much.

Together We *WILL* Find The Cure!

www.progeriaresearch.org

Learning From Each Other:
PRF Road to the Cure Using Registry, Database, Natural History Studies

Photo Courtesy of PRF

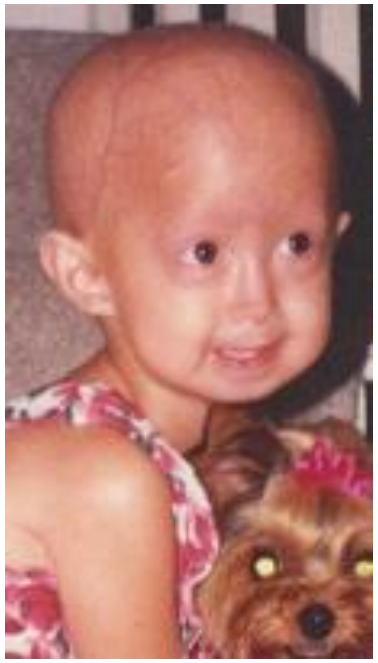
Provide you with some of the key thematic lessons learned through our journey with progeria, so that we can all become better, faster and stronger towards curing our patients.

Because TIME is not on our side…

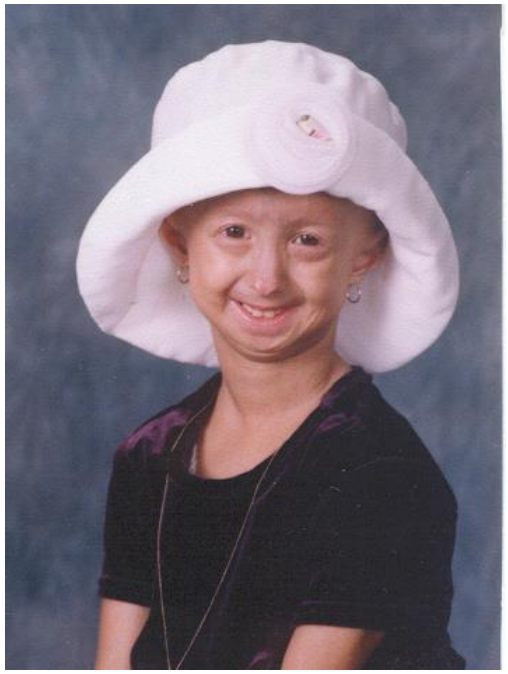
This Is Progeria (HGPS)

Rachel: Newborn

Toddler



2nd grade



9 years old

- Segmental Premature Aging
- Autosomal Dominant
- Lifespan Ave. 14.6 yrs. (5-21y) without treatment
- Premature atherosclerosis, CV failure

1998 - There Was No Hope…

Photo Courtesy of PRF

- 2 or 3 scientists working on Progeria
- No Research Funding
- Was this a genetic disease?
- No Central Source of Clinical Information
- Clinical Disease Poorly Defined
- No Treatment Prospects
- No Place for Families and Physicians to go for Help

The Progeria Research Foundation - 1999

Photo Courtesy of PRF

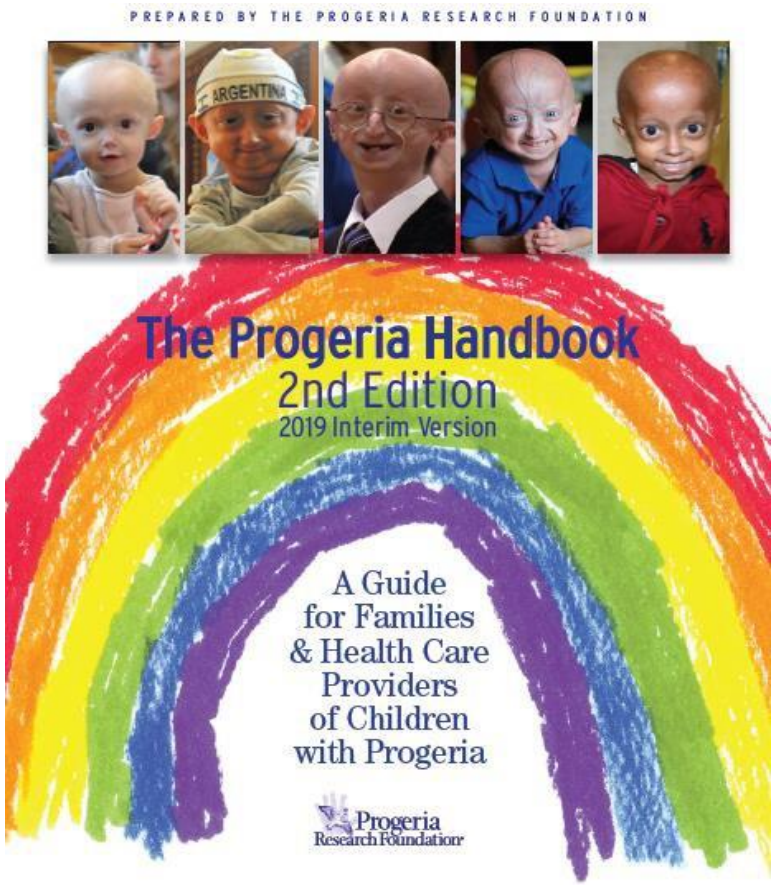
Mission

- ❑ Cause
- ❑ Treatment
- ❑ Cure

Together We *WILL* Find The Cure!

www.progeriaresearch.org

A Few Milestones



- Gene Mutations Discovered and Defined (Nature, 2003)
- CV-faithful Progerin-producing Mouse Models Developed
- Natural History Study at NIH Clinical Center (NEJM, 2008)
- 4 Clinical Treatment Trials – fully enrolled months after initiation – 107 children from 42 countries
- World's Progeria Experts at Boston Children's Hospital
- 130-Page Clinical Care Handbook
- Plasma Progerin Biomarker in Validation (Circulation, 2021)

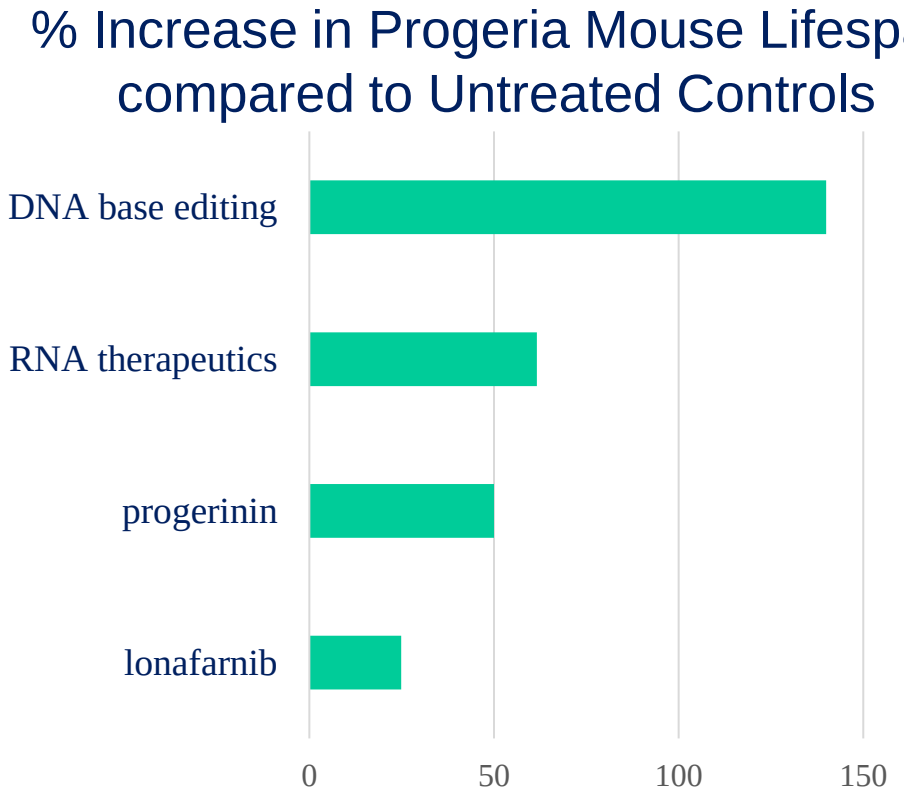
Progeria Research Foundation
FOR THE CHILDREN ♥ FOR THE CURE

Nov 30, 2020: PRF Joins only 5% of Rare Diseases with an Approved Drug

Photo Courtesy of PRF

- 21 years from Registry initiation to approval
- 13 y. of continuous clinical trials with lonafarnib
- Lifespan Extension Avg. 4.2 yrs (JAMA, 2023)

What's Next?



NONE of These Accomplishments Would Be Possible Without the PRF International Registry, Database, & Natural History Studies

Photos Courtesy of PRF

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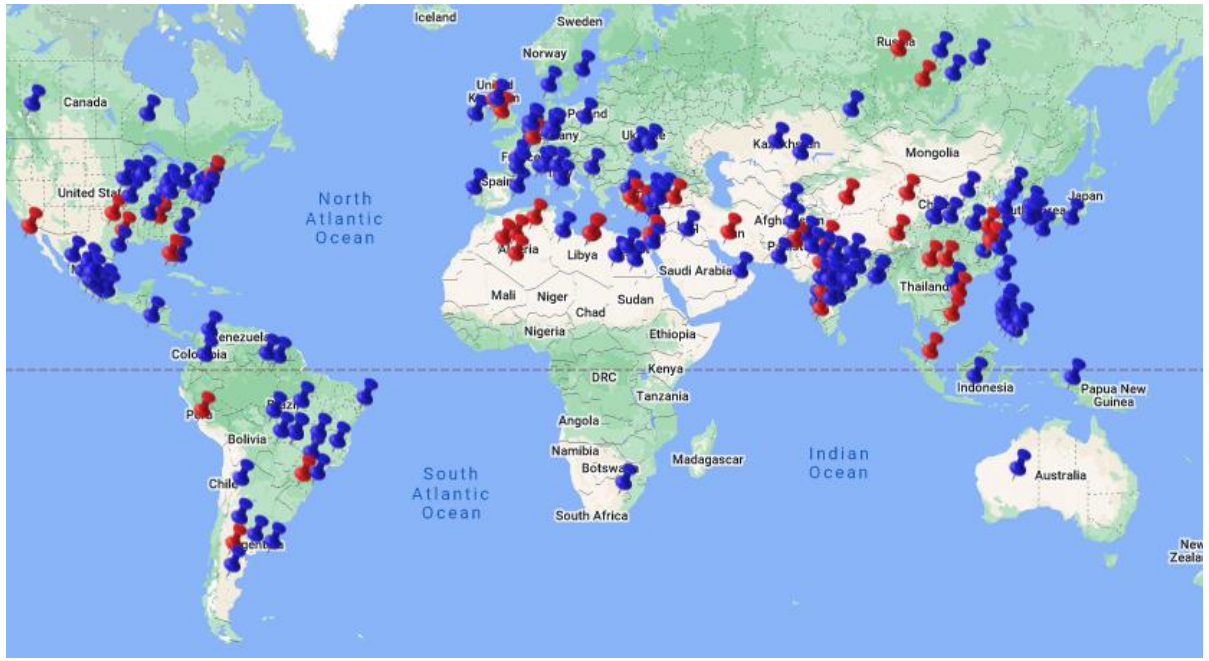
PRF Progeria International Registry:
~40% of World's Population Living With Progeria

- **Top Priority Upon Contact with MD or Patient Family**
- **Unconsented**
- **Longitudinal Communication → Trust,Education → Program, Trial Participation**
- **Info packets sent to MD and Family Immediately**



149 Patients
51 Countries
35 Languages

Photo Courtesy of PRF

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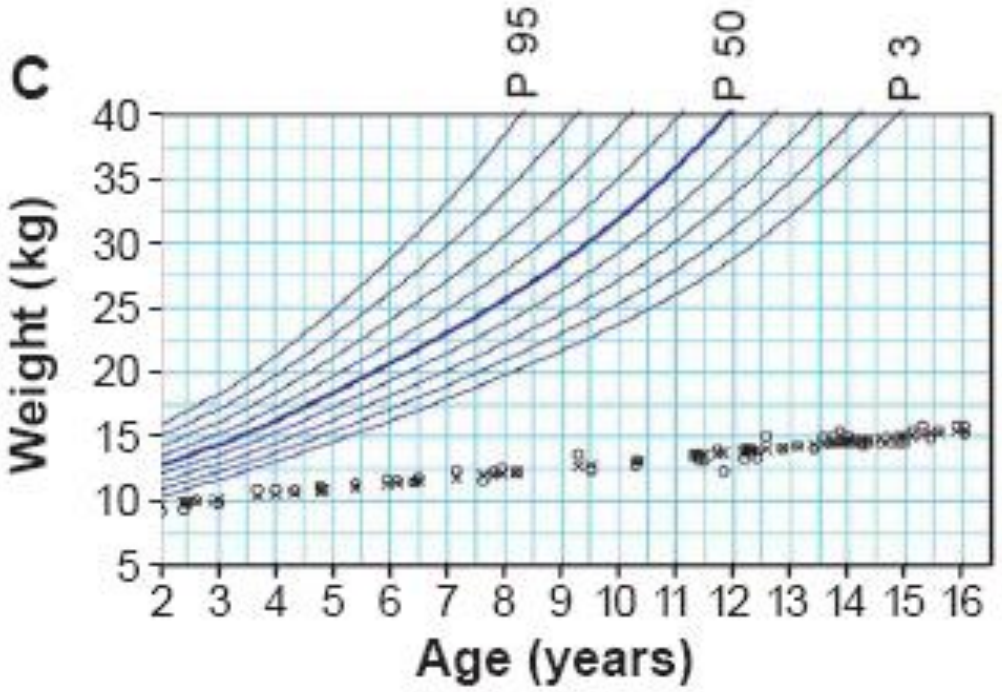
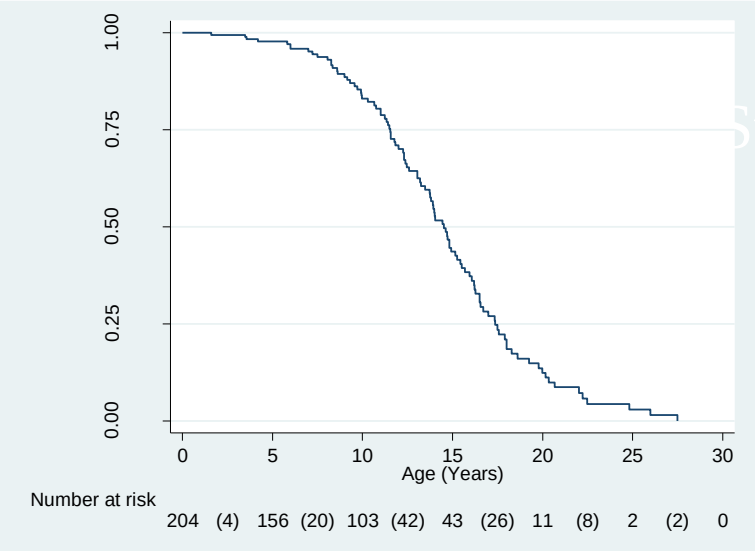
Medical & Research Database

- **Consented Program (IRB-approved)**
- **Longitudinal Collection of Clinical Data**
- **Outcomes must be objectively evaluable, statistically abnormal, affecting how a patient feels, functions or survives**



- ✓ **Primary Outcome for the Natural History Study at NIH and First 2 Clinical Trials came from Database Weight Analysis**
- ✓ **This outcome did not show improvement, but the evaluation gave us our first trials, an important gateway**
- ✓ **34 Peer-reviewed Publications**

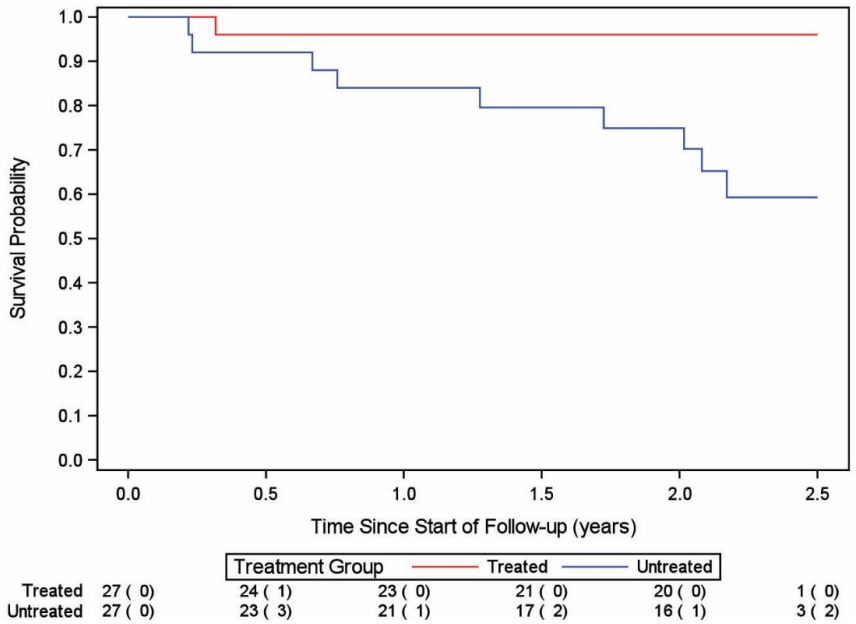
PRF Registry and Database Survival Data, With Time On Therapy, Was The Primary Outcome Used for Drug Approval



Circulation

American Heart Association

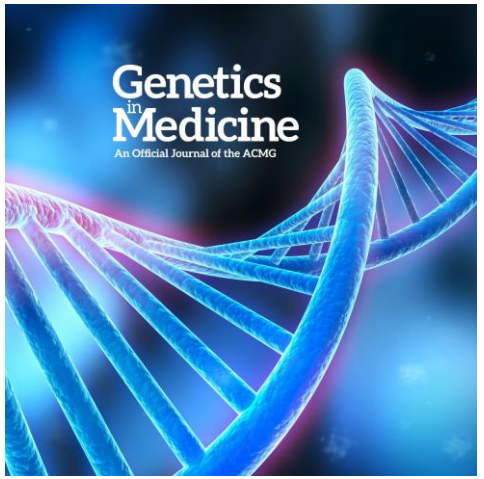
Impact of Farnesylation Inhibitors on Survival in Hutchinson-Gilford Progeria Syndrome
Leslie B. Gordon, Joe Massaro, Ralph B. D'Agostino, Sr., Susan E. Campbell, Joan Brazier, W. Ted Brown, Monica E. Kleinman and Mark W. Kieran



JAMA | Preliminary Communication

Association of Lonafarnib Treatment vs No Treatment With Mortality Rate in Patients With Hutchinson-Gilford Progeria Syndrome

FDA Special Report



Suzuki, et al, 2022

Long-term Survival Benefit of Lonafarnib Also Came From The Registry and Database: 2.2→4.3 years…

Dual Purpose: Progeria Treatment Trials Also Serve As Natural History Studies

Photo Courtesy of PRF

- **29 Scientific articles published from BCH Progeria clinical trial data**
- **Now that lonafarnib is the standard of care, a new "natural history" on this medication must be defined, to use as comparison to any new drug added to lonafarnib in a trial**
- **We are continually working to define a primary outcome measure for future trials**

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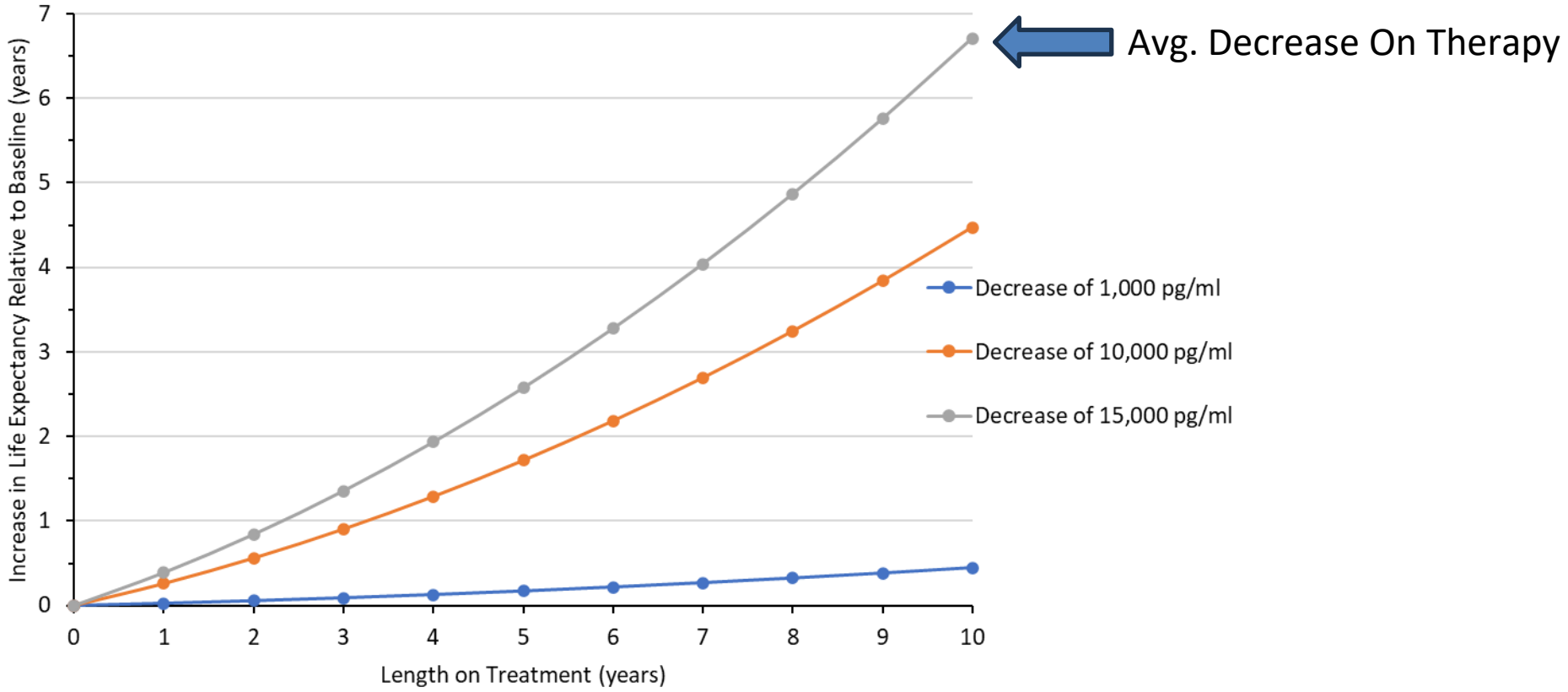
FOR THE CHILDREN ♥ FOR THE CURE

Registry and Database Survival Data Essential for Defining Plasma Progerin Biomarker Being Validated as our Primary Trial Biomarker Outcome Measure



- Lonafarnib Therapy: Lifespan Benefit with Decreased Progerin
- The lower you go, the longer you stay low, the greater the benefit

A Few Take-home Messages

Photo Courtesy of PRF

- **Patient families are passionate <u>partners</u>.**
- **Always assume your data will be used for drug approval, so use RedCap or similar database system**
- **Raw data will be useful many times over, so safeguard your source data.**
- **Patient Registries and Nature History Studies are critical foundational tools for the Cure.**

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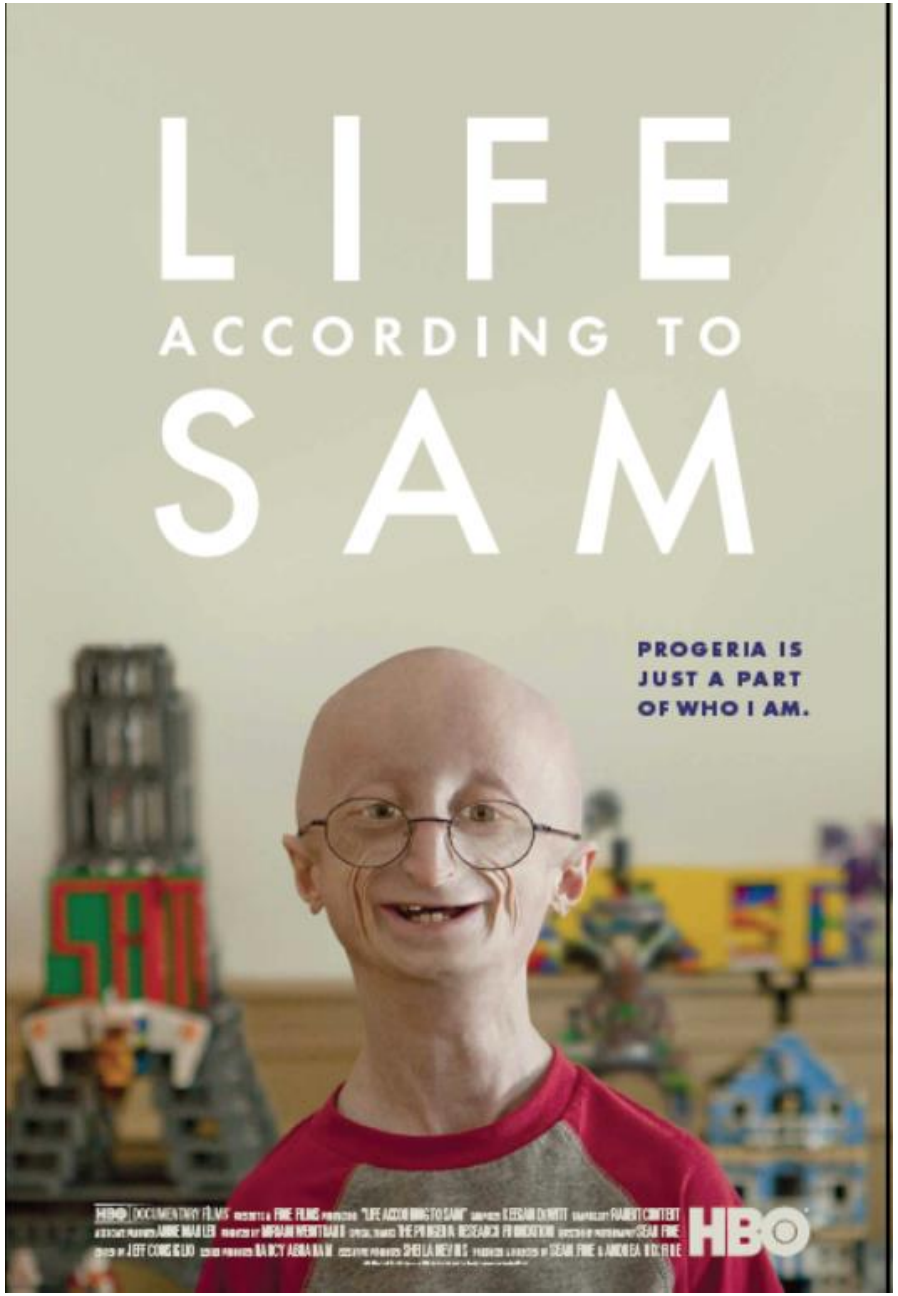


Thank You!

Reagan-Udall Organizers

Many Talented Collaborators

Progeria Research Foundation
FOR THE CHILDREN ♥ FOR THE CURE

Together We *WILL* Find The Cure!

Getting Started: Developing Registries and Designing Natural History Studies

Eileen King, Ph.D.
Michael Wagner, Ph.D.
Data Management and Coordinating Center
Rare Diseases Clinical Research Network
Cincinnati Children's Hospital Medical Center

May 13, 2024

RARE DISEASES
CLINICAL RESEARCH NETWORK

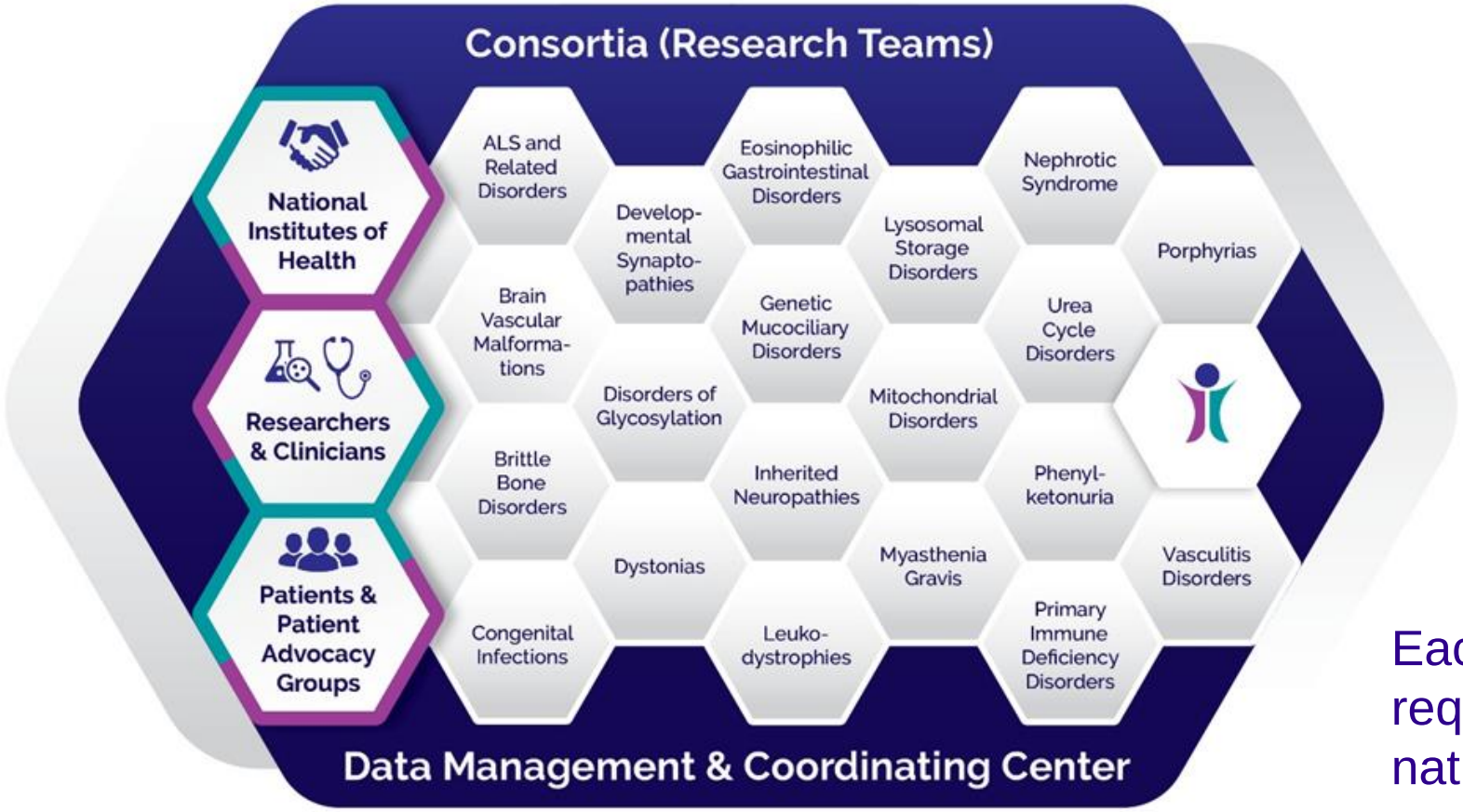
Agenda

- Overview of Rare Diseases Clinical Research Network (RDCRN)
- Data Collection, Formatting and Quality Assurance
- Data Storage, Maintenance and Sharing

RARE DISEASES
CLINICAL RESEARCH NETWORK

RARE DISEASES
CLINICAL RESEARCH NETWORK

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



Each consortium is required to have a natural history study.

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

Funded by the National Institutes of Health

- Now in its fourth 5-year funding cycle
- Led by the National Center for Advancing Translational Sciences (NCATS) through its Division of Rare Diseases Research Innovation (DRDRI).
- Established by Congress under the **Rare Diseases Act of 2002**
- Findings from the RDCRN have contributed to the **approval of 8 treatments** by the FDA.

RARE DISEASES
CLINICAL RESEARCH NETWORK

Data Collection, Formatting, and Quality Assurance

RARE DISEASES
CLINICAL RESEARCH NETWORK

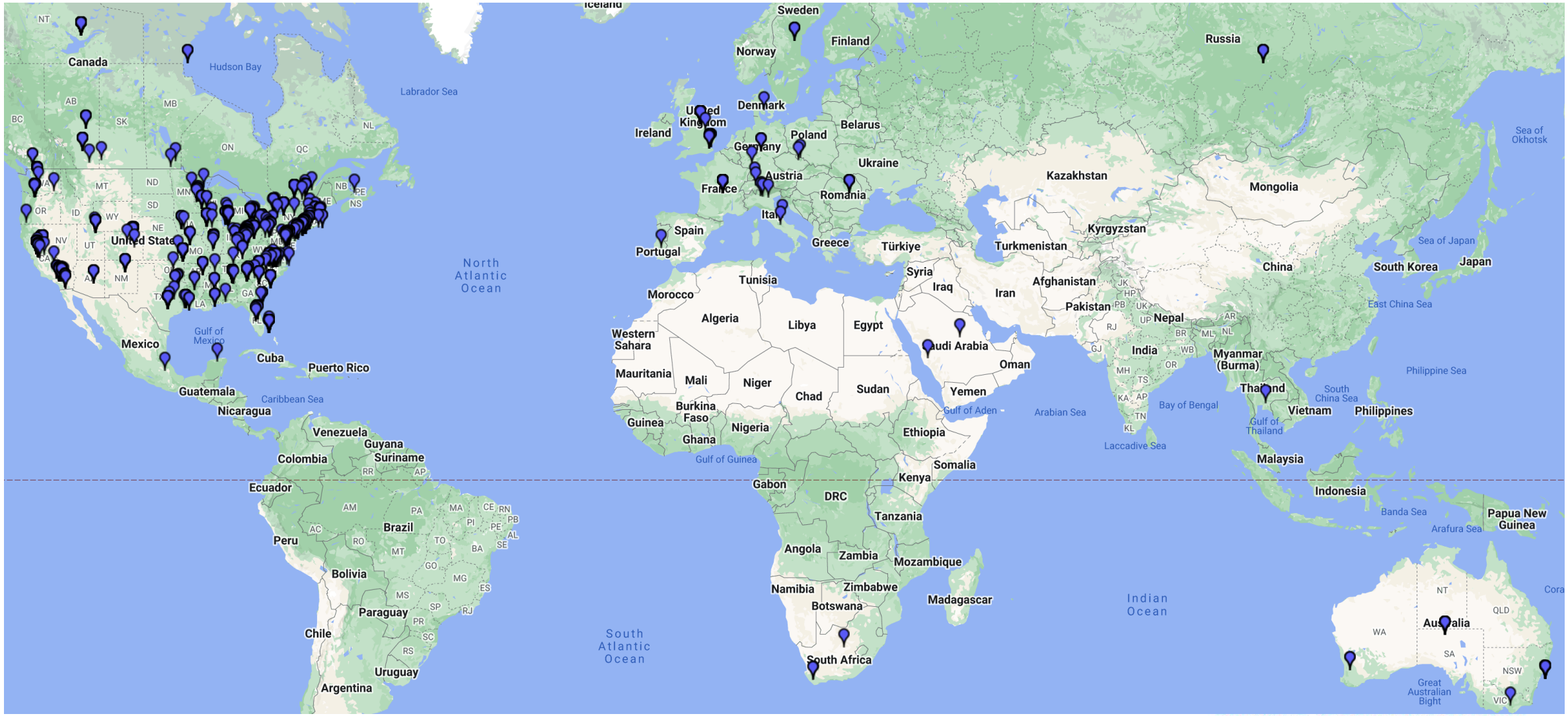
Data Collection Platform for RDCRN Natural History Studies: REDCap (Research Electronic Data Capture)

- A secure, web-based EDC system designed and supported by Vanderbilt U. featuring
  - an intuitive interface for validated data capture
  - audit trails for tracking data manipulation and export procedures
  - automated export procedures for seamless data downloads to common statistical packages
  - procedures for data integration and interoperability with external sources via APIs.

- Widely available, well supported by most academic health centers (7178 institutions, 156 countries, 2M projects, 3.1M Users)
- Projects and data are very portable
- CCHMC was early adopter and has deep expertise
- Good support for data standards in REDCap, availability of form libraries, great community support

RARE DISEASES
CLINICAL RESEARCH NETWORK

RDCRN REDCap logins (9/2022-8/2023)



Data Quality, Integrity, Standards for RDCRN

DMCC has policies and procedures in place

Every study has these 4 documents

- Data Management Plan (DMP)
- Data Quality Plan (DQP)
- Data Transfer Specifications (DTS)
- Database Lock Checklist

RARE DISEASES CLINICAL RESEARCH NETWORK

Data Standards for RDCRN Studies

CDISC/CDASH Standards whenever applicable

When CDISC not available, reference REDCap Shared Library, NDA Repository, NLM Library

Downloads direct from instrument publishers

Looking forward, increased use of direct REDCap links to CDASH forms and CDEs

https://bit.ly/3UopqZj - RDCRN REDCap codebook

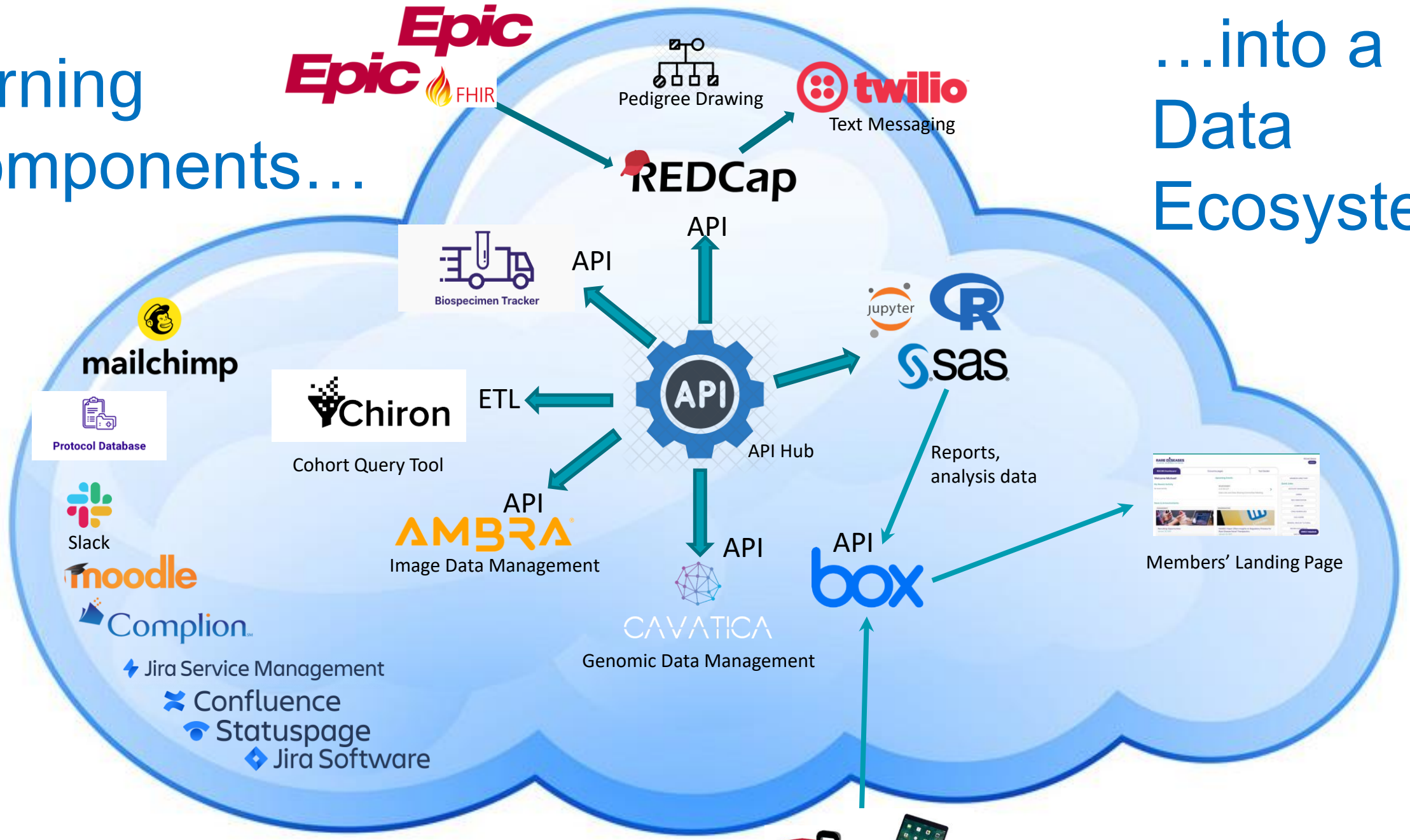
RARE DISEASES CLINICAL RESEARCH NETWORK

Data Storage, Maintenance and Sharing

RARE DISEASES
CLINICAL RESEARCH NETWORK

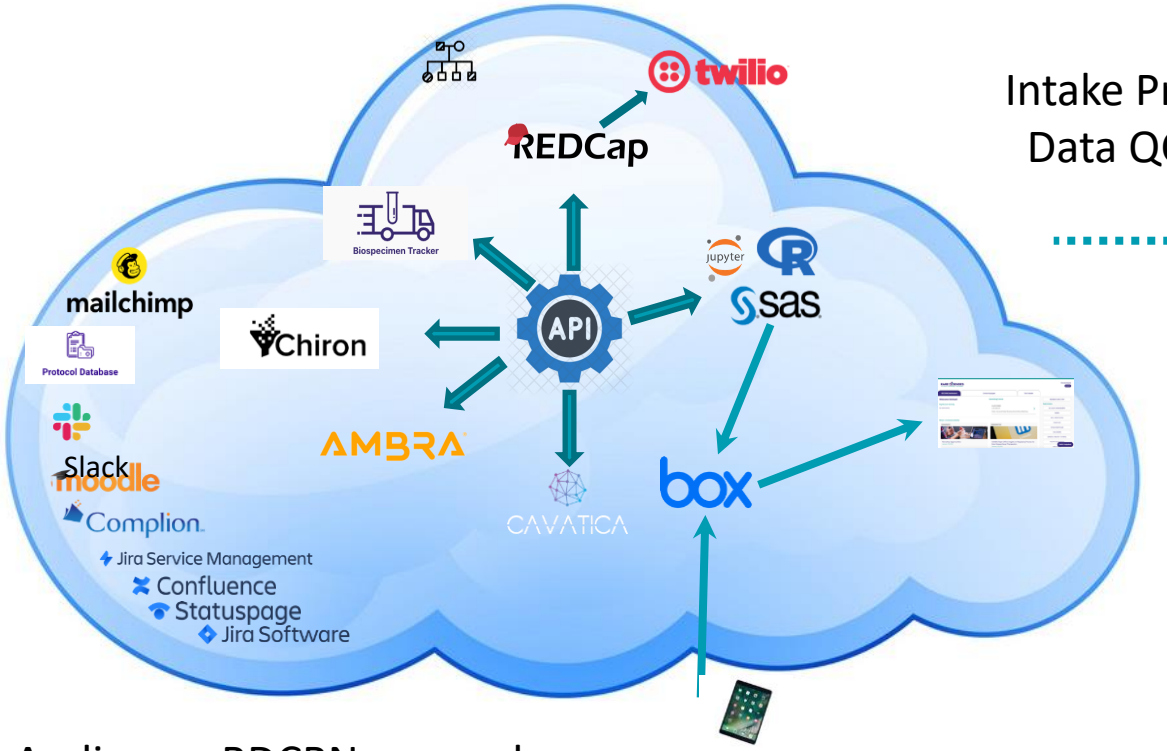
Turning Components…

…into a Data Ecosystem

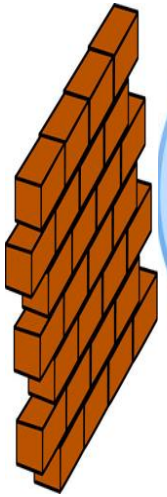


Operational Environment

RDCRN Data Repository



Intake Process: Metadata
Data QC, Data Use Limitations



Access Request Process

Intake Process

Palantir

Audience: RDCRN researchers
Authentication: RDCRN login page
Authorization: Consortia
Data governance: Consortia and DMCC
Internal data sharing

Audience: Public
Data Governance: NIH
NIH-regulated access and authorization
Official NIH repository

RARE DISEASES
CLINICAL RESEARCH NETWORK

RDCRN Data Sharing Framework

- NIH required Rare Disease Consortia to share data funded by RDCRN.
- DMCC developed framework: template language for DUAs and sharing agreements.
- DMCC helps consortia to document participant-level data use limitations in REDCap as metadata.
- NCATS Data Access Committee will adjudicate Data Repository access requests and ensure appropriate data use.

RARE DISEASES
CLINICAL RESEARCH NETWORK

Principles of Data Sharing – Informed Consent

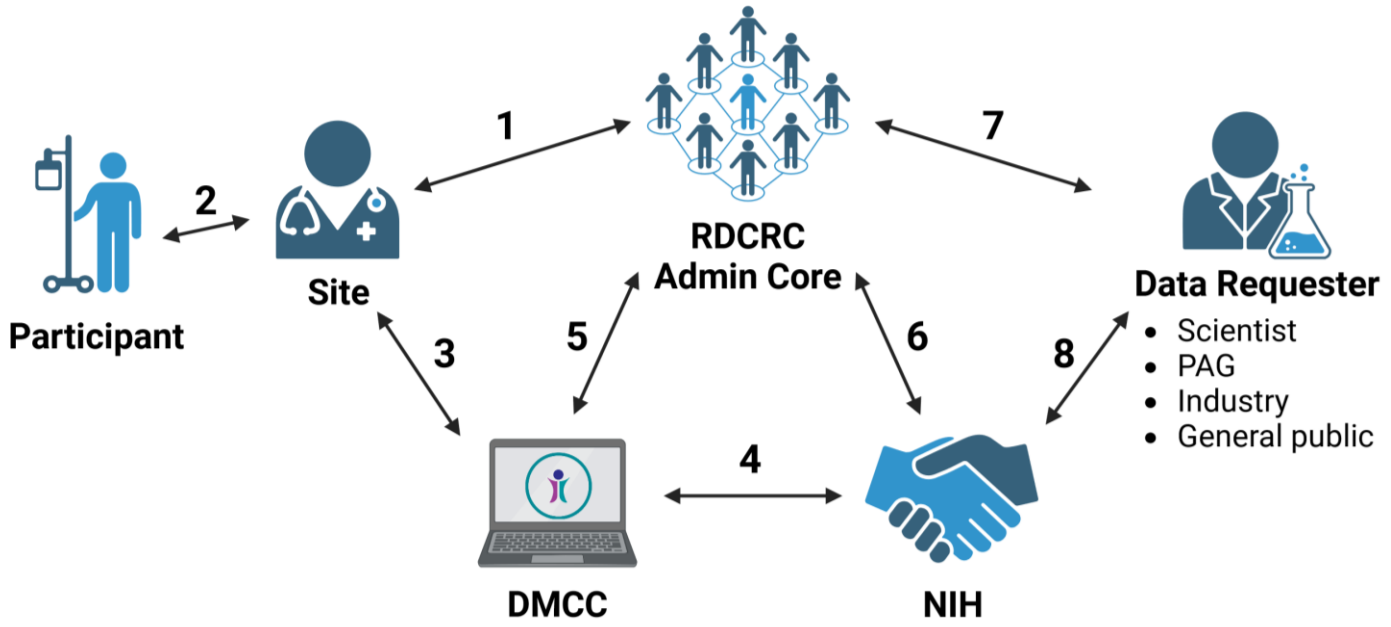
Informed Consent should include language that allows broad data sharing while protecting confidentiality of the participant:

- Sharing data with the Admin Core of the RDCRC as a limited data set.
- Sharing data with DMCC.
- Sharing data with other researchers for future studies.
- Allowing transfer of data, without identifiers, to a federal data repository.
- Options for restricting data sharing that investigators deem necessary to offer the participant (e.g., as mandated by the IRB).
- Incorporation of participant selections/consent category into the research database.

https://www.rarediseasesnetwork.org/research/data-sharing-and-standards/data-sharing-resources

RARE DISEASES
CLINICAL RESEARCH NETWORK

Relationships Among The Parties Involved In Data Sharing



1. Subcontract Award
2. Informed Consent
3. Data Use/Hosting Agreement
4. U2 Cooperative Agreement
5. Data Use/Transfer Agreement
6. U54 Cooperative Agreement
7. RDCRC Data Sharing Policy & Data Use Agreement
8. Federal DAC & Data Use Agreement

RARE DISEASES
CLINICAL RESEARCH NETWORK

RDCRN Data Repository - Required Metadata

Hard Requirements

- Schedule of Events
- Protocol Synopsis
- Data Dictionary
- Codebook
- Extramural Institutional Certification
- Consent Table

Soft Requirements

- IRB Approved Protocol
- Data Management Plan
- Data Quality Plan
- Annotated Blank CRFs

RARE DISEASES
CLINICAL RESEARCH NETWORK

RDCRN Data Repository – QC Framework

Hard Requirements

- Compare
  - Participant IDs in data tables to consent table
  - Variables from data dictionary to contents of data table
- Check for proper delimiters, carriage returns
- Convert dates to age at visit/event

Soft Requirements

- Compare
  - Schedule of Events (SoE) to visit/events in data
- Run Variable Code/Value Consistency report
- Check for version differences in submitted data sets

RARE DISEASES CLINICAL RESEARCH NETWORK

RDCRN Data Repository – QC Framework

Hard Requirements

- Participant ID Anonymization
- Create Study ID for RDCRN Data Repository
- QC Checks for non-clinical data (i.e., imaging, EEGs, ECHO, etc.)
  - Convert dates to age at event/visit
  - Check for Participant ID; match to clinical data and consent table
- PII flagging process

RARE DISEASES
CLINICAL RESEARCH NETWORK

Summary

- Natural history data for patients with rare diseases is critical for advancing rare disease research to speed diagnosis and identify new treatments
- Data must be collected and managed using state-of-the-art systems, processes and procedures to ensure high quality data
- NIH-funded studies are required to share data with the general research community which maximizes its value for clinical trial readiness and approval of treatments

RARE DISEASES
CLINICAL RESEARCH NETWORK

Thank you

5U2CTR002818

NIH National Center for Advancing Translational Sciences

COLLABORATE. INNOVATE. ACCELERATE.

Tiina Urv, Ph.D.
Joanne Lumsden, Ph.D.
Sam Michael, Ph.D.

CCHMC DMAC, IS4R & Research IT teams
RDCRN Project Managers
RDCRN Consortia and research participants, who entrust their data to us!

RARE DISEASES CLINICAL RESEARCH NETWORK

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Rare Research Report

UNITED PORPHYRIAS ASSOCIATION

Advancing Awareness, Research and Therapies

Kristen Wheeden
President

UNITED PORPHYRIAS ASSOCIATION

porphyria.org

Our Patient Community

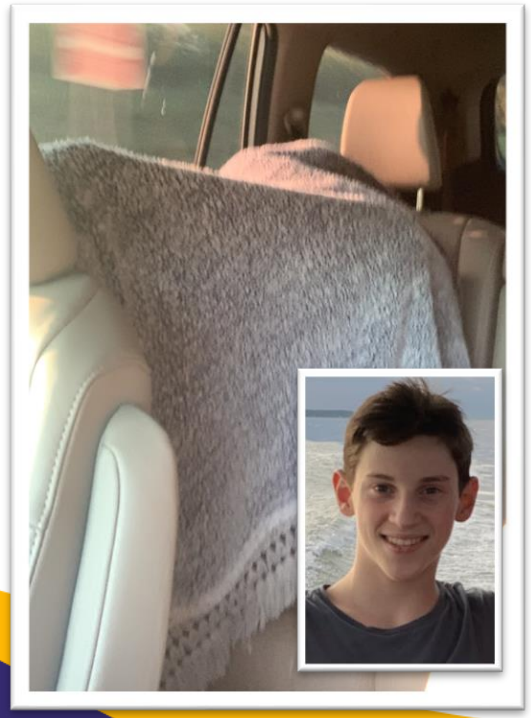
"Like putting my hand in a fire then cutting it with a knife"

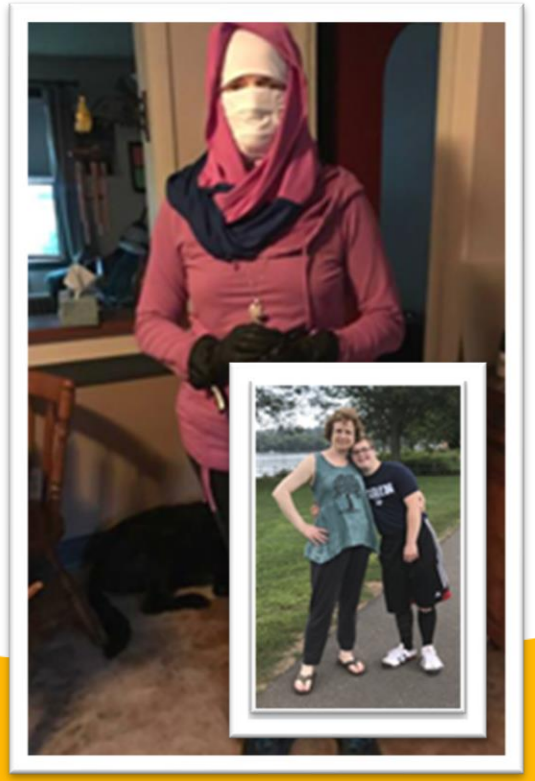
"There are no words in the English language to describe the pain"

"Like I'm trapped in a cage"

"Like being in boiling water"

"Like a chemical burn"





United Porphyrias Association

Research | Education | Awareness | Advocacy | Support

SCIENTIFIC ADVISORY BOARD
UNITED PORPHYRIAS ASSOCIATION

The PRESIDENT'S COUNCIL
UNITED PORPHYRIAS ASSOCIATION

UNITED PORPHYRIAS ASSOCIATION

PATIENT REGISTRIES

PATIENT REGISTRY IN PORPHYRIA

- ✓ Established in 2008
- ✓ 1000+ Participants
- ✓ 14 Academic Institutions/Study Sites
- ✓ Separate Contact Database (CRM)
- ✓ Results
  - ✓ Publications
  - ✓ Studies
  - ✓ Patient Reported Outcome measures

UNITED PORPHYRIAS ASSOCIATION

PATIENT REGISTRY CONSIDERATIONS

- ✓ **Objectives**
  - ✓ Research
  - ✓ Clinical Care
  - ✓ Advocacy and Funding
- ✓ **Stakeholder Engagement**
  - ✓ Engaging patients
  - ✓ Collaboration with researchers
  - ✓ Regulatory involvement
- ✓ **Ensure**
  - ✓ Inclusivity
  - ✓ Data Quality
  - ✓ Privacy and Ethics

UNITED PORPHYRIAS ASSOCIATION

PATIENT REGISTRY BEST PRACTICES

- ✓ Standardized Data Collection
- ✓ Technology Utilization
- ✓ Collaboration
- ✓ Considerations for rare diseases

UNITED PORPHYRIAS ASSOCIATION

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Addressing Challenges in Registry and Natural History Data Collection

Presenters

Benjamin Forred, MBA, ACRP-CP
Sanford Research

Zohreh Talebizadeh, PhD
Global Genes

Reactor Panel

Henry Kaminski, MD, George Washington University
Suzanne Pattee, Office of the Commissioner, FDA
Dominique Pichard, MD, MS, National Center for Advancing Translational Sciences, NIH

REAGAN-UDALL FOUNDATION FOR THE FDA

Addressing Challenges in Registry and Natural History Data Collection – Bioinformatics plans, Ethics, and Data Sharing & Privacy

Benjamin Forred
Director, Translational Research & the CoRDS Registry
Sanford Research

SANFORD RESEARCH

What is CoRDS?

- CoRDS is a patient registry for all rare diseases, unaffected carriers & the undiagnosed - it ties together patients, advocacy groups, and researchers.
- Unlike many other registries, as a Sanford Health sponsored initiative, CoRDS is made available at no cost to patients, advocacy groups, or researchers. It is free and it always will be.

Setting yourself up for effective bioinformatics approaches

- Standardize questions using established data elements
  - NIH common data elements & CoRDS
  - Interoperability with other formats (CDISC, OMOP, etc.)
- Discrete fields used contributes to clean data and decrease analysis time
  - Can lead to effective translation into other languages
- Systematic procedures for ingesting large datasets from external sources

Ethics Considerations

- Data needs to be collected the right way from the start
  - IRB approved protocol & consent documents
  - Privacy laws & regulations (21 cfr part 11, HIPAA, GDPR, etc.)
- Simply put: Participants must know what they're getting into when they sign on to participate. They have rights. It's your job to know them AND protect them.

Using and Sharing Data

- Put a governance and procedure around data sharing
  - CoRDS has an internal scientific advisory council that reviews requests for data
- Identifiable or deidentified data?
  - Be aware of the difference
  - You absolutely have to adhere to the language in the informed consent form
- Security measures around sharing data
  - HIPAA covered entity?
  - SFTP sites are commonly used
  - Get very clear answers before committing to a tool
  - Legal agreement with the recipient

Thanks to all of our participants – and thank you for your attention

Benjamin.Forred@sanfordhealth.org

Research.sanfordhealth.org

RARE-X Research Program:
Virtual Data Collection and Connection
Serving All Stakeholders in Rare Disease

Zohreh Talebizadeh, PhD

Senior Director, RARE-X Research Program

May 13, 2024

Global Genes® Allies in Rare Disease + RARE-X A Research Program of Global Genes

What Is RARE-X?

RARE-X, *a program of Global Genes*, launched in April 2021, to **accelerate** rare disease research & treatments by **removing barriers** for data collection & sharing

The speed and productivity of innovation in rare disease is limited by cost and lack of access to standardized, structured patient data

Data exists, but is captive within silos

Data is not in a structured, standardized format that is useful to research/patient communities

Data doesn't yet exist; many new diseases and most groups don't have resources to collect data properly

Global Genes RARE-X

RARE-X Data Collection Platform (DCP)

RARE-X Supports:

- Individuals (n=1, undiagnosed)
- Patient Communities (small or large)
- Disease Consortium (body system or symptom)

Patients / Individuals

Patient Communities

Disease Consortiums

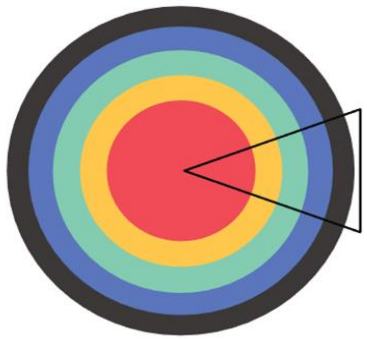
Branching Logic:

- Series of surveys - based on answers, additional prioritized & validated surveys open up

Consent & Data Sharing Preference

Demographics & Role

"Head to Toe" Survey
General Medical, Health & Development



1. **General core**
   - *"Head to Toe Survey"*
2. **Disease core (by domains)**
   - *HPO- mapped domain-specific data*
3. **Supplemental disease data**
   - *Detailed disease-specific data*
4. **Integrated &/or federated data**
   - *EMR/ EHR, clinical reports, custom curation*
5. **Exploratory study data**
   - *Research study-based, raw WGS data*

Level 2 Survey (ex: Neuro)

Level 2 Survey (ex: Cardiac)

Level 2 Survey (ex: Renal)

Survey Layer 3

Survey Layer 3

Survey Layer 3

Survey Layer 3

Validated Instrument

Validated Instrument

Validated Instrument

Validated Instrument

Layer 5 + - Continued buildout of Layered Patient Report Data layered and accessed based on preferences – Branch Chain Logic

Global Genes RARE-X

Patient-Reported Outcomes (PROs)

Domains Implemented:

- Neurodevelopmental
- Neurodegenerative
- Neuromuscular
- Central Disorders of Hypersomnolence

In Process:

- Primary Immune Deficiency (90% completion)
- Cognitive Decline & Associated Depression (adult onset neurodegenerative) (20% completion)

Expert Working Groups for Domain Development

Data Surveys Built to Generate Research-Grade, Comparable Data

Clinicians and scientists from industry and academia serve side-by-side with patients on expert working groups to identify robust data collection surveys, usually from standard measures.

Expert Working Group Formed

Prioritize Domains, Deep Review

Landscape to Identify Measures

Evaluate and Select Measures

License & Implement Measures

Global Genes RARE X

The RARE-X Partner Ecosystem

RARE-X has built a fully integrated platform to support patients as partners in research and has also developed a service model to support biopharma & researchers.
A turn-key comprehensive solution for patients.

Patient Advocates & Orgs

Patient owned & stewarded data

Technology & platform for data collection & sharing

GDPR compliance, data privacy, and governance & consents

No cost to patients or their orgs

Education & communications support

Sponsored studies & consortia

Researchers

In-depth engagement with patient orgs and development of registries

Natural history studies including clinician-reported data

Analysis platform powered by Broad, facilitated by ontology architecture

Federated learning & data connection for deeper analysis

Sponsored studies & consortia

BioPharm

Data sharing post study completion

Clinical trial readiness surveys

Patient identification for recruitment into clinical trials

Federated learning & data connection for deeper analysis

Sponsored studies & consortia

Global Genes RARE-X

RARE-X Data Overview

RARE-X

by the numbers

**As of May 7, 2024*

67
Disease Communities

106
Patient Advocacy Groups

7,704
Participants Enrolled

90
Countries
~39% ex-US

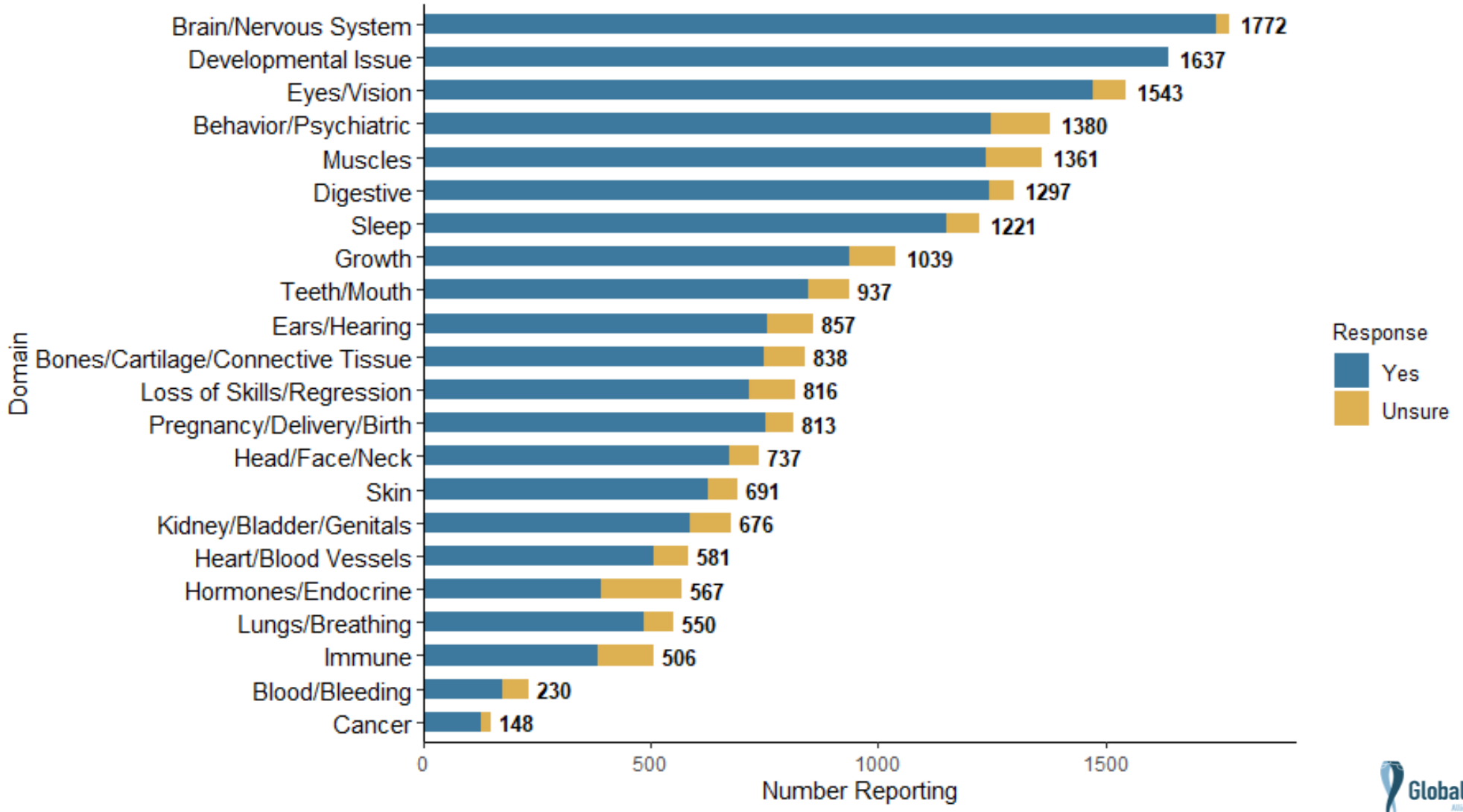
51%
Overall % of Surveys Completed

615
Reports uploaded with genetic testing information

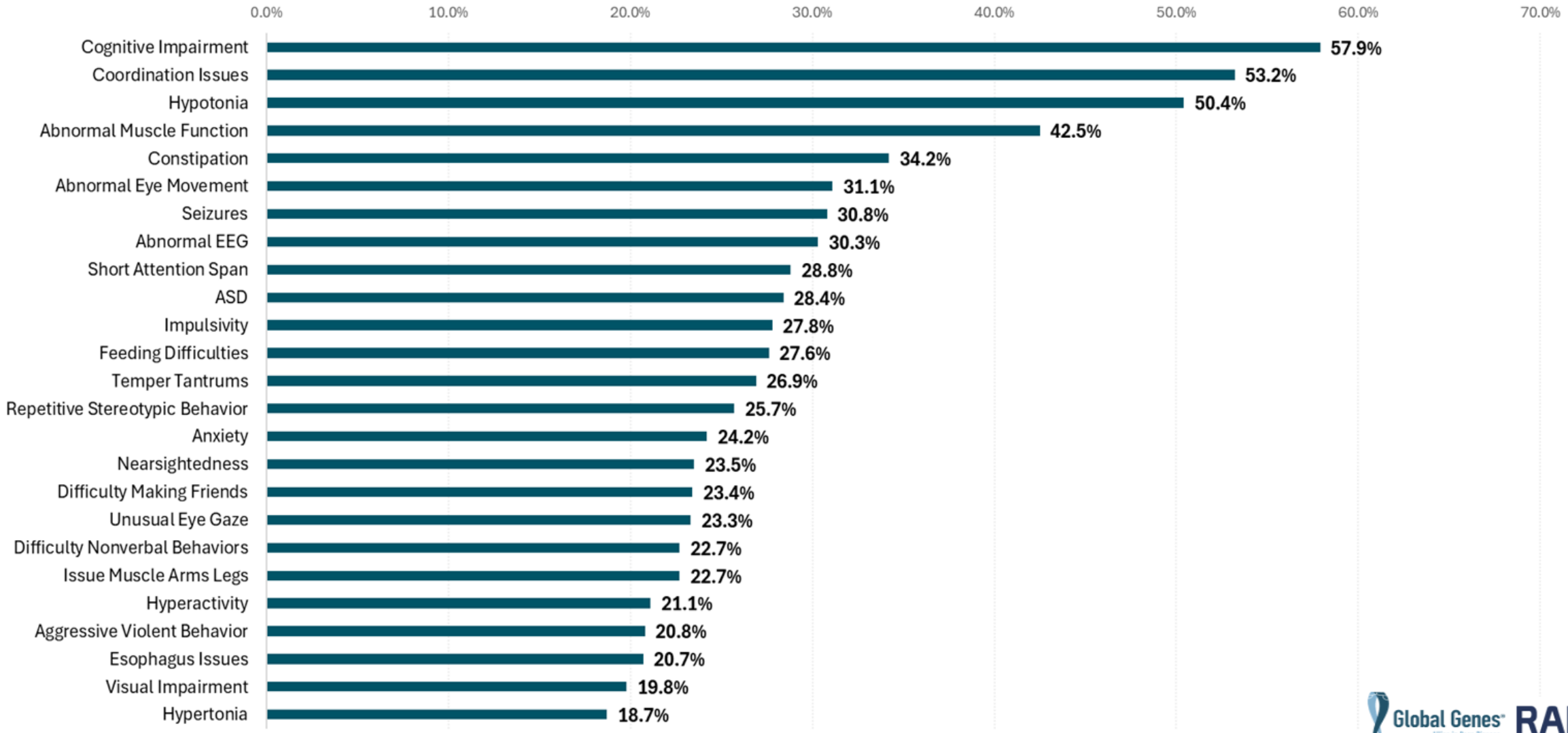
62%
Brain & Nervous System is top domain for patients symptoms

78%
Respondents reported having concern about development

Domains Patients Experience Symptoms in



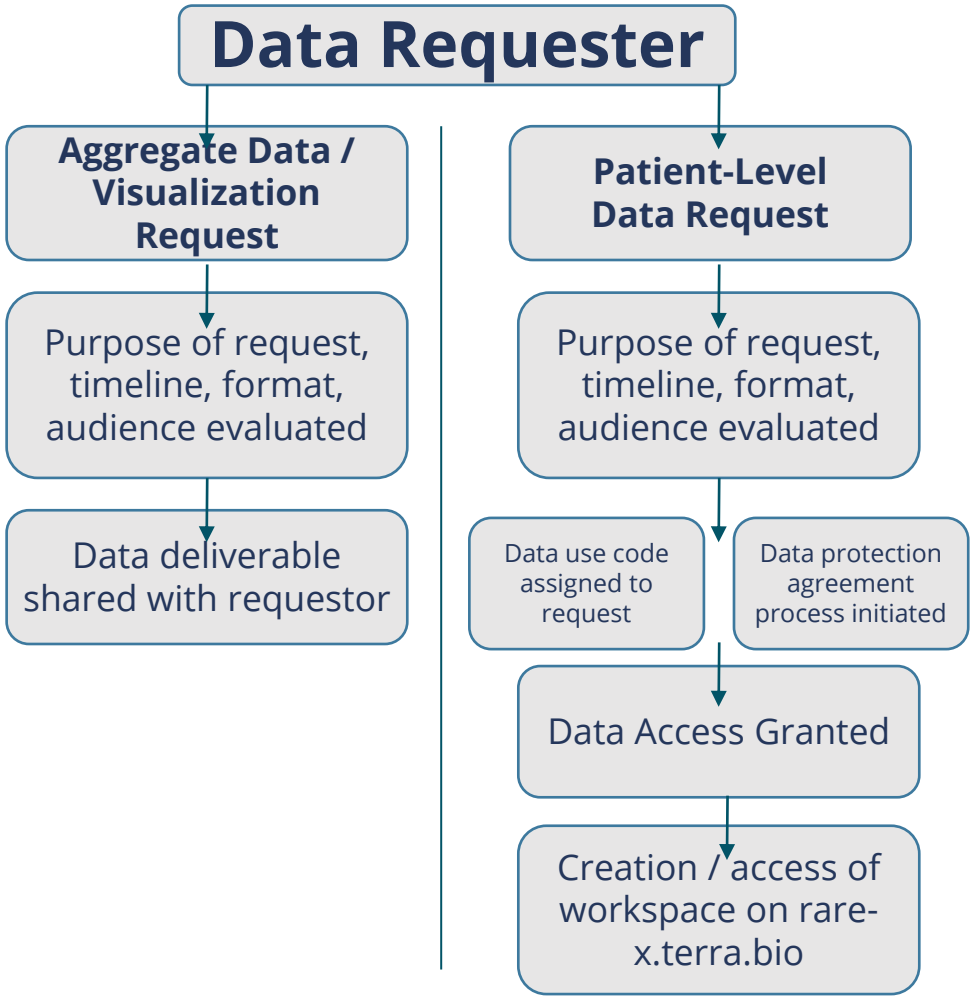
Top Symptoms Reported across the DCP



Data Access

Global Genes® Allies in Rare Disease + RARE X A Research Program of Global Genes

Data Access



The RARE-X consent process enable the RARE-X program to assign data use ontologies and allows different levels of data access to requesters. Enrollees always have access to and control of, all their own data.

There are 2 types of external data access requests

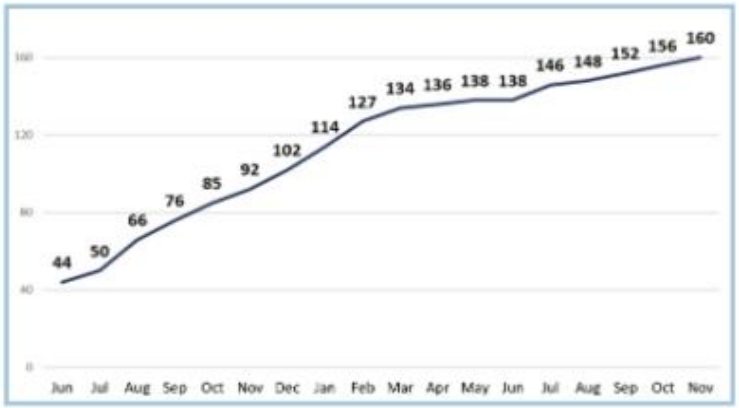
- Aggregate data (survey level counts, graphs, etc) via a project share.
- Participant level de-identified data (Via https://rare-x.terra.bio/)

All requesters are required to complete a **Data Access Request** form that outlines the requested data usage as well as data protection procedures.

- This allows Global Genes to track data use and analysis projects and timelines.
- All data requests are reviewed by **Global Genes RARE-X Data Access Committee**. This is to ensure the requestor's needs are being fulfilled as well as data protection requirements are met.

Global Genes RARE-X

Data Visualization Request Examples



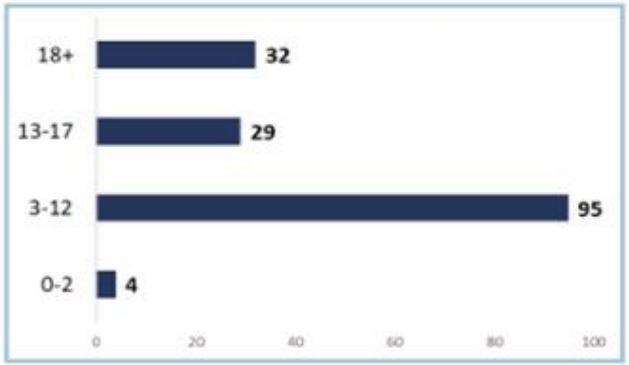
RAREX
A Research Program of Global Genes

PARTICIPATION OVER TIME

The number of **participants currently enrolled** in the PAG data collection program is **160**.

DISTRIBUTION BY AGE GROUP

Over half of participants fall in the age range of **3 to 12 years old** with the second most common age category being **participants aged 18 and above.**



84

Total enrollees that identify as **Male**. This makes up **52.5% of all participants**.

70

Total enrollees that identify as **Female**. This makes up **44% of all participants**.

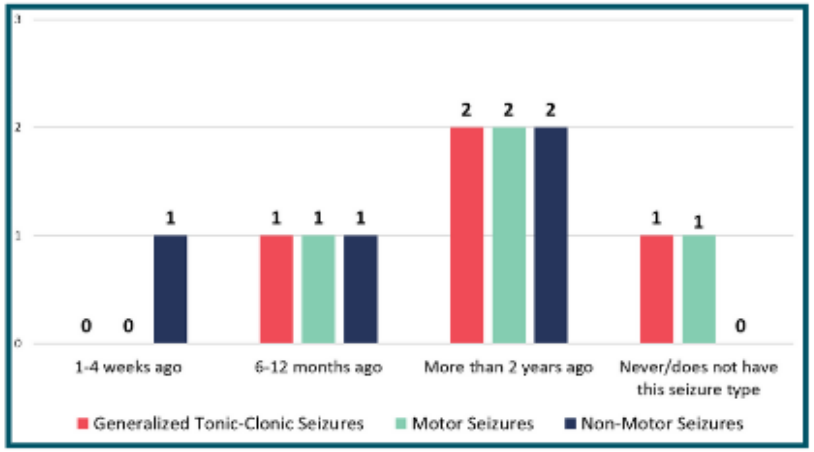
6

Total enrollees that identify as **Non-binary** or selected that they **Prefer Not To Answer.**

Data Visualization Request Examples

OF 4 PAG RESPONDENTS, 100% REPORTED THAT THE CHILD HAS EPILEPSY OR THE CHILD HAS HAD A SEIZURE.

When did the last Generalized Tonic-Clonic Seizure, Motor Seizure, and Non-Motor Seizure occur?



RARE X
A Research Program of Global Genes

CURRENT EPILEPSY SYNDROMES REPORTED BY RESPONDENTS

Childhood. Benign epilepsy with centrotemporal spikes (BECTS)	1
DeSanto Shinawi Syndrome	1
Not a syndrome (nonsyndromic, uncertain, too early to tell)	1
Does not have epilepsy	1

50%

Reported that the patient's epilepsy type is **both focal & generalized**

50%

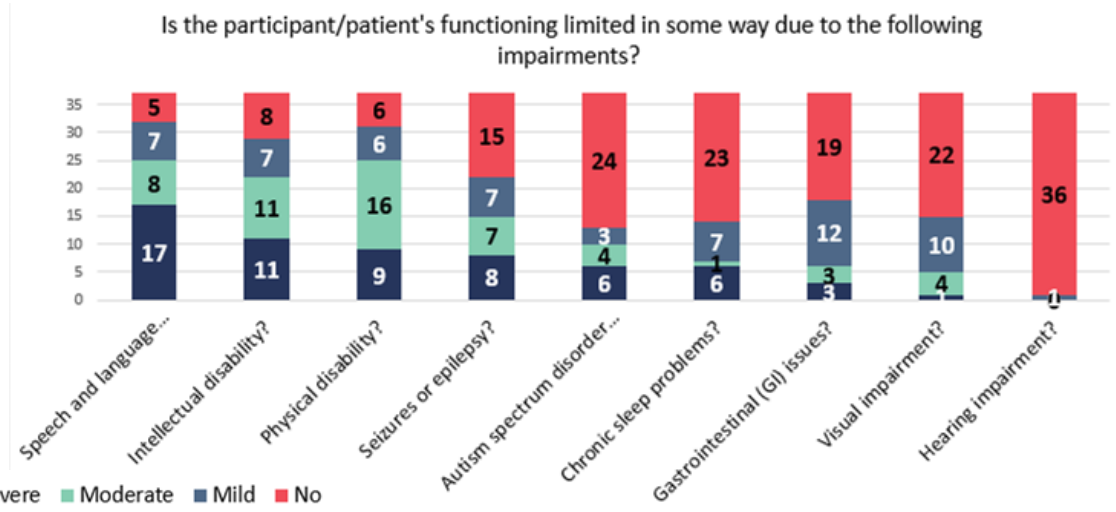
Reported that the patient's epilepsy type is **unknown**

100%

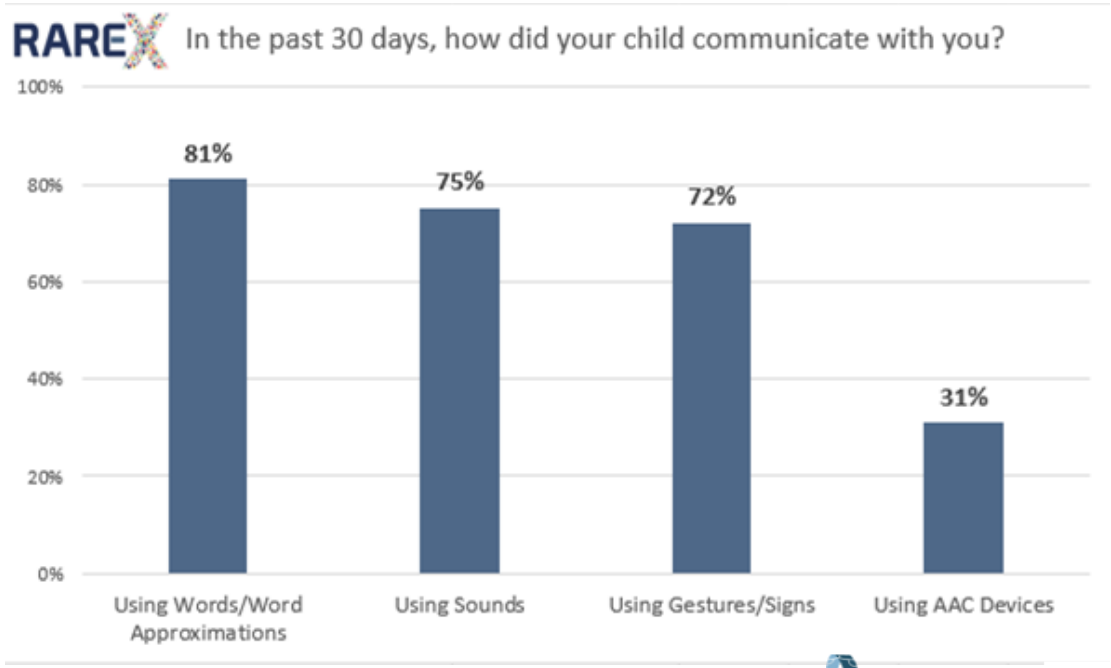
Of patients who have epilepsy reported that it is **NOT treatment resistant**

Data Visualization Request Examples

Is the participant/patient's functioning limited in some way due to the following impairments?	Severe	Moderate	Mild	No
Speech & language impairment	17	8	7	5
Intellectual disability	11	11	7	8
Physical activity	9	16	6	6
Seizures or epilepsy	8	7	7	15
Autism spectrum disorder (ASD)	6	4	3	24
Chronic sleep problems	6	1	7	23
Gastrointestinal (GI) issues	3	3	12	19
Visual impairment	1	4	10	22
Hearing impairment	0	0	1	36

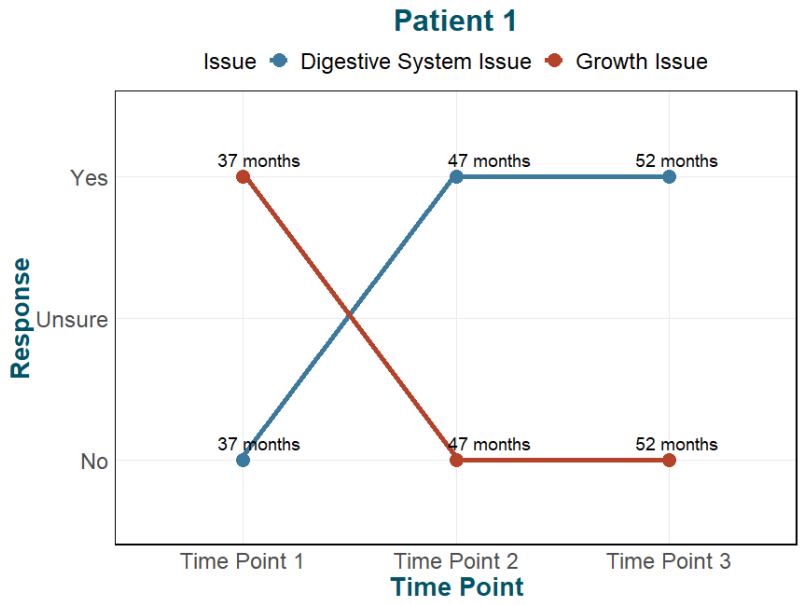


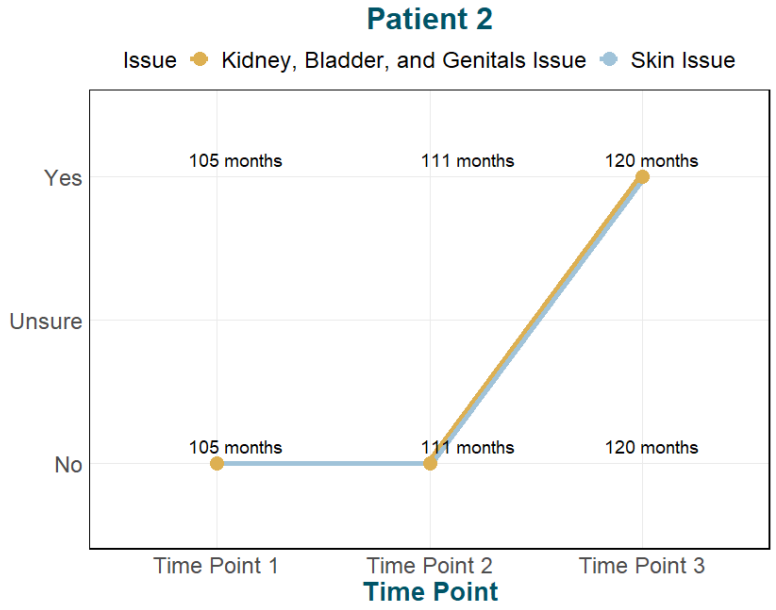
How patient communicated in past 30 days	% of all respondents	Number respondents
Using words/word approximations	81%	26
Using sounds	75%	24
Using gestures/signs	72%	23
Using AAC devices	31%	10

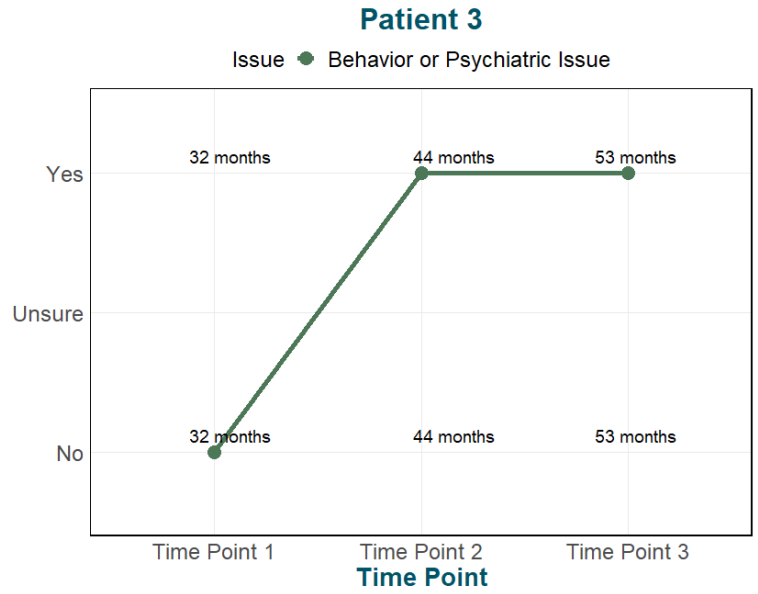


Longitudinal Data Collection Example

Three different patients with the same rare disease







Applications

Global Genes® Allies in Rare Disease + RARE X A Research Program of Global Genes

Applications

- **PRO Survey Validation**
  - Implement established surveys for validation in larger population
  - Development of new surveys addressing unmet needs, validated against established measures on RARE-X platform
- **Contribute to Natural History Studies**
  - Partner with IRB approved natural history study to administer & transfer PRO data to data collection site, enabling participants to update symptomes
  - Participants participating in RARE-X & natural history study to complete relevant PRO data one time for both studies, accelerating real word data collection on disease progression
- **Research Consortia**
  - Bring together diverse stakeholders to create collaborative data collection program with a specific aim
- **Partnership & Data Integration**
  - Rich repository of genetic data mapped to phenotypic data collected in platform
  - Robust data collection available to researchers

Partnership & Data Integration

With the Commission for Novel Technologies for Neurodevelopmental CNVs ("Commission")

Background: RARE-X previously completed biosample collections as a part of a sub-study that was developed in partnership with the Commission for Novel Technologies for Neurodevelopmental CNVs ("Commission").

RARE-X and the Commission partnered with the biotechnology company Illumina, and **sent blood samples to the Illumina team for long-read whole genome sequencing, short-read whole genome sequencing, and methylation testing**.

This partnership has led to a **rich repository of genetic data that is being mapped to phenotypic data that has been collected on the RARE-X** platform.

Many participants were also given clinical assessments at family conferences by partnering clinicians, or had clinical data collected at a Collaborative Clinic that enabled data sharing.

This effort has ultimately **allowed for large and robust data collection in a consortium of three ultra-rare disorders**. **The data collected is available to researchers upon request, encouraging research** into these rare and under-researched diseases.

Contribute to Natural History Studies

To get real world data on disease progression Patient-Reported Outcomes (PROs) are utilized to collect data based on signs/symptoms observed by the participant or a caregiver.

PROs are often given in a clinician office for the patient to take home and return at the next appointment. **RARE-X can partner with an IRB approved natural history study to administer and transfer the PRO data to the data collection site.** This partnership will **allow participants who are participating in both RARE-X, and a natural history study to complete the relevant PRO data a single time for both studies**.

Participants can go in an **update their symptoms on both a scheduled and as needed basis**. The ability to update their symptoms will help **capture the common symptoms/patterns but also patterns that were previously not visible**.

Conclusion

PAST:
Accomplishments

Stakeholder Partnership for PRO Data Collection
Established diverse partnerships for bi-directional input

Symptom-Based Data Collection
Enhanced understanding of disease manifestations by collecting patient-reported symptom data

Cross-Disease Database
Facilitated studying commonalities and differences across diseases

Genetic Data Curation
Developed workflow for curating genetic data from reports

Patient-Preferred Data Sharing
Implemented patient-preferred data sharing

Aggregate Data Reports
Developed templates for aggregate data reports

Individual-Level Data Access
Enabled secure access to individual-level data

Longitudinal Data Collection
Collected data from multiple timepoints

Research Interest Growth
Garnered increased researcher interest despite limited dissemination

PRESENT: Promises

PRO Surveys
Piloted implementation of select PRO surveys, facilitating prioritization for large-scale natural history studies.

Open Science Data Challenge (OSDC)
Initiated an OSDC to promote broader access to our registry and encourage innovative analysis in rare disease.

Data Mapping
Piloted data mapping to external clinical datasets, expanding the scope and utility of our database.

Natural History Studies
Facilitated linkage with natural history study datasets, enhancing the richness and depth of available data.

Translation
Initiated a translation workflow to broaden the accessibility and reach of our platform, promoting inclusivity and diversity.

FUTURE: Challenges & Opportunities

Protocol Standardization
Help to facilitate **coordinated** efforts to address the lack of standard protocols for PRO data collection efforts.

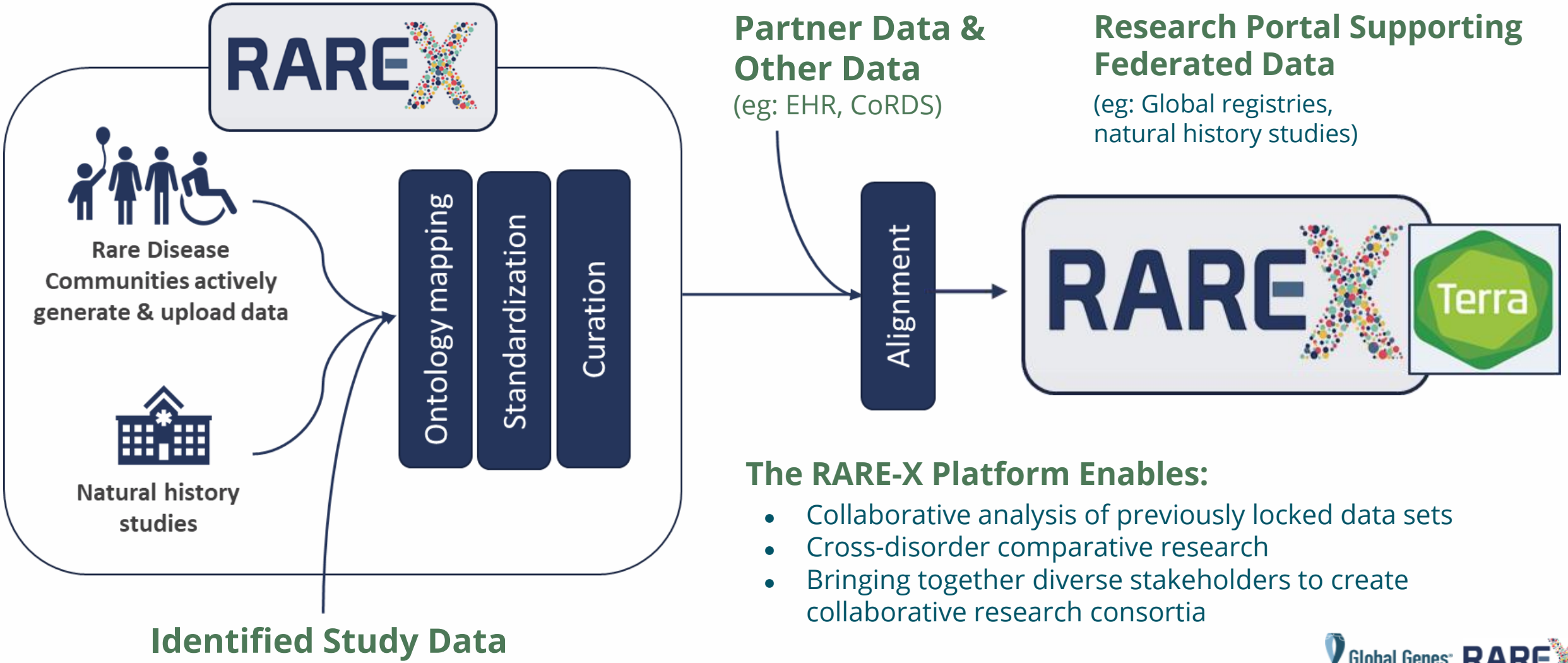
Evaluation Frameworks
Identify standardized **metrics** for evaluating the impact of PRO data collection efforts.

Analytical Feature Expansion
Identification and expansion of **analytical features** to streamline dynamic and real-time data mapping, enhancing usability and effectiveness of PRO data.

Longitudinal Data Workflow
Create a standard analytical **workflow** to leverage longitudinal data points while taking into consideration their inherent variation, to enhance the utility and accuracy of analyses derived from longitudinal PRO data.

National Taskforce Establishment
Landscape/Scope/Advocate the need for new dedicated funding pipelines to support the future direction of PRO data collection harmonization efforts and **sustainability** of these unique resources.

Visual Summary: Data Generation, Alignment, Federation



The RARE-X Platform Enables:

- Collaborative analysis of previously locked data sets
- Cross-disorder comparative research
- Bringing together diverse stakeholders to create collaborative research consortia

RARE-X

A Research Program of Global Genes

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Jade Gosar
Data Analyst

Ugo Ugwuowo
Data Analyst

Funding Opportunities

Philip J. Brooks, PhD
National Center for Advancing Translational Sciences, NIH

Katherine Needleman, PhD, RAC
Office of Orphan Products Development, FDA

REAGAN-UDALL
FOUNDATION
FOR THE FDA

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

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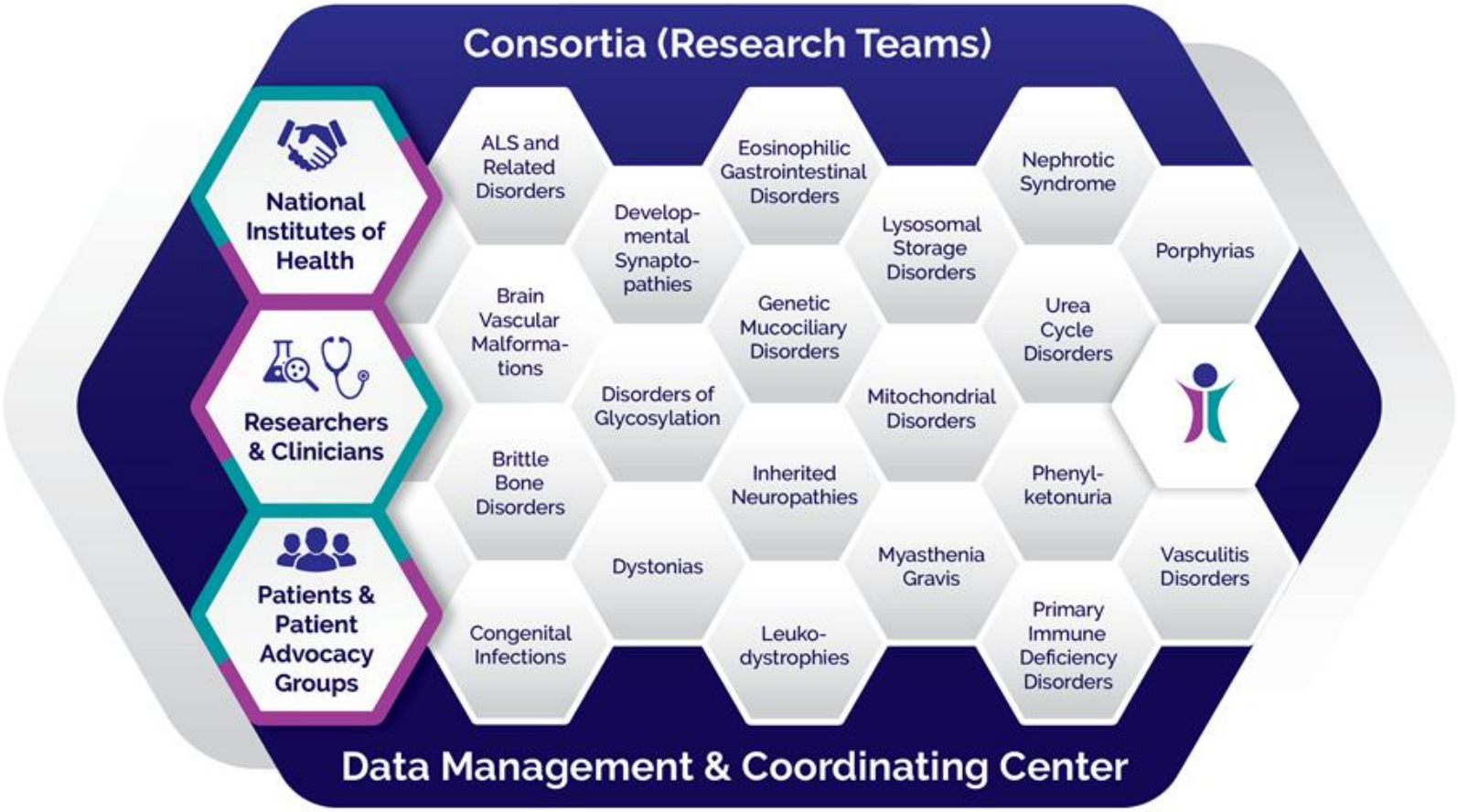
National Center for Advancing Translational Sciences

RARE DISEASES CLINICAL RESEARCH NETWORK

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



Current 2024

National Center for Advancing Translational Sciences

National Center for Advancing Translational Sciences

National Institute of Dental and Craniofacial Research

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Allergy and Infectious Diseases

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Neurological Disorders and Stroke

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institute of Mental Health

National Heart, Lung, and Blood Institute

National Institutes of Health
Office of Dietary Supplements

Every RDCRN consortium:

Studies at least 3 related rare diseases

Career Enhancement Core
Works to develop the next generation of rare disease researchers

Admin Core
Is a partnership of researchers and clinicians, patients and patient advocates, and the NIH

Pilot/Feasibility Governance Core
Supports innovative pilot projects

Clinical Research Projects
Conducts 2-4 clinical research projects, including a natural history study

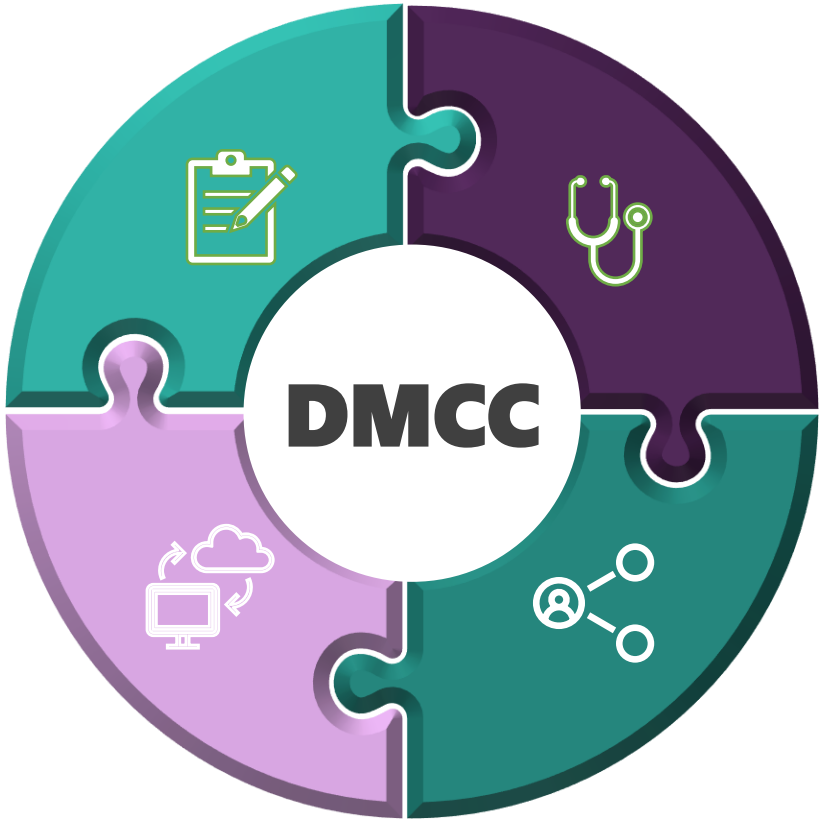
DMCC
Is supported by a central Data Management and Coordinating Center

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

Promotes patient engagement and broad research dissemination

National Center for Advancing Translational Sciences

RARE DISEASES CLINICAL RESEARCH NETWORK

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*

12 FDA-approved treatments for 11 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
CEGIR	EOHILIA	budesonide oral suspension	eosinophilic esophagitis (**EoE**)	Takeda	February 2024

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PAR-24-206

Rare Diseases Clinical Research Consortia (RDCRC) for the Rare Diseases Clinical Research Network (RDCRN) (U54 Clinical Trial Optional)

The following types of studies are not responsive to this NOFO.

Applications proposing such studies will be considered non-responsive, will be withdrawn from review, and not considered for funding.

- Single site clinical studies
- Phase III Clinical Trials as part of Clinical Research Projects
- There are fewer than three rare diseases included
- There is not at least one longitudinal natural history study
- There are either less than two or more than four research projects submitted
- There is no patient advocacy group involved
- Basic sciences studies
- Applications that propose any type of animal studies within the RDCRC. The use of in vitro models must be relevant to clinical endpoints (i.e., testing drugs, validating biomarkers versus more basic research)

National Center for Advancing Translational Sciences

RARE DISEASES CLINICAL RESEARCH NETWORK

Rare Diseases Clinical Research Consortia (RDCRC) for the Rare Diseases Clinical Research Network (RDCRN) (U54 Clinical Trial Optional)

Key Dates

Posted Date	April 02, 2024
Open Date (Earliest Submission Date)	July 12, 2024
Letter of Intent Due Date(s)	30 days prior to the application due date

Application Due Dates			Review and Award Cycles		
New	**Renewal / Resubmission / Revision (as allowed)**	**AIDS - New/Renewal/Resubmission/Revision, as allowed**	**Scientific Merit Review**	**Advisory Council Review**	**Earliest Start Date**
August 13, 2024	August 13, 2024	Not Applicable	February 2025	May 2025	July 2025

All applications are due by 5:00 PM local time of applicant organization.

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.

https://grants.nih.gov/grants/guide/pa-files/PAR-24-206.htm

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NCATS

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National Center for Advancing Translational Sciences

OOPD's Funding Opportunities for Rare Diseases

Katherine Needleman, MS, PhD, RAC
Director, Orphan Products Grants Program
FDA/OOPD
May 13, 2024

FDA/NIH/NCATS/Reagan Udall Foundation Public Workshop:
Natural History Studies and Patient Registries In the Development of Rare Disease Treatments

Office of Orphan Products Development

- The Office of Orphan Products Development (OOPD) provides incentives for sponsors to develop products for rare diseases.
- **Mission**: To promote the development of drugs, devices, biologics, and medical foods for patients with rare diseases and special populations.

DESIGNATION PROGRAMS	
1	Orphan Drug Designation & Exclusivity
2	Rare Pediatric Disease (RPD) Designation
3	Humanitarian Use Device Designation (HUD)

GRANT PROGRAMS	
1	Orphan Products Clinical Trials Grant Program
2	Orphan Products Natural History Grant Program
3	Pediatric Device Consortia Grant Program
4	Rare Neurodegenerative Disease Grant Program

Learn more about OOPD Grants programs:
Office of Orphan Products Development | FDA

Orphan Products Grants Program

- **Established:** 1983
- **Overall Budget**: ~$19M
- **Goal**: To advance the development of orphan products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis or treatment of rare diseases or conditions
- **Clinical Trial Grants**
  - Funding ~ 75 ongoing studies
  - Focus on efficiency and innovative trial designs
  - Grants have led to over 85 product approvals
  - Publications, impact on field
- **Natural History (NH) Grants**
  - Launched Program in 2016
  - Currently funding 14 grants
  - Potential impact for clinical trial development and supporting regulatory decisions
  - Collaborations with industry and patient groups and publications

Rare Neurodegenerative Disease Grant Program

- **Established:** upon enactment of the ACT for ALS in December 2021.
- **FY2024 Budget:** $5M
- **Purpose**: Grants and contracts to public and private entities to cover costs of research on, and development of interventions intended to prevent, diagnose, mitigate, treat, or cure ALS and other rare neurodegenerative diseases in adults and children, including costs incurred with respect to the development and **critical evaluation of tools, methods, and processes**
- To learn more about this program, see:

Rare Neurodegenerative Disease Grant Program | FDA

Funding Opportunities Details

- **Eligibility:**
  - Foreign or domestic, public or private, for-profit or nonprofit entities (state and local units of government) are eligible; Federal agencies may not apply
  - The disease proposed to be studied meet the definition of a rare disease (prevalence of fewer than 200,000 persons in the US)
- **Budget:**
  - Yearly budget depends on the RFA. See RFA for limits.
- **How to Apply:**
  - Grants.gov
  - Instructions in the SF424 (R&R) Application Guide, except where noted otherwise
  - Helpful Hint documents for all FOA on OOPD's website
  - Registrations required to submit (e.g., SAM, eRA Commons, grants.gov)
  - Start Early!
- **Review and Awards:**
  - Reviewed by experts in the field
  - Number of awards is contingent upon FDA appropriations and submission of a sufficient number of meritorious applications
  - Funding dependent on **quality of application** and **availability of Federal funds**

OOPD Funding Opportunities

- Clinical Studies of Orphan Products Addressing Unmet Needs of Rare Diseases (R01)
  - Receipt Dates: October 22, 2024
  - Resubmission Only Receipt Dates: June 4, 2024; June 3, 2025
  - FOA Number: RFA-FD-23-001
- Efficient and Innovative Natural History Studies Addressing Unmet Needs in Rare Diseases (R01)
  - Receipt Dates: February 13, 2024
  - FOA Number: RFA-FD-22-001
- Natural History and Biomarker Studies of Rare Neurodegenerative Diseases (U01)
  - Receipt Dates: May 6, 2024
  - FOA Number: RFA-FD-24-024

Apply through Grants.gov – links in the RFA

Funding opportunities for rare disease research | FDA

OOPD Contact Information

For more information on OOPD programs go to:

www.fda.gov/orphan

Still have questions?

Email us at orphan@fda.hhs.gov
Email: katherine.needleman@fda.hhs.gov

Call us at 301-796-8660


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Lunch

The meeting will resume at 1:35 pm ET

REAGAN-UDALL FOUNDATION FOR THE FDA

Natural History Studies and Registries in the Development of Rare Disease Treatments

Hybrid Public Workshop

May 13, 2024 | 10am-4pm *(eastern)*

A workshop prepared in collaboration with the Food and Drug Administration and the NIH National Center for Advancing Translational Sciences

REAGAN-UDALL FOUNDATION FOR THE FDA