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FDA Center for Drug Evaluation and Research and Johns Hopkins Center of Excellence in Regulatory Science and Innovation (CERSI) Workshop

Addressing Challenges in the Design and Analysis of Rare Disease Clinical Trials: Considerations and Tools

May 2 – 3, 2023

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May 2, 2023

Collection and Use of Fit-for-Purpose Data for Rare Disease Drug Development

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Welcome

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Session 1:
How to Collect Quality and Fit-for-Purpose Data

Moderator: Scott Winiecki, MD
Team Lead
Rare Diseases Team, Division of Rare Diseases and Medical Genetics,
Office of New Drugs, Center for Drug Evaluation and Research, FDA

U.S. FOOD & DRUG ADMINISTRATION

CDER-JHU CERSI Workshop

Regulatory Perspectives on Real-World Data

2 May 2023

John Concato, MD, MS, MPH
Associate Director for Real-World Evidence Analytics
Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Disclaimer

- Views and opinions expressed are those of the presenter and should not be attributed to the Food and Drug Administration
- No conflicts of interest exist related to this presentation
- Mention of a commercial product should not be construed as actual or implied endorsement

Objectives

- Recognize historical context leading to current use of the terms “real-world data” and “real-world evidence”
- Understand main components of FDA’s Real-World Evidence Program, emphasizing guidance development
- Identify challenges and potential contributions of using real-world data and real-world evidence

‘Real-World’ Definitions (from 2018 FDA Framework)

Real-World Data (RWD) are data relating to patient health status and/or delivery of health care **routinely collected from a variety of sources**

- **electronic health records (EHRs)**
- **medical claims data**
- **product and disease registries**
- **data from digital health technologies in non-research setting**
- **other data sources that can inform on health status, such as questionnaires**

Real-World Evidence (RWE) is clinical evidence regarding the usage and potential benefits/risks of a medical product **derived from analysis of RWD**

Generated using various study designs—including but not limited to **randomized trials (e.g., pragmatic clinical trials)**, externally controlled trials, and observational studies

Background on 'Big Data'

Origin: term appeared in computer science literature during 1990s, often referring to data too large to be stored in then-conventional storage systems

Contemporary usage: *Big Data* represents "[…] shorthand for advancing trends in technology that open the door to a new approach to understanding the world and making decisions" (Lohr S, *New York Times*, 11 Feb 2012)

Perspective: modern technology has increased quantity and forms of available data as well as the speed to merge and manipulate data, yet integration and analysis of large-scale data has always been integral to epidemiology

21st Century Cures Act of 2016

- **FDA established a program to evaluate the potential use of real-world evidence (RWE) to:**
  - **Support a new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Draft framework issued in December 2018:**
  - **Describe sources of RWE, challenges, pilot opportunities, etc.**
- **Draft guidance for industry issued in Sep, Oct, Nov, Dec 2021**
- **Standard for substantial evidence remains unchanged; commitments met for Prescription Drug User Fee Act (PDUFA) VI; new Advancing RWE initiatives in PDUFA VII**

Background on 'Real-World Evidence'

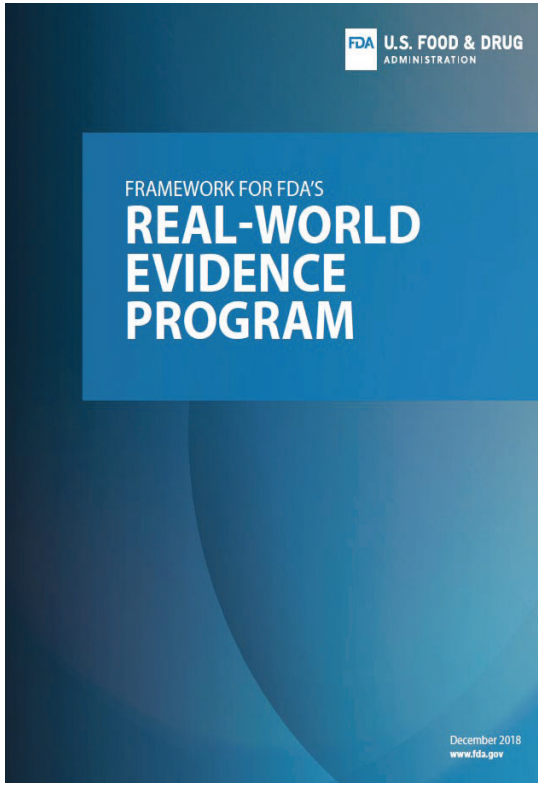
Origin: "real world" is a non-specific modifier; "real-world data (RWD)" and "real-world evidence (RWE)" appeared in medical literature as of the 1970s or earlier, in various contexts (*terms to be defined in subsequent slide*)

Contemporary usage: RWD and RWE have specific regulatory implications

Perspective: older epidemiologic terms were sufficient, but emergence of big data and enactment of 21st Century Cures has led to sometimes confusing use of different taxonomies for study design

Example: "RWE study" is not synonymous with "observational study"; additional details are needed to classify study design

FDA's Real-World Evidence (RWE) Program



- **Applies to Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), & Oncology Center of Excellence (OCE) – *Note: Center for Devices and Radiological Health (CDRH) has separate program***

- **Multifaceted program to implement RWE:**
  1) internal processes
  2) external stakeholder engagement
  3) research ("demonstration") projects
  4) guidance development

https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

1) Internal and 2) External Engagement

- **Real-World Evidence Subcommittee *internal* activities, w/ membership comprised of FDA staff from multiple CDER and CBER Offices:**
  - **providing oversight of policy development on RWE (e.g., guidances)**
  - **offering resources and leadership (e.g., to review divisions)**
  - **other activities**

- **RWE Subcommittee *external* activities include:**
  - **providing feedback on early-stage proposals from sponsors, vendors, etc.**
  - **discussing initiatives presented to Subcommittee for consideration**

- ***Additional* activities, beyond the Subcommittee, include:**
  - **holding FDA- or Center-level public meetings on RWE-related topics**
  - **conducting FDA small business & industry webinars, speaking engagements**

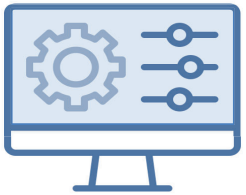
3) RWE Demonstration Projects – Examples

Data

- ‘OneSource’ project to improve quality of EHR data
- Collection and use of EHR data from neonatal intensive care units

Study Design

- RCT-DUPLICATE trial emulations
- Statistical approach for RCT designs w/ ‘hybrid’ control arms



Tools

- Evaluation of confounded treatment effects
- Targeted learning framework for causal effect estimation

4) FDA Draft RWE Guidance – Sep-Dec 2021

Guidance for Industry

DRAFT GUIDANCE

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

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

Data Standards for Drug and Biological Product Submissions Containing Real-World Data

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

RWE Draft Guidance – EHR/Claims Data

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

September 2021
Real World Data/Real World Evidence (RWD/RWE)

EHR/Claims Data Guidance – Overview

Focus of draft guidance:

- **Selection of data source(s) to appropriately address the study question**
- **Development and validation of definitions for exposures, covariates, outcomes**
- **Data provenance during accrual, curation, analysis**

Note: choice of study design and method of statistical analysis are outside of guidance scope

RWE Draft Guidance – Registry Data

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

DRAFT GUIDANCE

November 2021
Real World Data/Real World Evidence (RWD/RWE)

Registry Data Guidance – Overview

Focus of draft guidance:

- **Registry fitness-for-use in regulatory decision-making, focusing on attributes that support collection of relevant and reliable data**
- **Linking a registry to other data source(s) for supplemental information, such as data from medical claims, electronic health records (EHRs), digital health technologies, or other registries**
- **FDA review of submissions that include registry data**

Note: The guidance does not provide recommendations on choice of study design or approach to statistical analysis

RWE Draft Guidance – Data Standards

Data Standards for Drug and Biological Product Submissions Containing Real-World Data

Guidance for Industry

DRAFT GUIDANCE

October 2021
Real-World Data/Real-World Evidence (RWD/RWE)

Data Standards Guidance – Overview

Focus of draft guidance:

- **Processes for managing RWD**
- **Conforming RWD to FDA data standards**
- **Mapping RWD to FDA submission standards**
- **Considerations for data transformations**

Note: this guidance applies regardless of the type of RWD

RWE Draft Guidance – Regulatory Considerations

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

DRAFT GUIDANCE

December 2021
Real World Data/Real World Evidence (RWD/RWE)

Regulatory Considerations Guidance – Overview

- **Marketing application to support safety/effectiveness of a drug must satisfy applicable legal standards to be approved or licensed, even if 21 CFR part 312 (Investigational New Drug Application) does not apply**
- **Two classifications of non-interventional studies:**
  1) ***involve only*** **analysis of data on use of marketed drug in routine practice**
  2) ***include*** **ancillary protocol-specified activities or procedures (e.g., lab tests, imaging studies, questionnaires)**
     - **FDA does not consider these types of studies to be clinical investigations under 21 CFR part 312**
     - **Nonetheless, protection of human subjects is critical; sponsors must ensure applicable requirements met per FDA regulations 21 CFR parts 50 (Protection of Human Subjects) & 56 (Institutional Review Boards)**

Draft Guidance: Externally Controlled Trials

Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

DRAFT GUIDANCE

February 2023
Real-World Data/Real-World Evidence (RWD/RWE)

https://www.fda.gov/media/164960/download

Externally Controlled Trials Guidance – Overview

Focus of draft guidance:

- **Importance of design considerations (e.g., finalize protocol before analyzing data)**
- **Data considerations for the external control arm (e.g., various comparability issues)**
- **Analysis considerations (e.g., "FDA does not recommend a particular approach")**
- **Considerations to support regulatory review (e.g., access to patient-level data)**

Note: Guidance does not address external control data a) based on summary-level estimates, or b) supplementing a control arm in a traditional randomized trial

Externally Controlled Trials Guidance (cont'd)

Excerpt from draft guidance:

IV. CONSIDERATIONS TO SUPPORT REGULATORY REVIEW

A. Communication with FDA

Sponsors should consult with the relevant FDA review division early in a drug development program about whether it is reasonable to conduct an externally controlled trial instead of a randomized controlled trial. As part of these discussions, sponsors should provide a detailed description of the (1) reasons why the proposed study design is appropriate, (2) proposed data sources for the external control arm and an explanation of why they are fit for use, (3) planned statistical analyses, and (4) plans to address FDA's expectations for the submission of data.

Final Guidance – Submitting RWD/RWE to FDA

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products

Guidance for Industry

September 2022
Procedural

https://www.fda.gov/media/124795/download

Status of FDA RWE Guidance – April 2023

Category	Topic	Status	Date
Data considerations	EHRs and claims data	draft published	Sep 2021
	Registry data	draft published	Nov 2021
Submission of data	Data standards	draft published	Oct 2021
Applicability of regulations	Regulatory considerations	draft published	Dec 2021
Design considerations	Externally controlled trials	draft published	Feb 2023
	RCTs in clinical practice settings	*draft in development*	–
	Non-interventional studies	*draft in development*	–
Procedural	Submitting documents	final published	Sep 2022

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

DRAFT GUIDANCE

December 2021
Clinical/Medical

Current Status of Real-World Evidence

Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.

Issue being addressed: More than five years after passage of the 21st Century Cures Act, the terms RWD and RWE are being used inconsistently and interchangeably

Content of article:

- **addressed two common misconceptions**
- **provided conceptual overview of study design**
- described FDA demonstration projects and guidance
- highlighted regulatory approvals
- offered path forward

N ENGL J MED 386;18 NEJM.ORG MAY 5, 2022

Misconceptions regarding RWD & RWE

Frequent instances of:

- ***Misconception #1 – RWD & RWE are new concepts*: "In reality, sources of data and types of study design haven't fundamentally changed, but electronic access to more detailed clinical data is evolving & the data are becoming more relevant and reliable"**
- ***Misconception #2 – A simple dichotomy of randomized trials vs. observational studies exists*: "In reality, clinical trials are defined by assignment of treatment according to an investigational protocol, and single-arm trials face challenges similar to those in observational studies in determining whether difference in clinical outcomes (compared to an external control group) represent actual treatment effects"**

N ENGL J MED 386;18 NEJM.ORG MAY 5, 2022

Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.

FDA

Randomized, Interventional Study		Nonrandomized, Interventional Study	Nonrandomized, Noninterventional Study
Traditional randomized trial using RWD in planning	**Trial in clinical practice settings, with pragmatic elements**	**Externally controlled trial**	**Observational study**
RWD used to assess enrollment criteria and trial feasibility RWD used to support selection of trial sites	Selected outcomes identified using, e.g., health records data, claims data, or data from digital health technologies RCT conducted using, e.g., electronic case report forms for health records data or claims data	Single-group trial with external control group derived from RWD	Cohort study Case–control study Case–crossover study

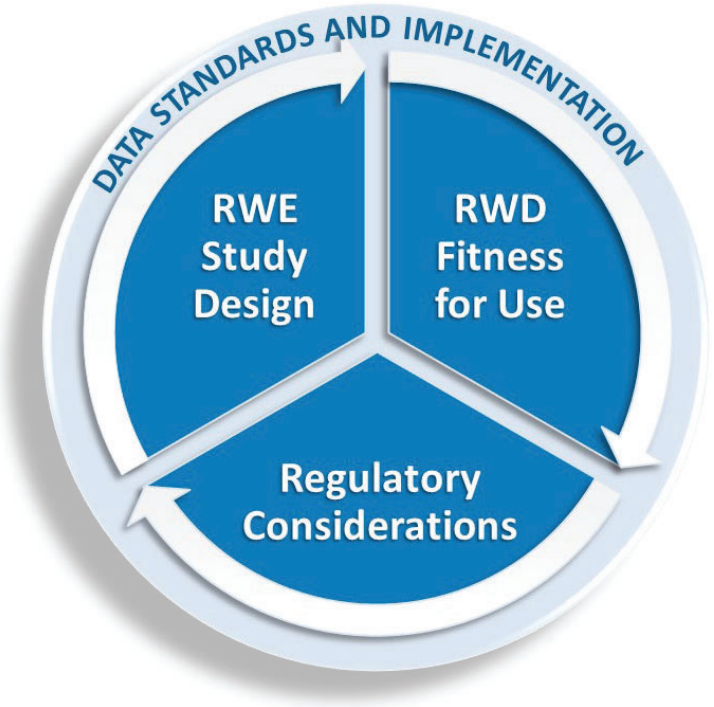
Generation of RWE

Increasing reliance on RWD

Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

RWE for Effectiveness: Overview of FDA Approach



Key considerations (from 2018 Framework):

- Whether the RWD are fit for use
- Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question
- Whether the study conduct meets FDA regulatory requirements

New Indication for Prograf® Based on RWE

- Prograf® (tacrolimus) approved for prophylaxis of organ rejection in patients receiving liver transplants in 1994 (later for kidney & heart) based on RCT evidence, and the drug is used widely in clinical care
- RCTs not done for lung transplant, but sponsor (Astellas Pharma US) submitted supplemental New Drug Application to FDA with non-interventional 'RWE' study
- Study data and design were evaluated according to FDA standards
- Approval for preventing rejection/death in lung transplant granted 16 Jul 2021

New Indication for Prograf® Based on RWE (cont'd)

Data: US Scientific Registry of Transplant Recipients (SRTR) data on all lung transplants in US during 1999–2017

Design and conduct: non-interventional (observational) treatment arm, compared to historical controls; analysis plan & patient-level data provided to FDA

Review: FDA determined this non-interventional study w/ historical controls to be *adequate and well-controlled*. Of note, outcomes of organ rejection and death are virtually certain without therapy, and the dramatic effect of treatment helps to preclude bias as explanation of results.

https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence

RWE – Representative Problems

Real-world data sources:

- issues related to data reliability and clinical relevance
- need for linkage to other data sources
- missing or "mistimed" data
- suitable capture of endpoints

Non-randomized study designs:

- threat of residual confounding
- problems with index date ("zero time")
- use of inappropriate comparator

Conduct of non-randomized studies:

- insufficient confirmation of *pre-specified* protocol and analysis plan
- issues related to FDA inspection

Summary

- "Big data" contributed to changes in how evidence generation is approached & described; research methods are also evolving

- FDA's RWE guidance & related efforts, along with other stakeholders, are addressing current challenges in using real-world data & evidence

- FDA will maintain evidentiary standards while considering RWD/RWE for regulatory decision-making

Acknowledgments

- Michael Blum, Phil Budashewitz, Jacqueline Corrigan-Curay, M. Khair ElZarrad, Tala Fakhouri, Kayla Garvin, Scott Gordon, Stefanie Kraus, Beth Kunkoski, Nahleen Lopez, Juanita Marner, Kristen Miller, Dianne Paraoan, Ken Quinto, Motiur Rahman, Leonard Sacks, Kim Smith

- Other colleagues in:
  - CDER Offices of Medical Policy, New Drugs, Surveillance & Epidemiology, Biostatistics, Regulatory Policy, Scientific Investigations, Strategic Programs, Translational Sciences
  - Center for Biologics Evaluation & Research; Oncology Center of Excellence; Center for Devices & Radiological Health
  - Office of the Commissioner

CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

How C-Path Uses the Latest Data Management and Data Science Techniques to Maximize the Value of Data

Ramona L. Walls, Exec. Dir. of Data Science

CDER-JHU CERSI Workshop on Rare Diseases
May 2, 2023

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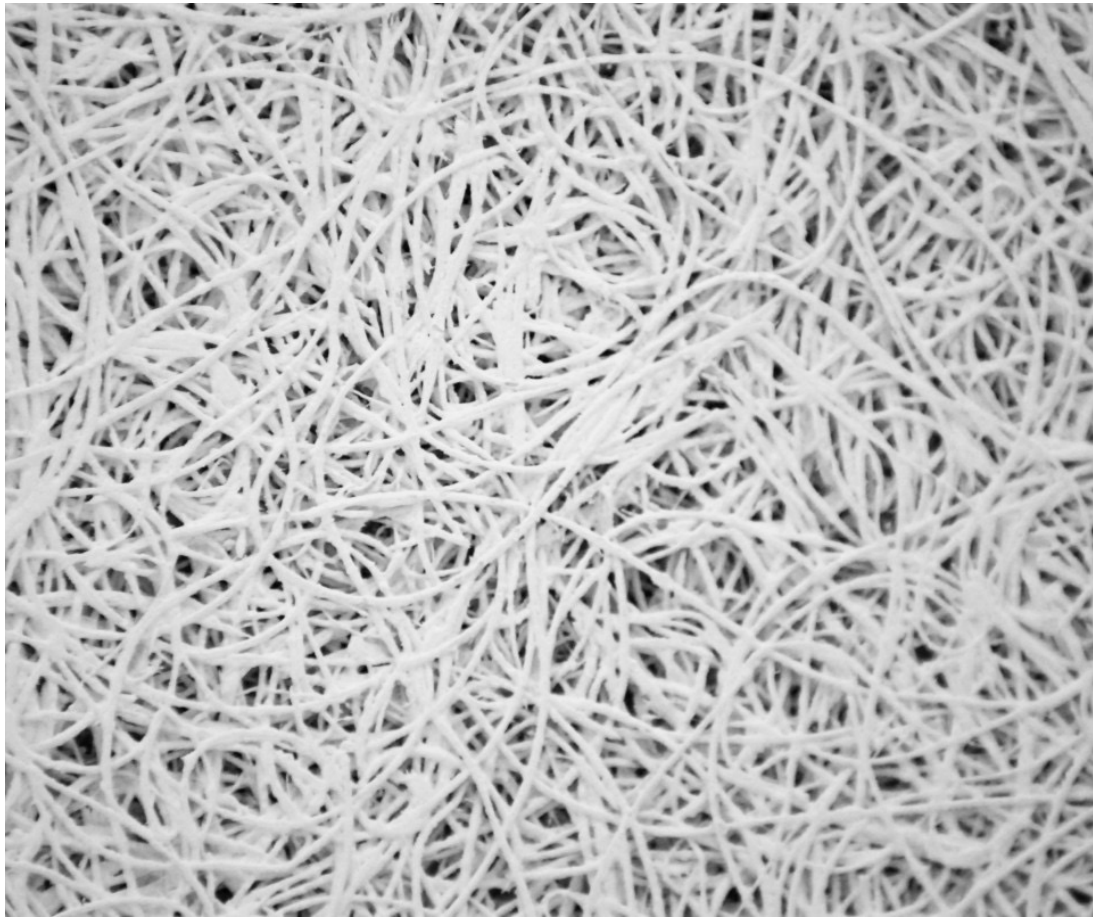
Rare disease data are rare

- Progress toward therapies for rare diseases is hampered by poor understanding of many diseases…
- …but there is a lot of potentially useful data out there.
- Unfortunately, those data are siloed, non-standard, and sometimes not usable due to data quality issues

Data quality concerns for reuse



- Lack of standardization (an gaps in standards)
- Siloed data sources (no access, different formats, different standards)
- Small patient populations are distributed among multiple sources without reliable methods for uniquely identifying patients

Who is C-Path and What Do We Do?

CRITICAL PATH INSTITUTE

Who We Are

CRITICAL PATH INSTITUTE

Mission

Critical Path Institute is a **catalyst for innovation that accelerates the path to a healthier world**

Vision

C-Path is an **indispensable partner of excellence in medical product development worldwide**, shaping innovative scientific and regulatory pathways to accelerate delivery of therapies for patients in need

C-Path Strengths

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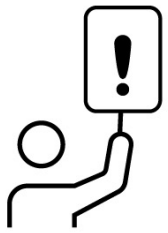
Unmet Medical Need



Core Competencies

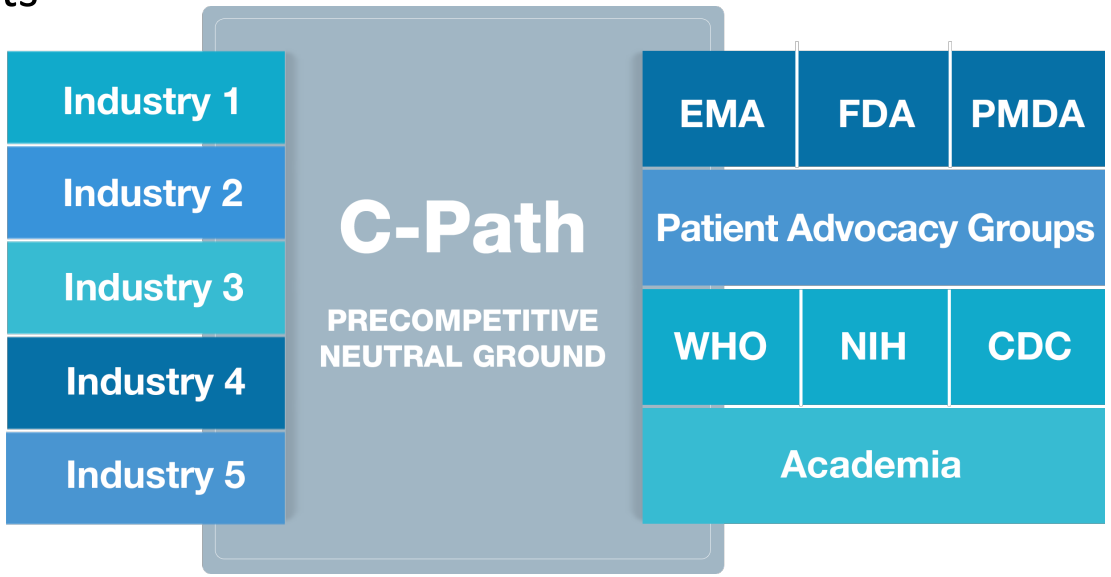
- Biomarkers
- Clinical Outcome Assessments
- Data Management and Standards
- Modeling and Analytics
- Regulatory/ Development Science

Bedrock Foundation: Unique Neutral Convener

DDTs and Other Solutions

How C-Path Works

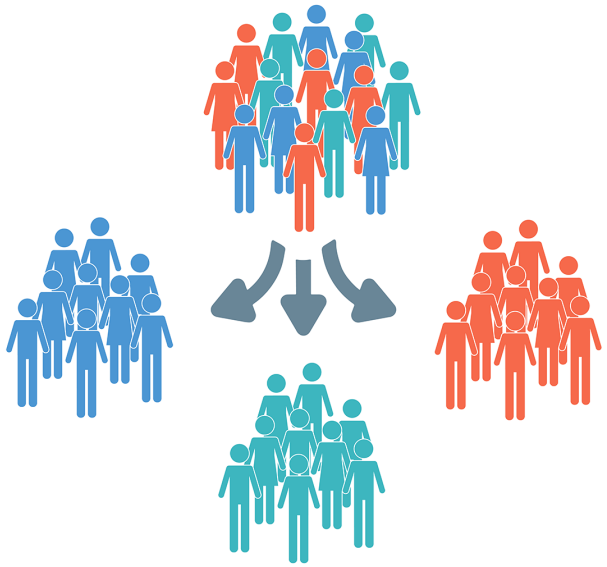
- Acts as a trusted, neutral third party
- Public-Private Partnerships
- Convenes scientific consortia of industry, academia and government for sharing of data and expertise
  - ✓ The best science
  - ✓ The broadest experience
  - ✓ Active consensus building
  - ✓ Shared risk and costs
- Enable iterative FDA/EMA/PMDA participation in developing new methods to assess the safety and efficacy of medical products



Official regulatory endorsement of novel methodologies and drug development tools

Why?

Not every drug works for every patient.
It is vital to target the right patients.

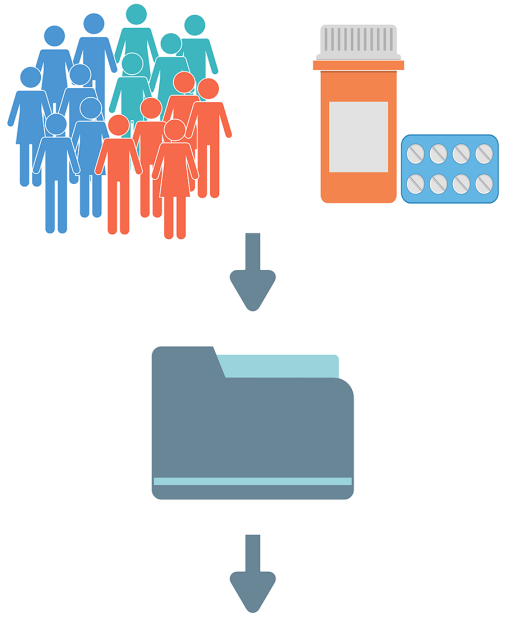


Who?

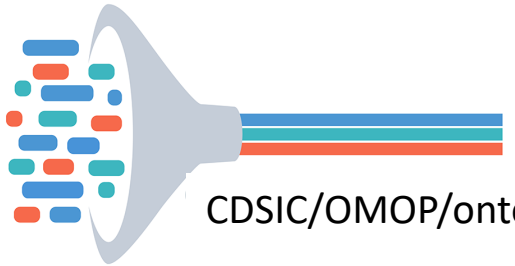
- Researchers
- Regulators
- Clinical trialists
- Advocacy groups

How?

Data from past clinical trials or RWD



Data standardization and integration



Informative models

What can a model do?

Information from model

Regulatory agencies

Results in

Right Target → Right Drug → Right Time → Right Patient → SUCCESS

Data Science Advances at C-Path

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C-Path Data Collaboration Center

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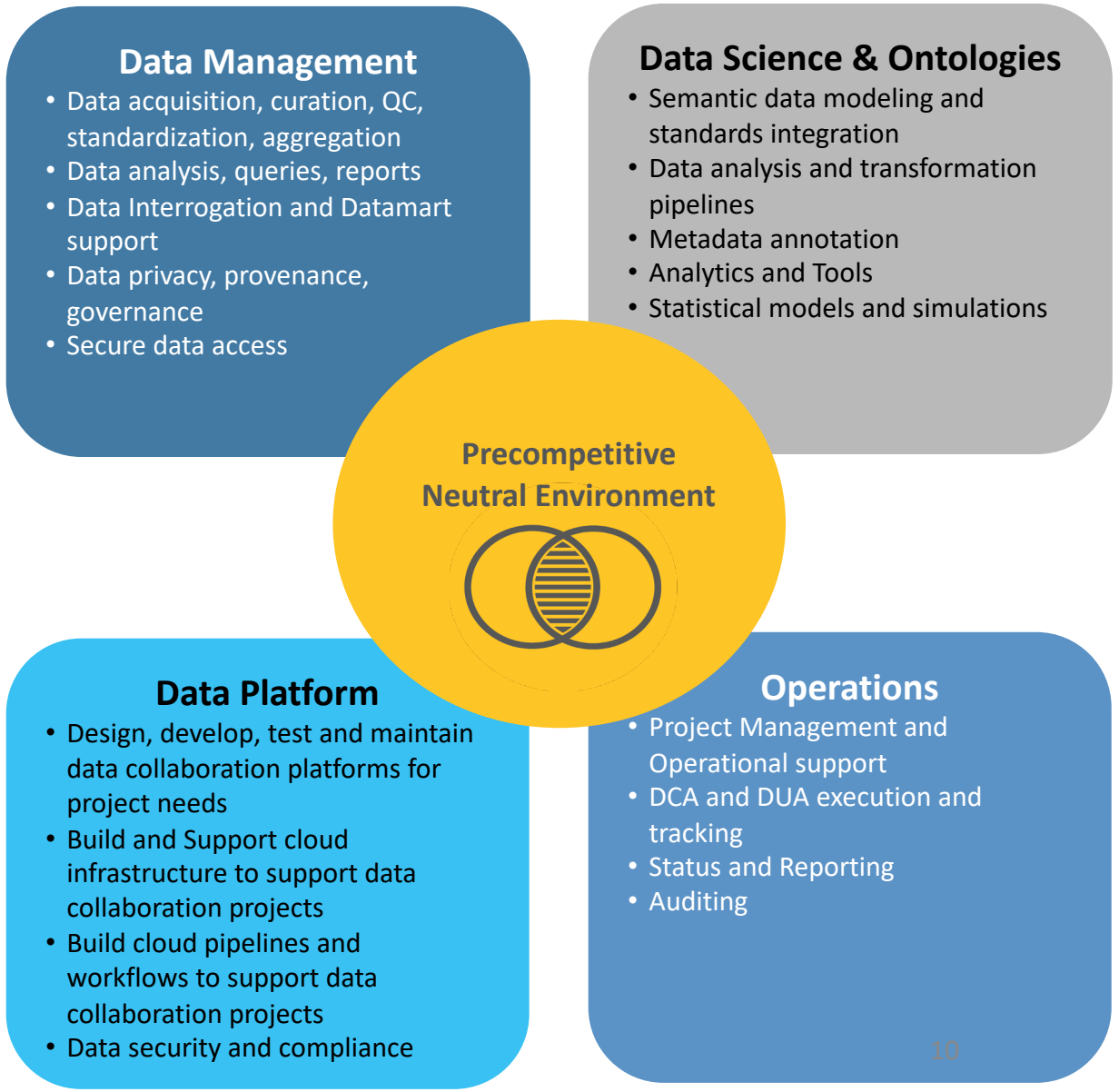
Mission: Enable multiple organizations to work together in a neutral setting and share data to maximize its value to inform medical product development and regulatory decision-making

How:

- Creation and administration of data storage and collaboration platforms
- Planning and execution of multi-source data standardization and aggregation
- Maximize the FAIRness of data by developing and integrating standards and semantic models, tools for consumption and sharing of data, performing data transformations that increase data accessibility, and by performing analyses that transform data into information
- Utilize robust, repeatable processes to ensure data integrity, security and protect patient privacy



FAIR Data Principles

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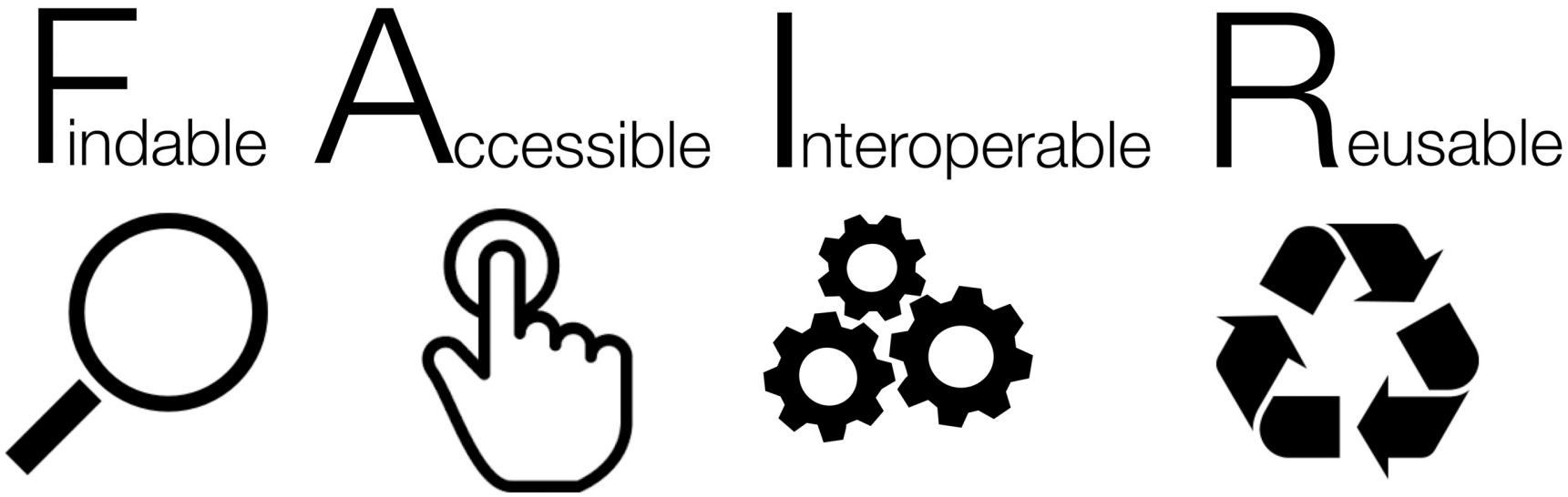

- Apply to both human and machine-driven processes
  - Humans have an innate understanding of semantics
  - Machines can operate at scale with less error
- See Wilkinson et al. 2016 https://www.nature.com/articles/sdata201618

DCC Approach to Data Management

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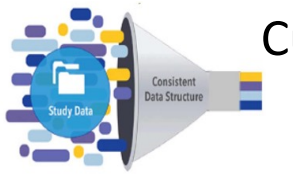
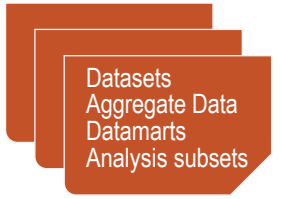
Data Contribution Agreement for each dataset

Transfer anonymized data through secure link



Curate, Standardize, Annotate Data

Integrate into Data Sharing Platform



Extract and
Analyze Data

DCC Approach to Data Management

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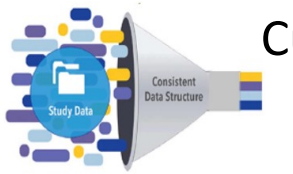
Data Contribution Agreement for each dataset

Innovations:
- Standard DCAs
- Machine readable DCAs

Transfer anonymized data through secure link



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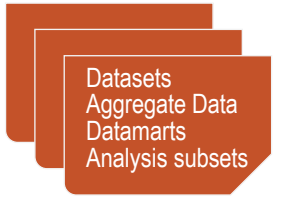
Integrate into Data Sharing Platform



Extract and
Analyze Data

DCC Approach to Data Management

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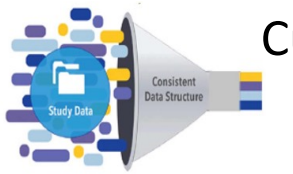
Data Contribution Agreement for each dataset

Transfer anonymized data through secure link

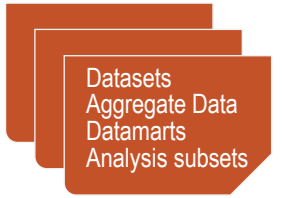
Innovations:

- Secure transfer via cloud services (AWS, Azure)
- Anonymization services
- Federated access



Curate, Standardize, Annotate Data

Integrate into Data Sharing Platform



Extract and Analyze Data

DCC Approach to Data Management

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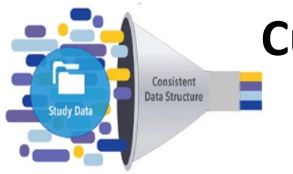
Data Contribution Agreement for each dataset

Transfer anonymized data through secure link

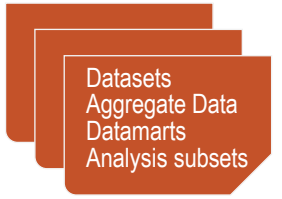


Curate, Standardize, Annotate Data

Innovations:

- Responsive curation
- Multiple standards (CDISC, OMOP, OBO)
- Scripting and automations
- Ontology and knowledge graph development

Integrate into Data Sharing Platform



Extract and Analyze Data

DCC Approach to Data Management

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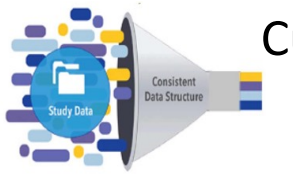
Data Contribution Agreement for each dataset

Transfer anonymized data through secure link

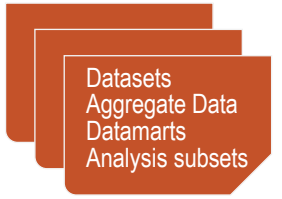


Curate, Standardize, Annotate Data

Innovations:

- Advanced search, discovery, visualization, subsetting
- Fine-grained, flexible access controls/sharing permissions
- Standardized DUAs

Integrate into Data Sharing Platform



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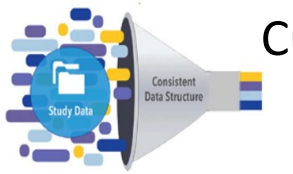
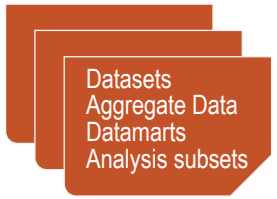


Curate, Standardize, Annotate Data

Integrate into Data Sharing Platform

Innovations:

- Built in data preview and analytics (R, SQL, VMs)
- Enhanced security (logging, TFA, restricted download)
- Shared analyses, bring your own data



Extract and Analyze Data

C-Path Data and Analytics Platform (DAP)

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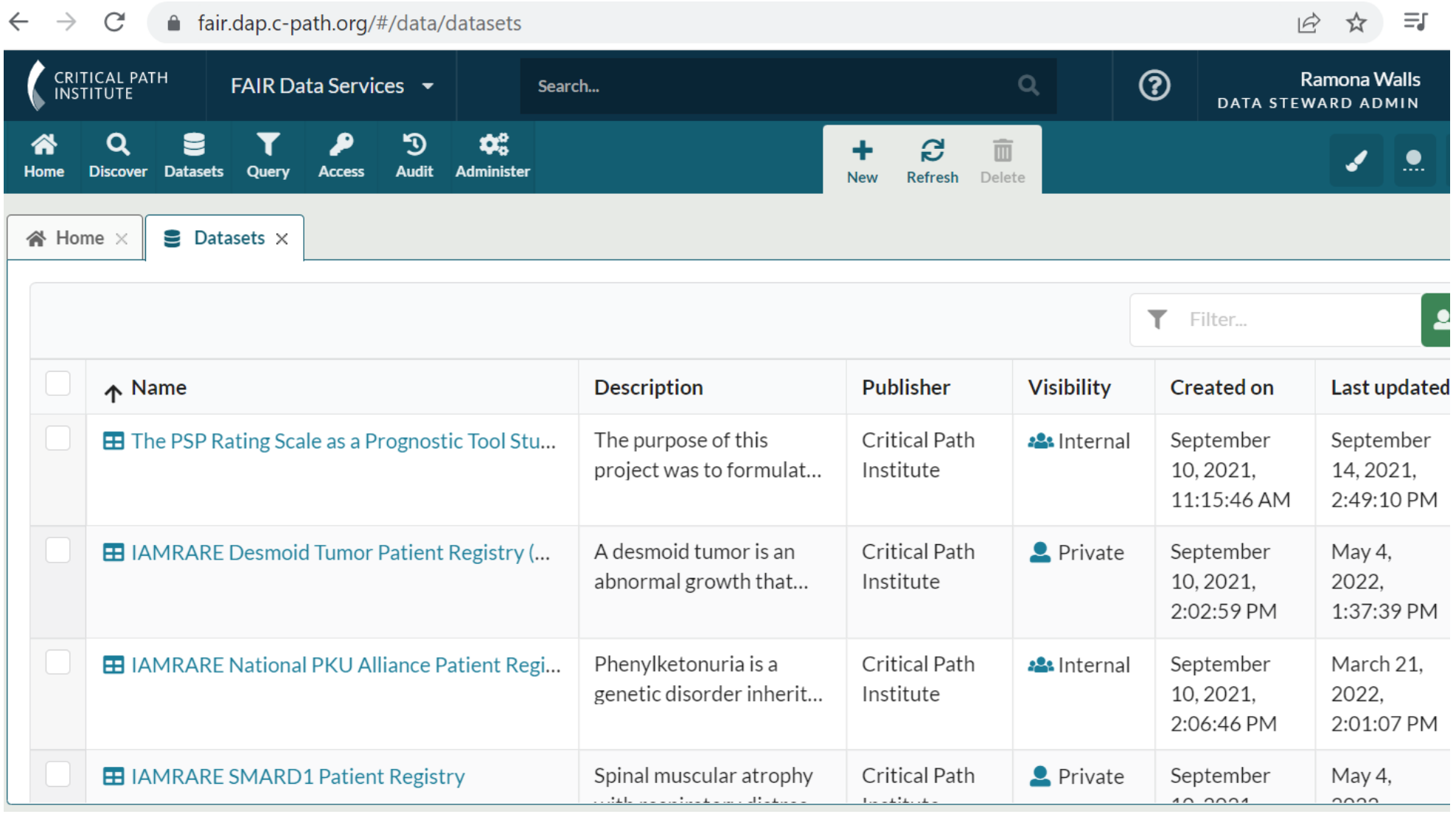

DAP Workspaces

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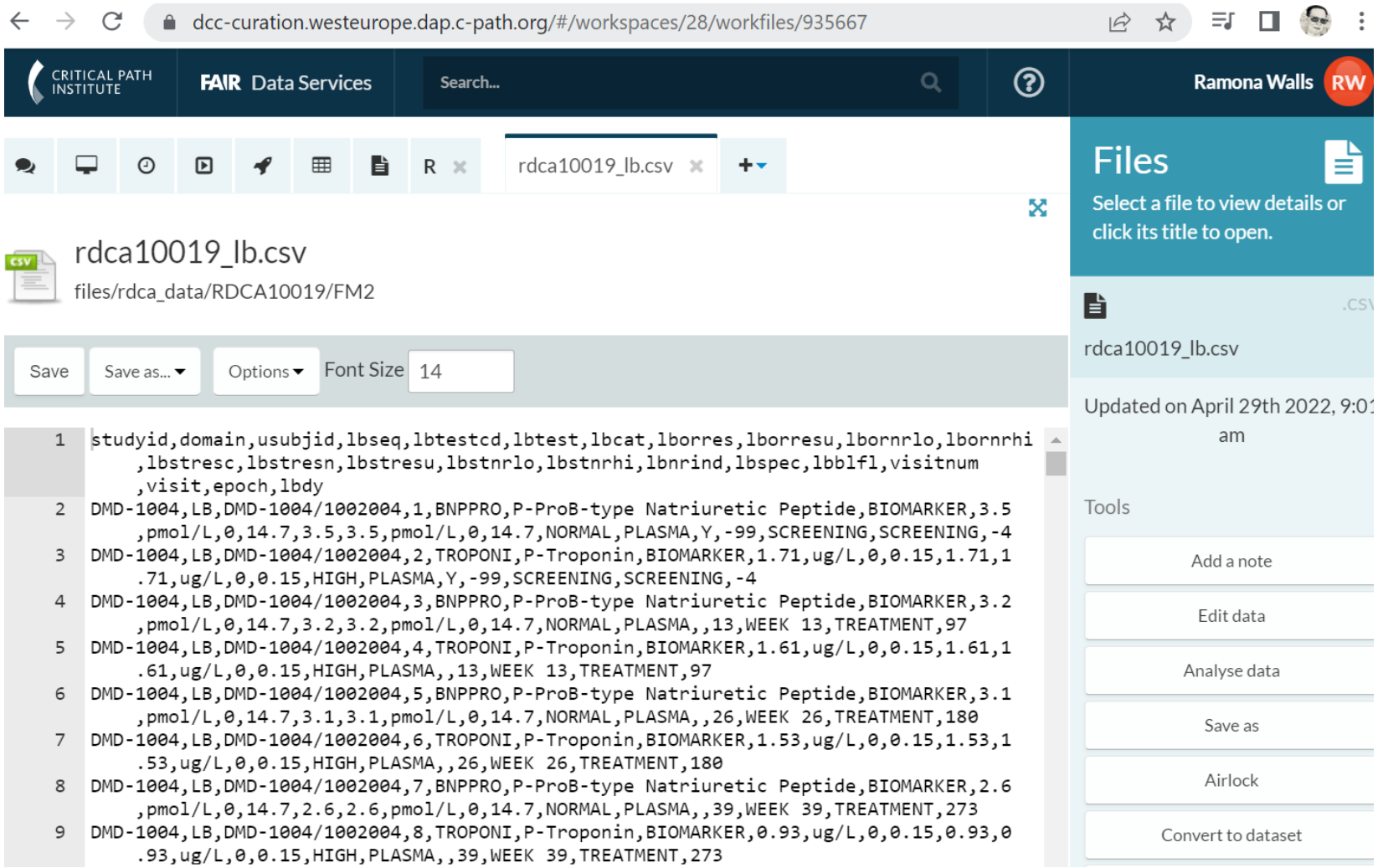

Standards, Ontologies, and Knowledge Graph

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- OMOP Common Data Model (CDM) is a baseline for long tail of registry data and EHR
  - Includes standard vocabularies such as SNOMED, LOINC, RXNORM
- CDISC Study Data Tabulation Model (SDTM) for clinical trial data
  - Many of our legacy datasets are already in SDTM
  - Standard vocabularies in NCIT are interoperable with OBO ontologies
- OBO ontologies for deep semantic discovery and analysis
- Rare disease knowledge graph of patient-level data that is interoperable with external data sources like Orphanet, Monarch, EJP-RD

Data + ontology = knowledge graph (KG)

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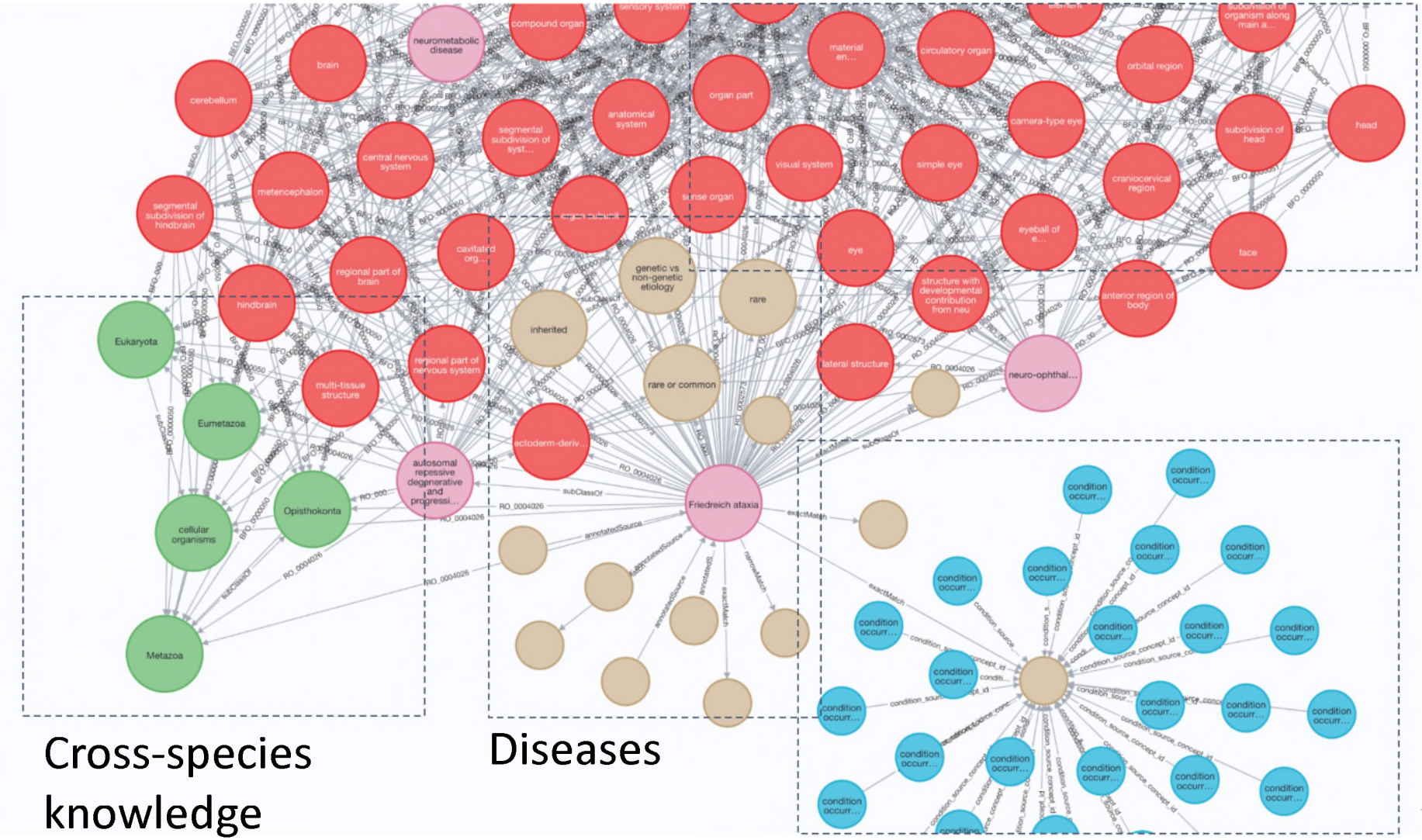

How data contributors can help

Good practices for small and large data generators/contributors

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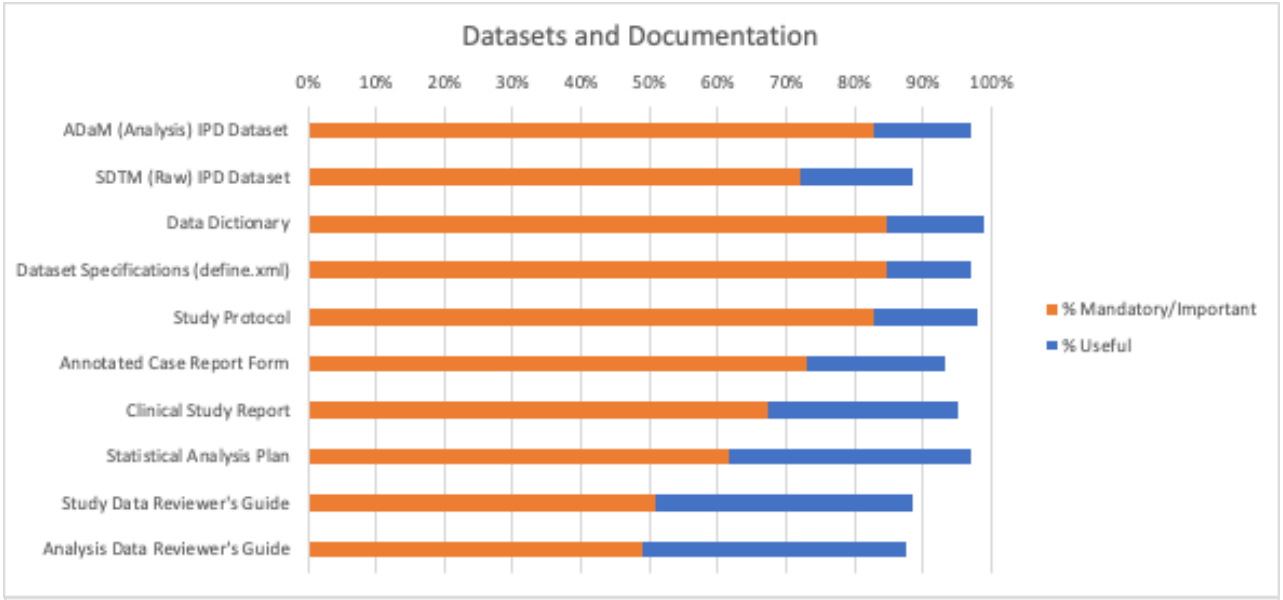
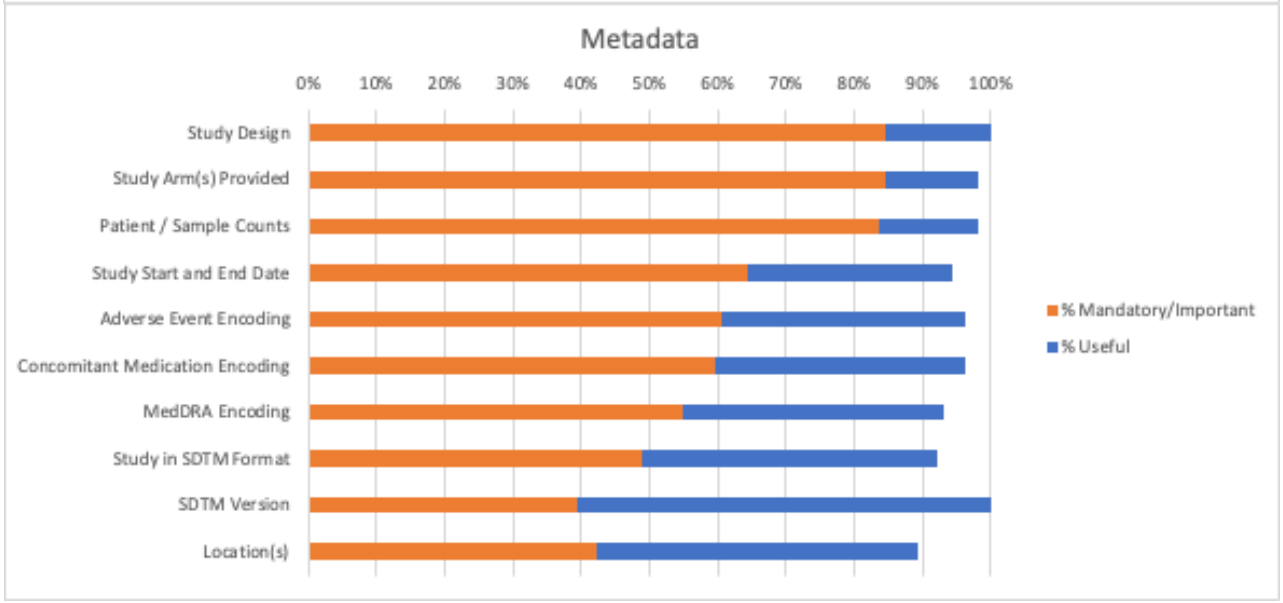
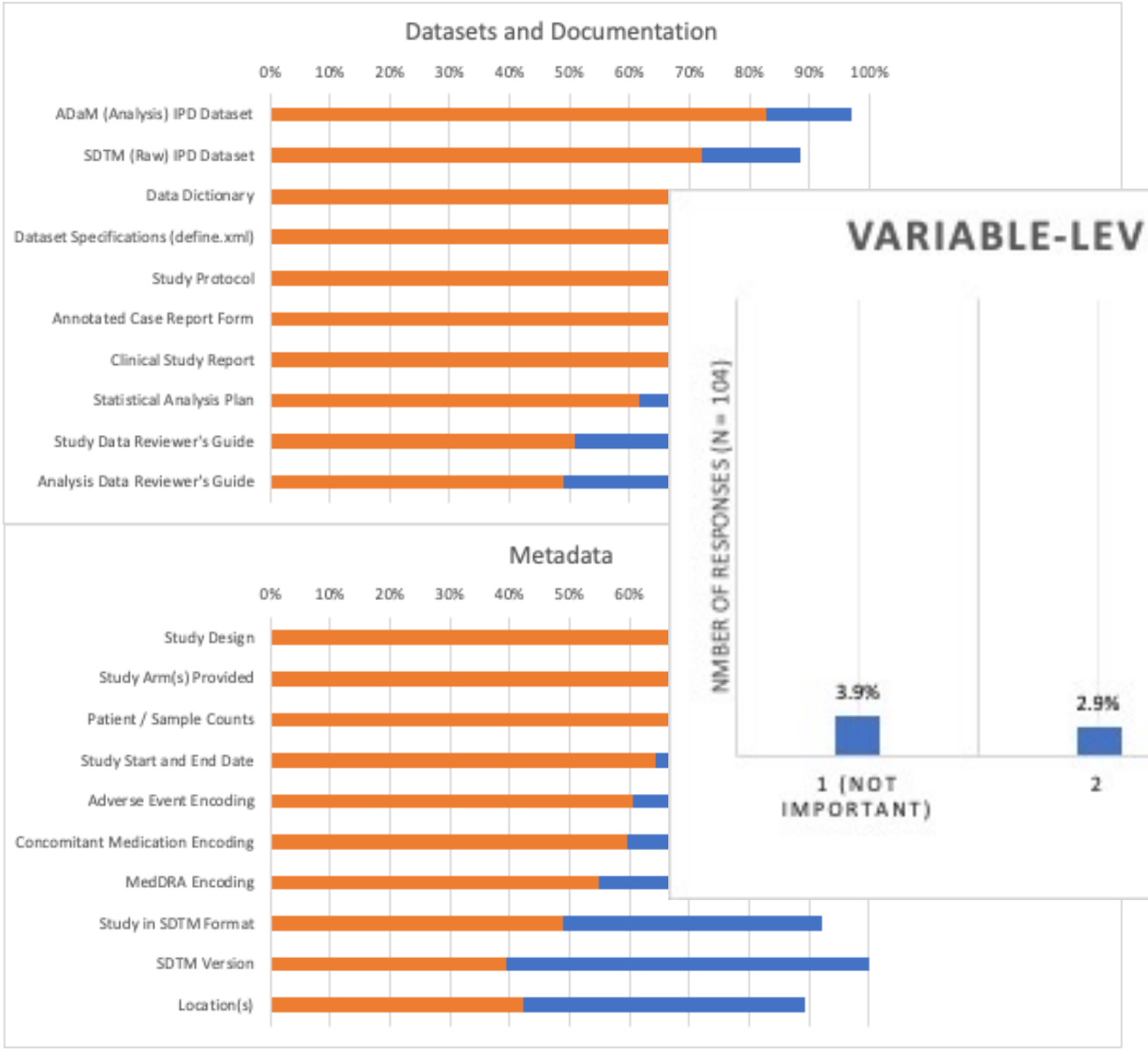
Mismatch between what is shared and what is needed

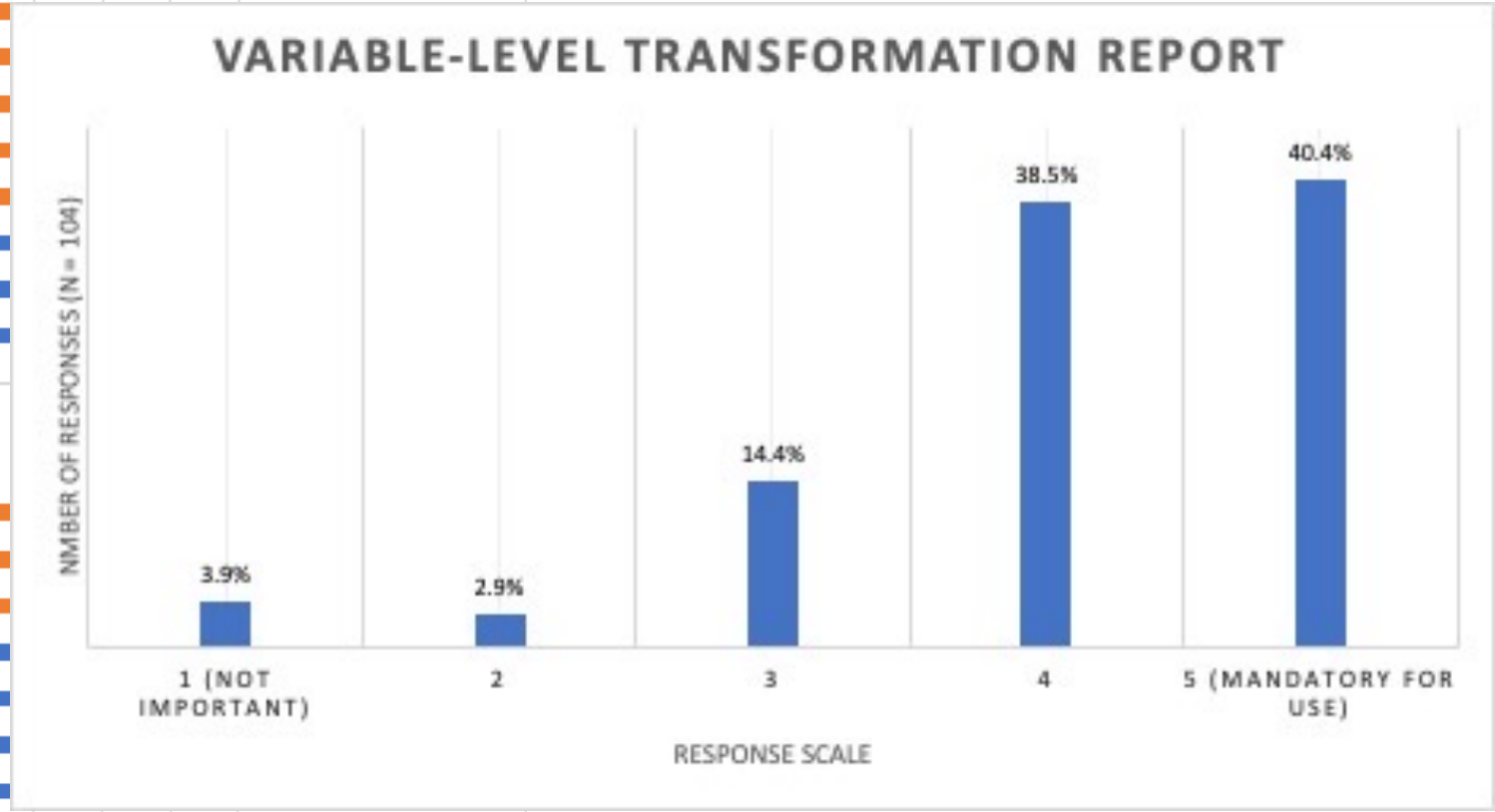




https://www.appliedclinicaltrialsonline.com/view/establishing-a-basis-for-secondary-use-standards-for-clinical-trials

Mismatch between what is shared and what is needed





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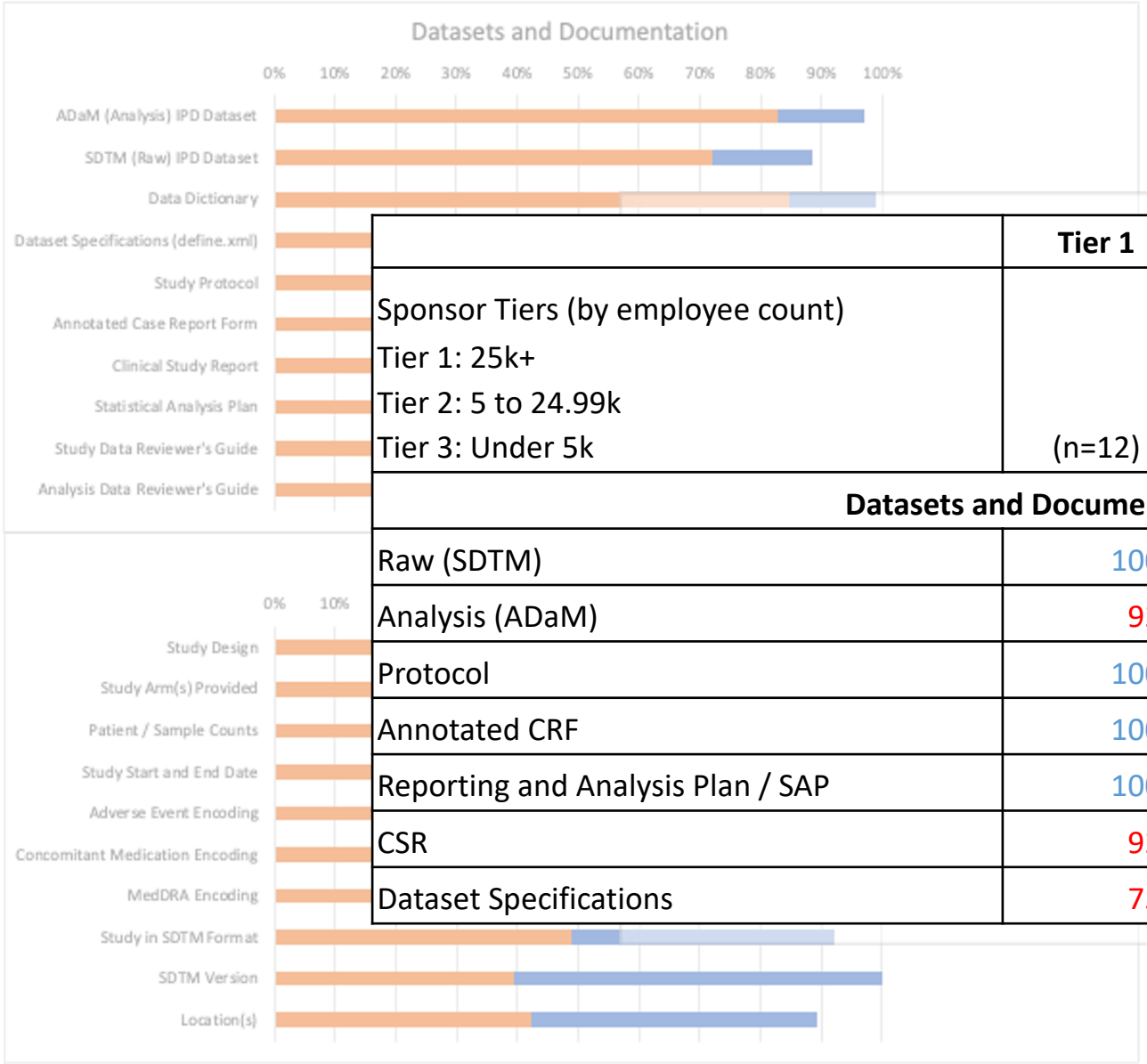
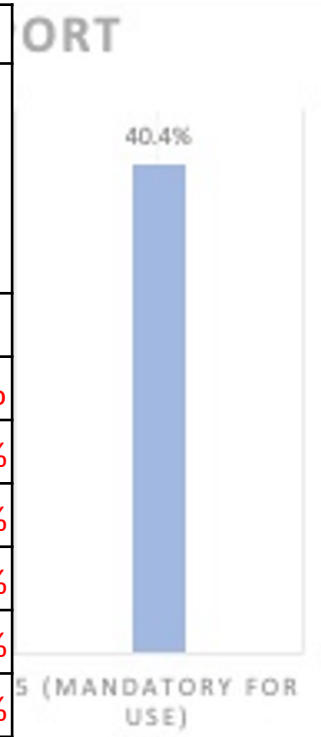


	Tier 1	Tier 2	Tier 3
Sponsor Tiers (by employee count) Tier 1: 25k+ Tier 2: 5 to 24.99k Tier 3: Under 5k	(n=12)	(n=11)	(n=6)
Datasets and Documentation			
Raw (SDTM)	100%	82%	83%
Analysis (ADaM)	92%	92%	67%
Protocol	100%	82%	83%
Annotated CRF	100%	73%	67%
Reporting and Analysis Plan / SAP	100%	82%	67%
CSR	92%	91%	33%
Dataset Specifications	75%	73%	50%



Data contributors should:

- Follow FAIR data principles
- Ensure proper anonymization and include anonymization report
- Use standard terminology and data models where possible
  - OMOP and SDTM
  - OMOP standard vocabularies, UMLS, NCIT, NIH CDEs
  - Human Phenotype Ontology (HPO) for "phenotype" descriptions
- Follow consistent data collection practices from year to year, at least aim for backwards compatibility
- Share dictionaries, protocols, other supplemental documents

Thank you!

Critical Path Institute is supported by the Food and Drug Administration (FDA) of the Department of Health and Human Services (HHS) and is 55% funded by the FDA/HHS, totaling $17,612,250, and 45% funded by non-government source(s), totaling $14,203,111. 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.

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RARE-X

Increasing the speed and productivity of innovation in rare diseases by increasing collection and access of structured and standardized patient data.

Vanessa Vogel-Farley (Global Genes: RARE-X)

5/2/2023
CDER - JHU CERSI Workshop Addressing Challenges in the Design and Analysis of Rare Disease Clinical Trials: Considerations and Tools

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

Data exists in silos & is unavailable for open research

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

Data doesn't yet exist; many communities are too young or don't have the resources to collect data for research.

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From Registries to Real-World Data

What Patient-Powered Registries Enable

Nominate Disease

Identify population of interest and understand where they are in the world

Launch Data Collection

Determine what data is needed

Create relevant patient-reported data collection modules

Launch DNA and clinical collection efforts (if relevant)

Design Trial

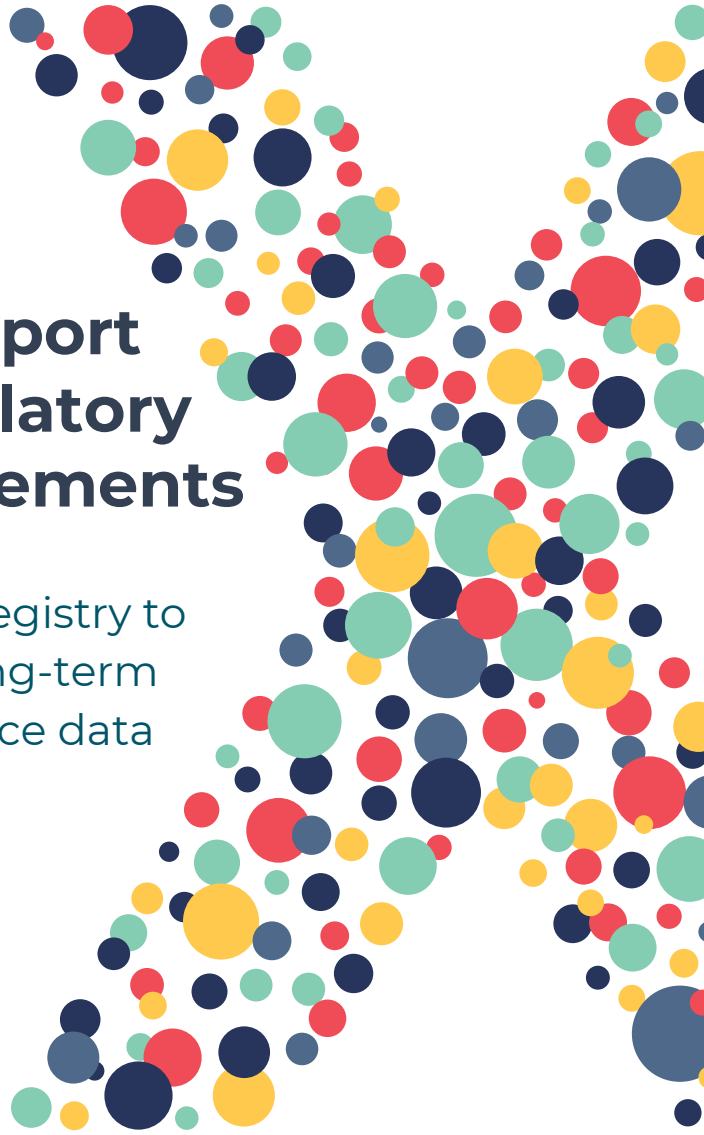
Use data to:

Inform trial enrollment criteria

Inform trial endpoints

Support Regulatory Requirements

Leverage registry to collect long-term surveillance data



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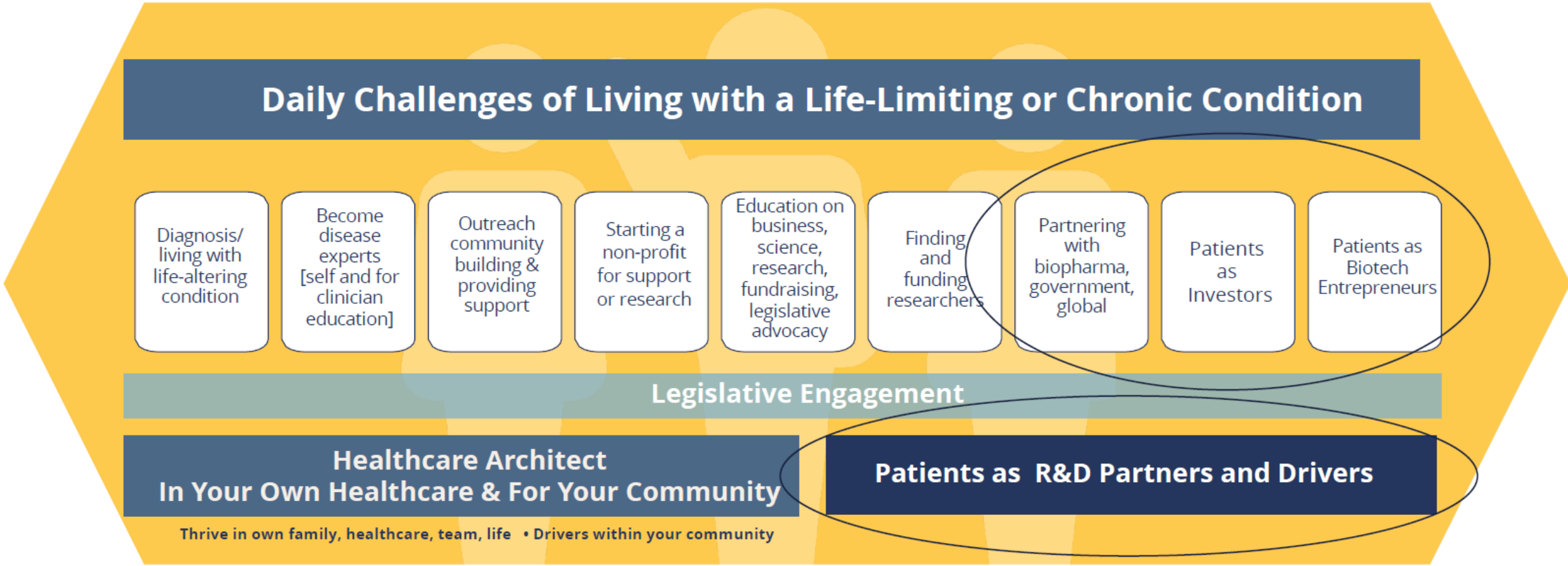
Advocacy Today: Opportunities & Challenges in Rare Disease



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Enabling Patients to determine sharing their data

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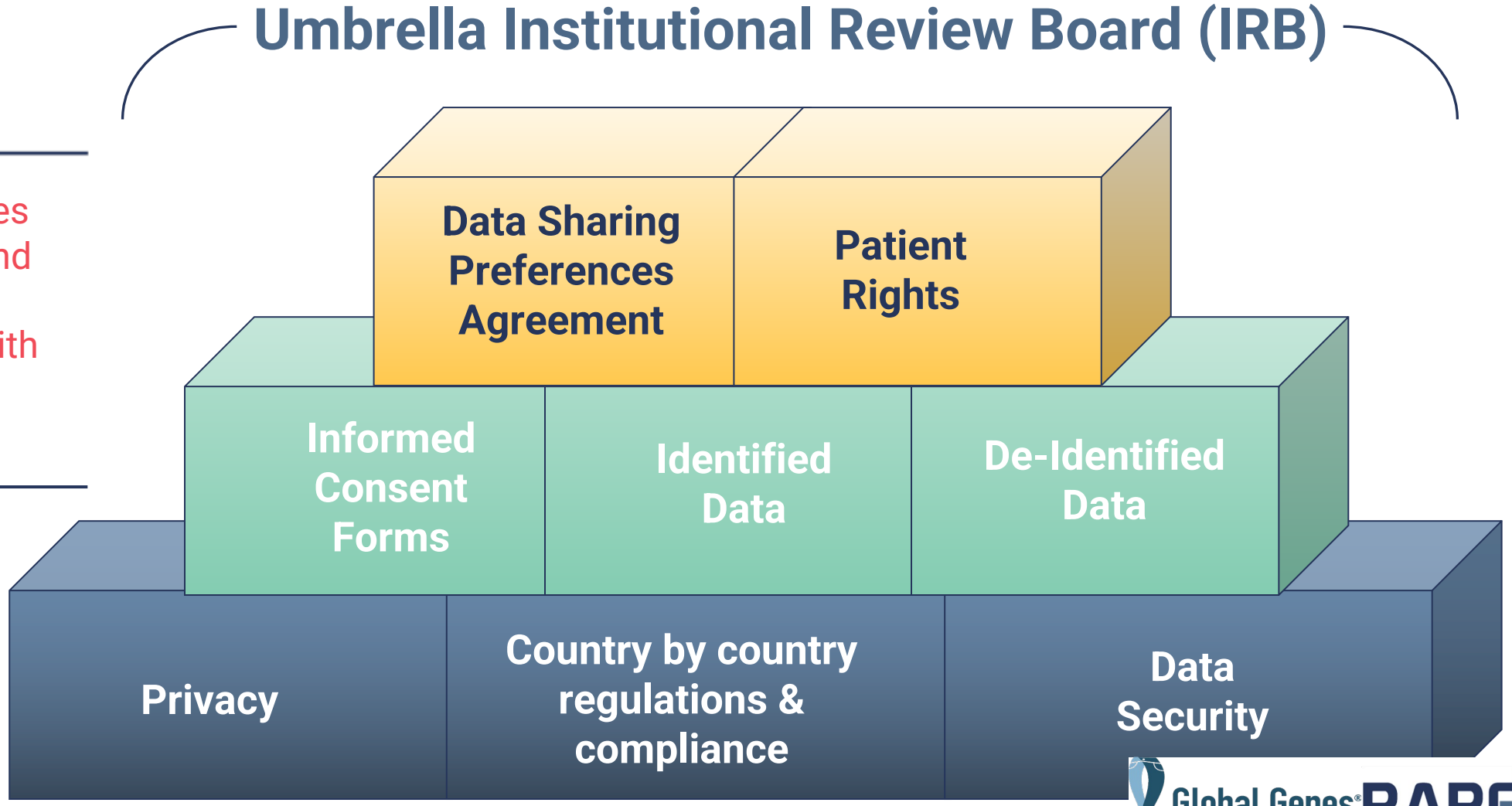
Data Governance is a Big Deal

RARE-X provides ALL Patients and Disease communities with Governance support



RARE-X

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Beyond Single Informed Consent: Data Sharing Survey

Type of research

You choose the **type of research** you would like your data to be used for. You must choose ***one*** of the following two types of research:

☐ 1. General Research

This is the broadest type of research. When you choose General Research, researchers may use your data for:

a. Health/Medical/Biomedical Research
Researchers can access and use your data to learn more about a health condition, its causes, symptoms, progression, and treatments. This type of research could include research on any health condition, even if it is not a rare disease.

and

b. Other kinds of studies that are not related to health such as

- Research on age, race, and ethnicity
- Research studying traits such as how long people live or how easily they may get sick
- Research about genetic traits of different populations
- Studies to develop survey questions to improve research

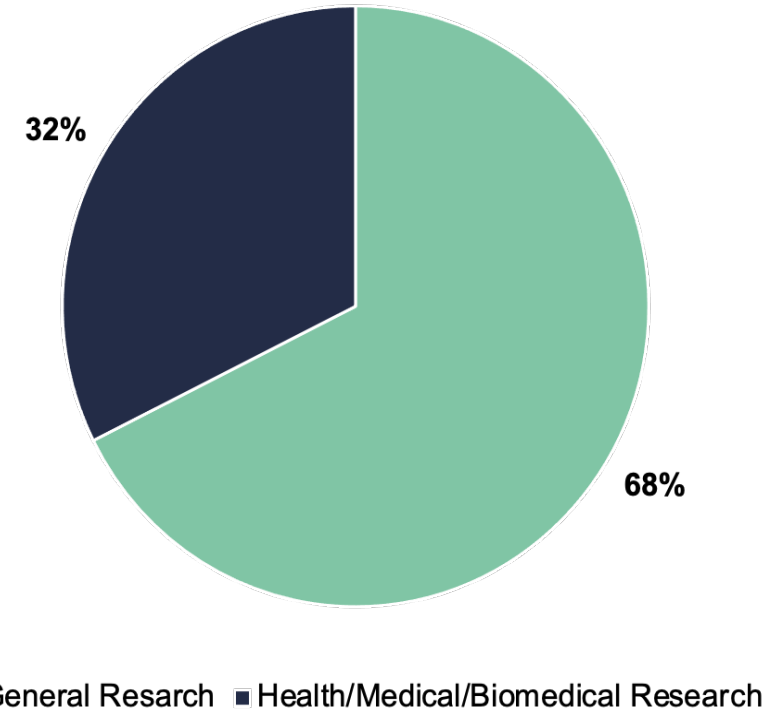
OR

☐ 2. Health/Medical/Biomedical Research

This type of research is narrower than type 1, General Research. If you choose just Health/Medical/Biomedical Research, ***your data may be used for fewer types of research studies than if you choose General Research.***

- Your data may ***only*** be used to learn more about a health condition, its cause, symptoms, progression, and treatments. (Research described in section 1.a above)
- Your data will ***not*** be used for other kinds of studies not related to health described in section 1.b. above.

100% would like their data shared:



Survey responses are dynamic and can be updated at any time.

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Leveraging Data Use Ontologies in a direct to the patient manner

FOR FASTER AND MORE EFFICIENT ACCESS TO DATA

Presentation of the data use options are shown as part of the consent process directly to the patient.

A separation of the represented data uses ontologies to enable the participant.

1. Review the potential data-sharing options multiple times
2. Update the data-sharing preferences outside of the consent document itself.
3. Use these ontologies in a machine-readable manner to speed the access to data in line with patient consent.

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Adaptation of language towards patient enabled data sharing

RARE-X Consent Choices DRAFT work	The Broad Consent Choice 2.3 – Choices for DCP 2.4 – Choice for Secondary Data Use Terms - Federated
1. Anyone wanting to study data associated with rare disease. This category includes **all** the researchers listed below. It also includes citizen scientists. Citizen scientists are people who research science in their spare time.	
2. All researchers with documented proof of professional standing in the research community. This category does not include citizen scientists. Saying yes to this category would include researchers who study conditions or symptoms that frequently occur in the general population	2.3.1 Health/medical/biomedical research: The primary purpose of the study is to investigate a health/medical/biomedical (or biological phenomenon or condition.
3. Researchers who are known to conduct research on the rare disease that you are afflicted with. This group of researchers is more limited than those in number 2. This category includes only researchers who specialize in your rare disease.	2.3.1 Health/medical/biomedical research: The primary purpose of the study is to investigate a health/medical/biomedical (or biological phenomenon or condition.
4. Only researchers that have had their studies reviewed by an Institutional Review Board (IRB) based on ethical and scientific principles. Researchers in this category must present proof of the IRB's approval of their study before they can access your information for their study.	2.4.5 **Ethics Approval Required (IRB)**: Approved users are required to provide documentation of local IRB/REB approval.
5. Data repositories[DA2] **operated by other organizations** may have access to your de-identified information**.** Allowing this type of sharing helps reduce duplication of efforts. It also would make your de-identified information available to a greater number of researchers.	
6. Commercial companies, such as drug companies and biotechnology for research.	2.4.9 Non-Profit Use Only (NPU): The data cannot be used by for-profit organizations nor for commercial research purposes

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Steps towards using standards at the time of data collection:

Foundation for RARE-X Data Collection Platform

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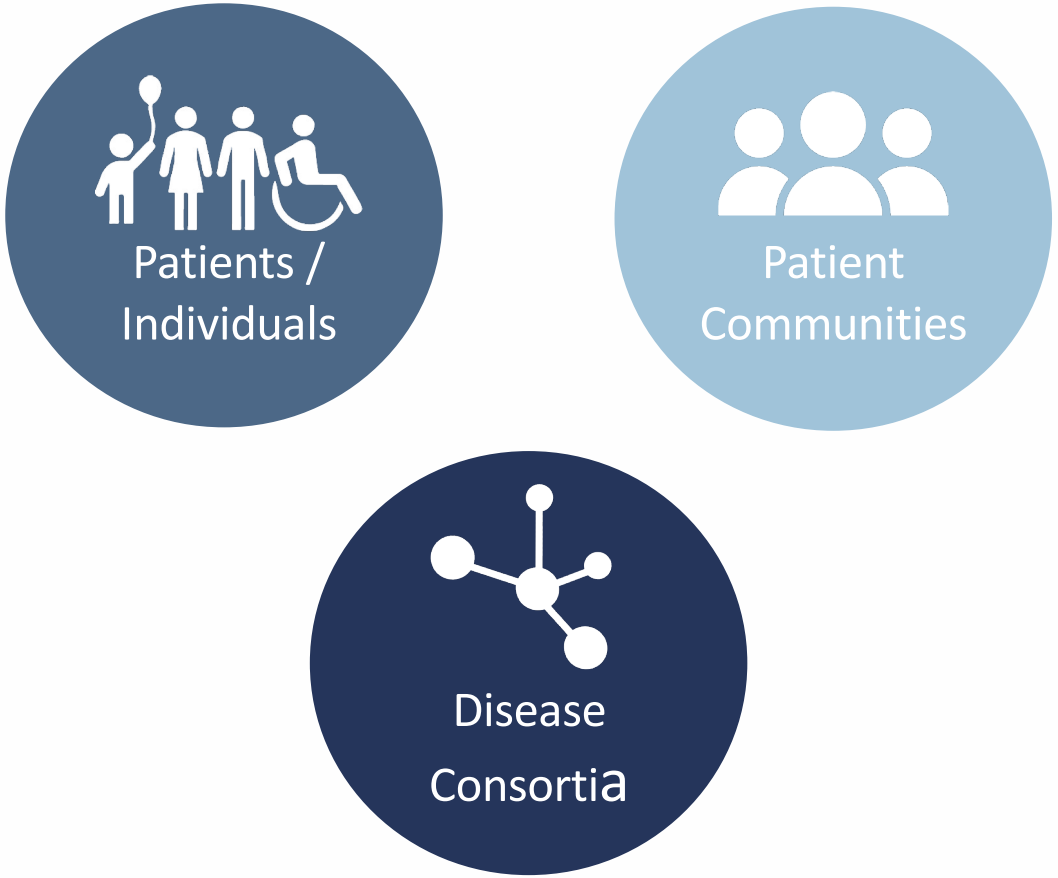
Data Collection Models

Stakeholder Support :

- Individuals (n=1, undiagnosed)
- Patient Communities (small or large)
- Disease Consortium (body system or symptom): bringing together several disease communities around a symptom (ex. vision or hearing loss)



Standards and guidance consulted by RARE-X

- Standards
  - CDISC (Clinical Data Interchange Standards Consortium: FDA standards)
  - Human Phenotype Ontology (Monarch Initiative)
  - Other sources of standardized questions and concepts
    - NIH Metathesaurus
    - NIH Common Data Elements Repository
    - PhenX
    - LOINC, SNOMED, OrphaNet, ICD
- Guidance
  - FDA
  - NCATS
  - Scientific community
  - Industry partners
  - Patients

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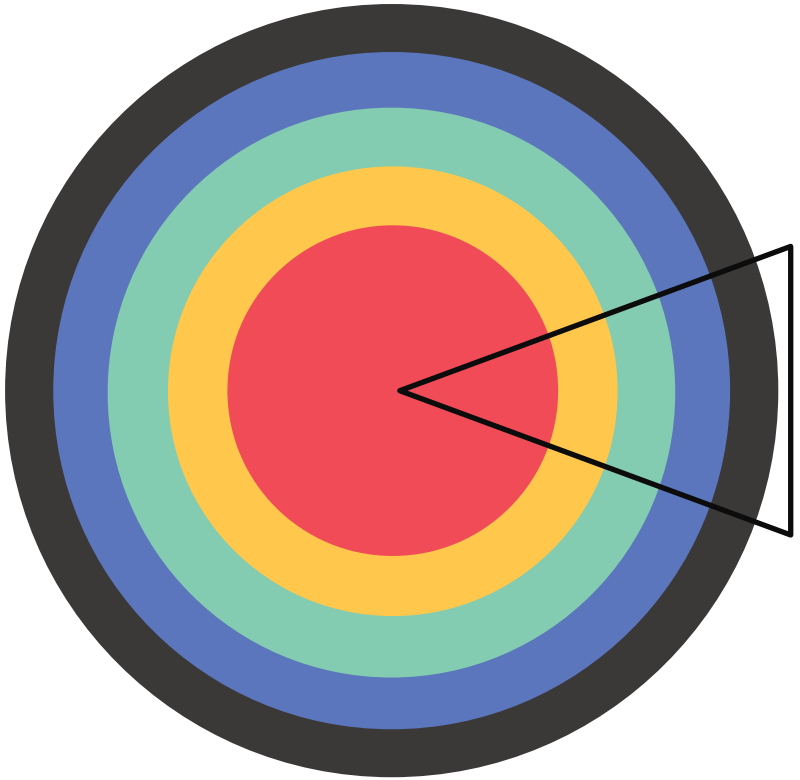
RARE-X: Data Standardization & Data Model

Provide the infrastructure to support comprehensive data collection for analysis.
Gather precise data, map it, layer it, share it.



Platform Development Strategy

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*

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Current RARE-X Focus

- **General Core**
  - A data element that can be consistently collected across studies in any disease or therapeutic area.
  - *RARE-X example:* Demographics
  - *Standards consulted*: CDISC, NIH CDE, NCATS
  - **Status: RARE-X General Core available with launch**
- **Disease Core**
  - A data element specific to a particular disease or therapeutic area.
  - *RARE-X examples*: Skin; Head/Neck; Kidney/Bladder
  - *Standards consulted*: Human Phenotype Ontology, CDISC, NIH CDE
  - **Status: RARE-X basic (HPO) phenotyping disease core available with launch**
- **Supplemental (Custom Surveys)**
  - A data element which is commonly collected in clinical research studies but whose relevance depends upon the study design (i.e., clinical trial, cohort study, etc.) or type of research involved.
  - *RARE-X example:* Homocystinuria-specific dietary questions
  - Standards consulted: CDISC, NIH CDE, NIH Metathesaurus, others
  - **Status: Developing on a case-by-case basis**

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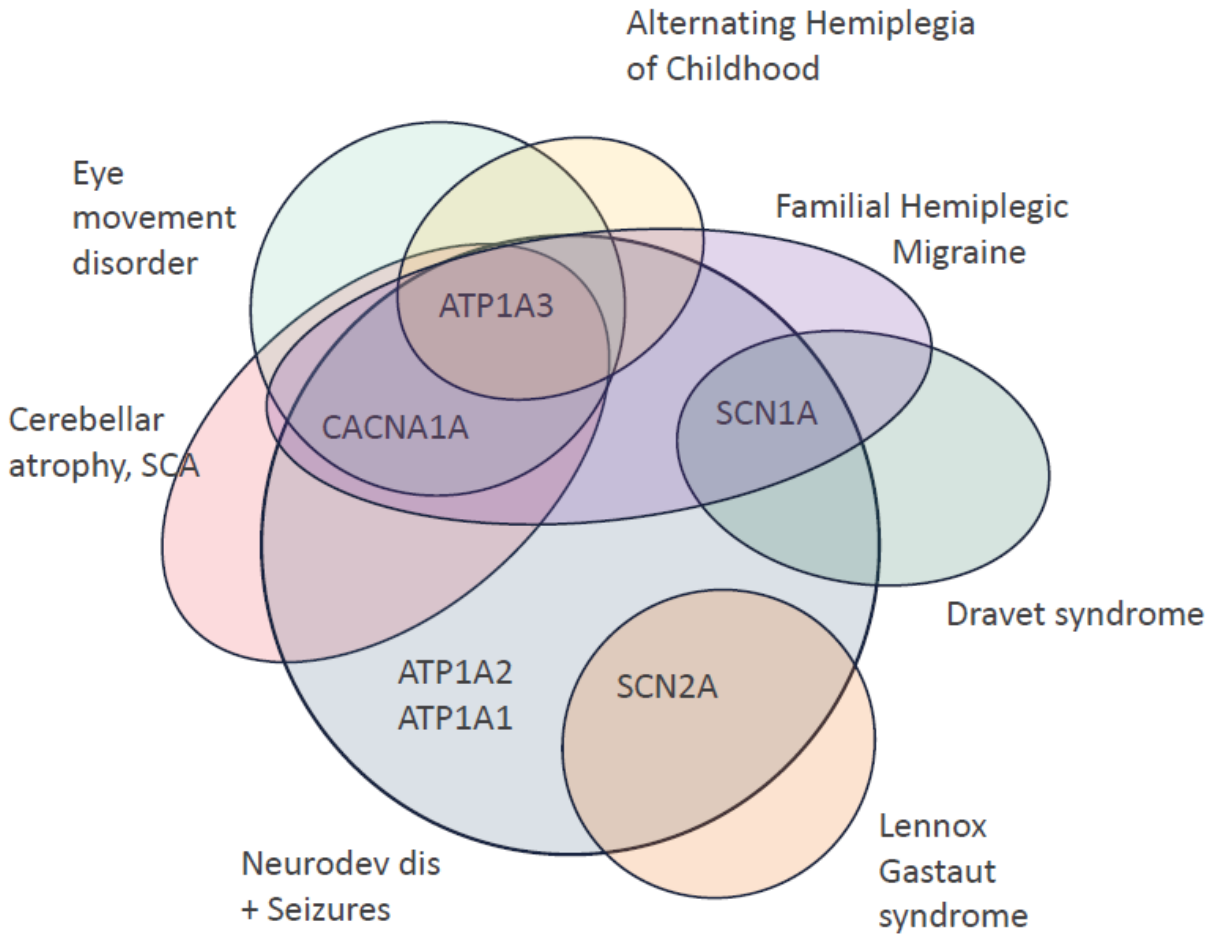
Data Use Case
Disease Overlap: Symptoms & Disease Biology

Example: Ion Channel Disorders on the RARE-X Platform

- AHC (Alternating Hemiplegia of Childhood
- CACNA1A
- Charcot-Marie-Tooth



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Domain Prioritization- Patient/CG Reported

Domain-based Standardized Modules – Machine Readable, GA4GH Compliant for Data Sharing

Domains in RARE-X

Demographics – NIH/RADAR/CDSC

General Medical - L1 & L2 (ClinGen)

- Health & Development
- Mother's Pregnancy
- Growth
- Hormone / Endocrine
- Eyes & Vision
- Behavior
- Skin
- Bone, Cartilage & Connective Tissue
- Digestive System
- Blood & Bleeding
- Brain & Nervous System
- Heart & Blood Vessels
- Head, Face & Neck
- Cancer
- Muscles
- Ears & Hearing
- Lungs & Breathing
- Digestive System
- Kidney, Bladder & Genitals
- Immune System
- Oral Health
- Quality of Life (Patient and Caregiver)
- Medication
- Medical Encounters
- Interventional or Medical Diets
- **Neurodevelopmental**
- **Genetic Testing Report Upload***

**Participant uploaded*

Current Domain Development

- **Neurodegeneration**
- **Neuromuscular**
- **Sleep**
- **Seizures / Epilepsy**
- Diagnostic Odyssey
- Medical Management
- Clinical Trial Readiness
- Lab Report Upload*
- Immunology

Expanding on General Medical Next Layers of Surveys

Domain Expansion & Depth

- **Autoimmune**
- Dermatology
- Respiratory
- Gastrointestinal
- Pain
- Mental Health
- Musculoskeletal
- Metabolic
- Blood
- Bone
- Hearing / Hearing Loss
- Renal
- Vision
- Rare Cancer
- Cardiology / Cardiovascular
- Endocrinology
- Medication usage
- Diet and Nutrition
- Mitochondrial
- Genetic Data Abstraction & Curation
- Surgery
- Transplant
- Medical Equipment
- Diagnostic testing
- Treatment/Effectiveness
- Disease-specific validated instruments
- Electronic Health Record (EHR) linkages
- Remote Monitoring linkages

Mapped to HPO, HL7, OMIM, Orphanet, CDC

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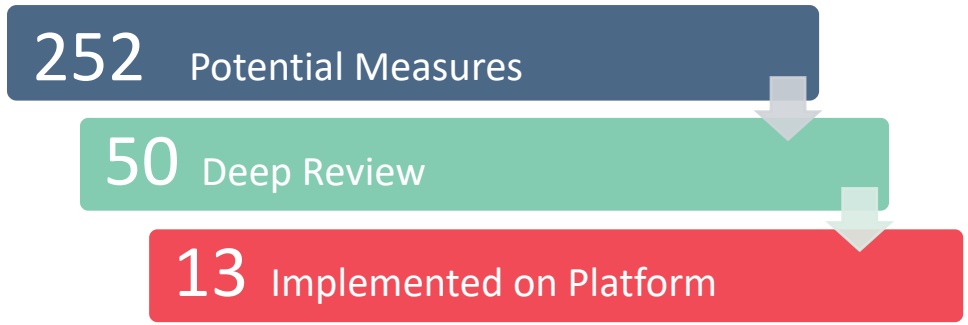
Prioritized and Modeled to Generate Research-Grade, Comparable Data

Example: Pediatric Neurodevelopmental Disorders

1. Expert working group formed
2. Symptom domains prioritized
3. PRO Measures landscaped & categorized
4. Measures narrowed for deep review & discussion
5. Final measures confirmed
6. License & implement on RARE-X platform
7. Publish expert working group recommendations



Multi-Disciplinary Expert Working Group

MD – Roche
PhD – COMBINEDBrain
MD – Colorado Children's
ScM, CGC – Boston Children's
PhD – LGS Foundation
PhD – DYRK1A Syndrome International Assn
MD, MS – Weill Cornell Medicine
MA – CACNA1A Foundation
SYNGAP Research Fund
MD, PhD – St. Jude's
MD, MHA – NIH / NCATS

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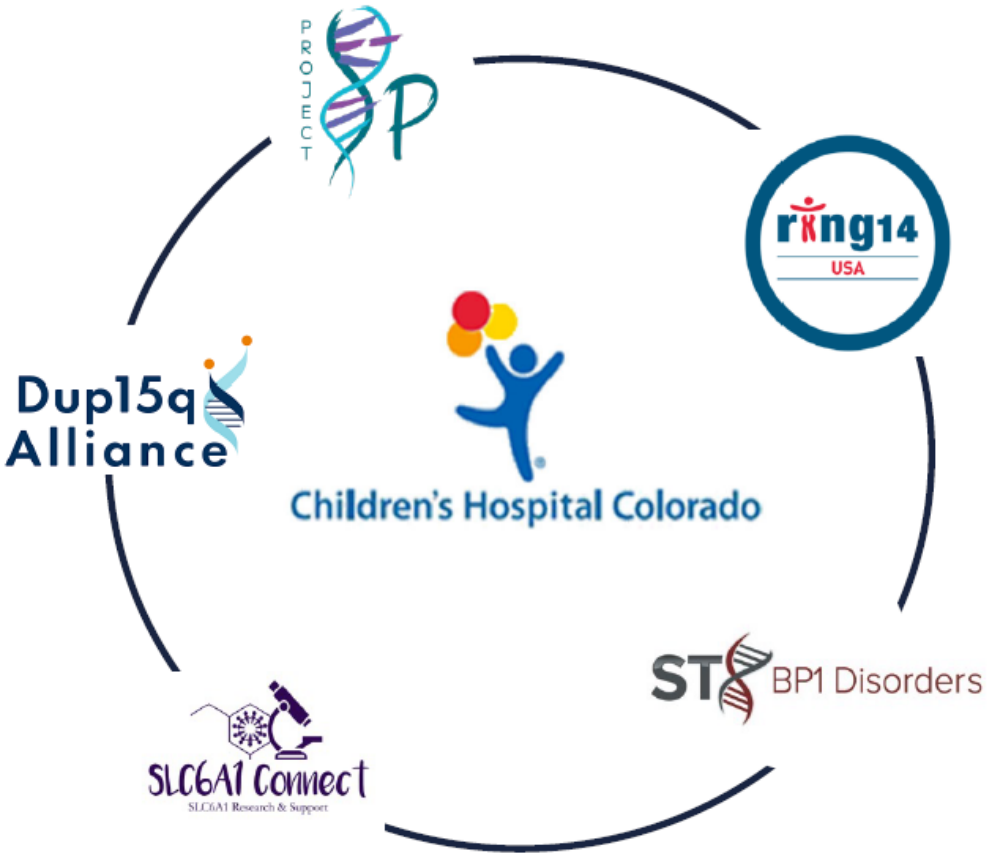
Data Collection and Use Case: Neurogenetics Clinic (NCRC)



Basket-style Natural History Study across Rare Diseases

- Clinical and research programs launched for multiple rare disorders
- COAs collected
  - Clinician-reported scales
  - Participant-reported scales
  - **RARE-X platform participant-reported scales**
- Clinician-reported data can be collected on site in a shared data model/map and then transfer to RARE-X to connect data sets for expanded usage
- **Future integration planned to allow direct clinician entry in RARE-X**

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How do ‘validated instruments’ fit in?

- Validated instruments are also known as questionnaires, PROs, or CROs that have been studied extensively using specific scientific criteria and statistical methods that give us confidence that they are reliable and valid in the population used to validate the instruments.
  - Example: an instrument validated in people with cancer may not be applicable to caregivers of children with rare epilepsy.
  - See the following slides for FDA definitions
- RARE-X maintains a library of more than 20,000 validated instruments which can be filtered by domain.

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Validated Instruments: Catch-22

- We need to use validated instruments for regulatory purposes
- Validated instruments often force us to use proxy reporting when true ObsRO is not possible (e.g. answering “how they feel” questions on behalf of people unable to communicate)
  - Results in data that may not represent what the patient is actually experiencing.
- Need in the rare disease space when it comes to ”validated” instruments”
  - The development of validated instruments that address these challenges
  - The acceptance and qualification of more appropriate instruments into existing standards (CDISC, FDA CRO Qualification)

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Can I use a questionnaire that is not ‘validated’ and still be CDISC compliant?

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Yes, but tread carefully…

- CDISC has recommendations for sponsors using questionnaires not currently defined in a CDISC QSR supplement to define scales on their own.
- Outside of the context of a specific trial, the use of instruments that have not been reviewed by FDA COA qualification process can result in data that are not considered reliable or valid by the scientific community.
- A list of CRO Qualification submissions can be found here:

  https://www.fda.gov/drugs/clinical-outcome-assessment-coa-qualification-program/clinical-outcome-assessments-coa-qualification-program-submissions

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Approaches to Connecting and Making Data Accessible

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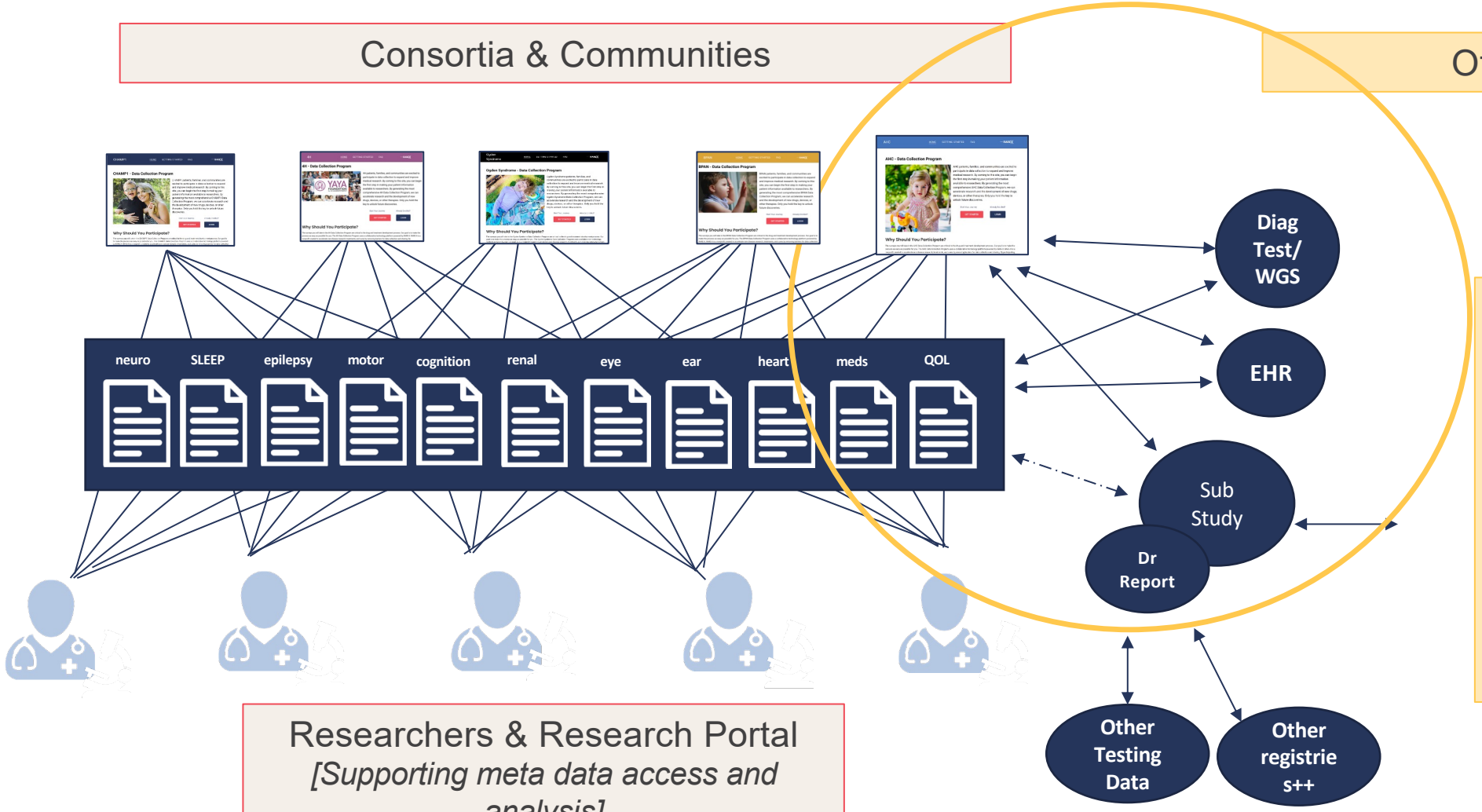
The Need to Interconnect and Support Other Data

Consortia & Communities

Other Data



Sub Studies Include:

- Biopharma-sponsored studies/surveys
- Embargoed Period
- Other Novel Disease-Specific Data
- Clinician Reported/NH Study Data

Researchers & Research Portal

[Supporting meta data access and analysis]

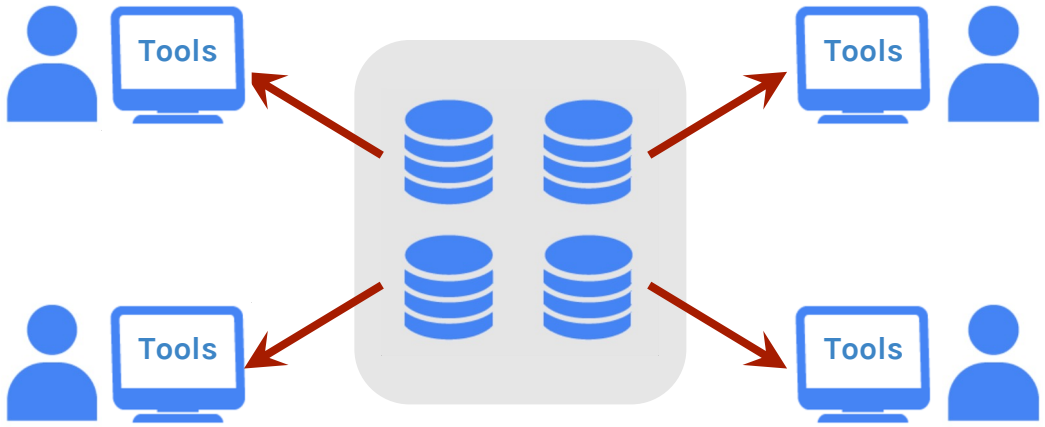
Federated Data:

[building an interconnected data ecosystem, connecting disparate data sets]

Inverting the Model of Data Sharing

Traditional approach

Bring data to researchers

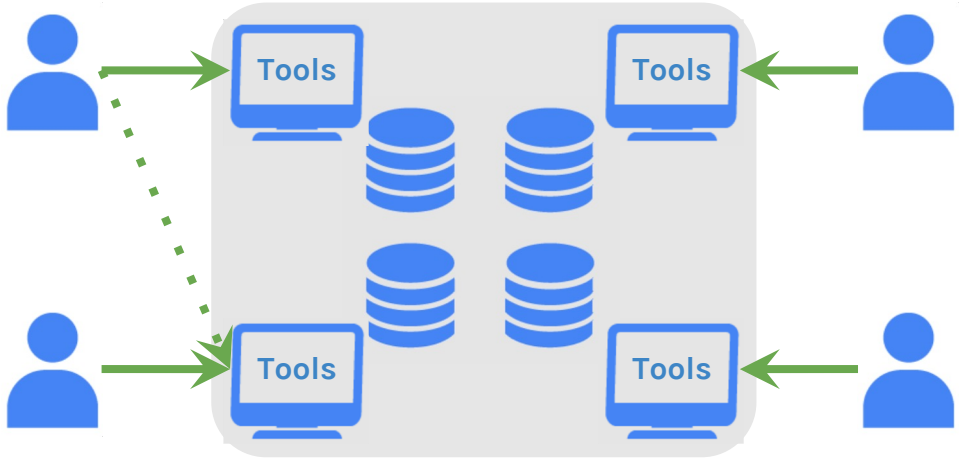


Discourages shared research

Data sharing = data copying
Few audit controls
Huge infrastructure needed
Siloed compute

Cloud-centric approach

Bring researchers to data



Facilitates collaboration

Cost
Threat Detection and auditing
Increased accessibility
Shared & elastic compute

Global Genes® RARE X
Allies in Rare Disease

Data Generation, Alignment, Federation

RARE X

Rare Disease Communities actively generate & upload data

Natural history studies

Ontology mapping

Standardization

Curation

Identified Study Data

Partner Data & Other Data

(eg: EHR, Academia, etc)

Alignment

Research Portal Supporting Federated Data

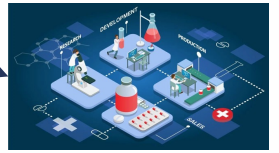
(eg: Global registries, natural history studies)

RARE X Terra

RDCA-DAP®

Rare Disease Cures Accelerator Data and Analytics Platform

Researchers/ Clinicians



Biopharma

Patient Communities

Open Science Platform Enables:

- Collaborative analysis of previously locked data sets
- Cross-disorder comparative research
- Accelerated therapeutic research path for rare diseases

Global Genes® Allies in Rare Disease

RARE X

Partner/Stakeholder 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 and Orgs

- ✓ Patient Owned and Stewarded Data
- ✓ Technology and Platform for Data Collection and Sharing
- ✓ All Data Governance & Consents
- ✓ Robust Research Ready Surveys
- ✓ Patient Engagement Team
- ✓ Education & Marketing Support

Researchers

- ✓ In-Depth Engagement with Patient Organizations and development of registries
- ✓ Natural History Studies including Clinician Reported Data
- ✓ Sponsored Studies
- ✓ Federated Learning and Data Connection for deeper analysis (ie. C-Path RD-CAP)

BioPharm

- ✓ Sponsored Studies
- ✓ Federated Learning and Data Connection for deeper analysis
- ✓ Data sharing post-study completion
- ✓ Clinical trial readiness surveys
- ✓ Patient identification for recruitment into clinical trials

Supporting basic research to: help characterize disease, create critical baseline data, future disease concept and progression models. Building a funnel and rigorous repeatable process for patient advocacy organizations.

Global Genes® RARE-X
Allies in Rare Disease

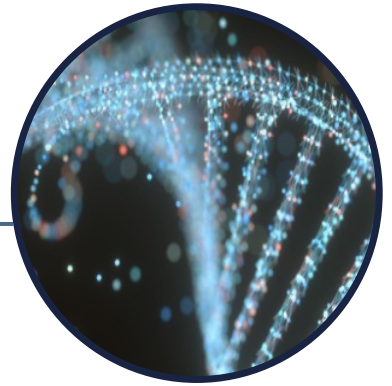
What Is RARE-X?

- RARE-X is a program of Global Genes created to accelerate rare disease research, treatments, and cures by removing barriers for data collection and sharing
- RARE-X is a platform to collect, connect, and share data

RARE-X is **not** a replacement for any current research or clinician-sponsored patient registries, but rather a prepared collaborator and partner. Ready to meet data where it is and enable its access, in whatever way it can compliantly be used.

Global Genes® RARE-X
Allies in Rare Disease

RARE-X: Facilitating Open Science for Progress with Patient-driven Data



RARE-X Provides

A Platform for collecting structured patient data (including clinical, PRO, molecular, & study data)

An open science platform to facilitate sharing of large high quality data sets to accelerate therapeutic research

-AND-

A full-service ongoing patient engagement and program management service to ensure participation & success

RARE-X is a Nonprofit Health Technology & Patient Advocacy Company Driving Success through Data Structure & Collaboration

Global Genes® RARE-X
Allies in Rare Disease

Thank you.

Together, we are powering progress for rare diseases.

CERSI
Johns Hopkins University

FDA U.S. FOOD & DRUG ADMINISTRATION

Q&A

John Concato, MD, MS, MPH
Ramona Walls, PhD
Vanessa Vogel-Farley, BA, BS

CERSI
Johns Hopkins University

FDA U.S. FOOD & DRUG ADMINISTRATION

Break

Upcoming Virtual FDA Workshop

FDA's CDER, CBER, and Duke-Margolis Center for Health Policy
Host
Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development

June 7 and 8, 2023; 1-5 pm
Link in the Chat

CERSI
Johns Hopkins University

FDA U.S. FOOD & DRUG ADMINISTRATION

Session 2:
Use of Data Sources to Inform Rare Disease Drug Development

Moderator: Christine Nguyen, MD
Deputy Director
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine,
Office of New Drugs, Center for Drug Evaluation and Research, FDA

Advancement of Drug Development Tools for Polycystic Kidney Disease (PKD) as Told Through the PKD Outcomes Consortium Story

CDER-JHU CERSI Rare Disease Workshop | May 2, 2023

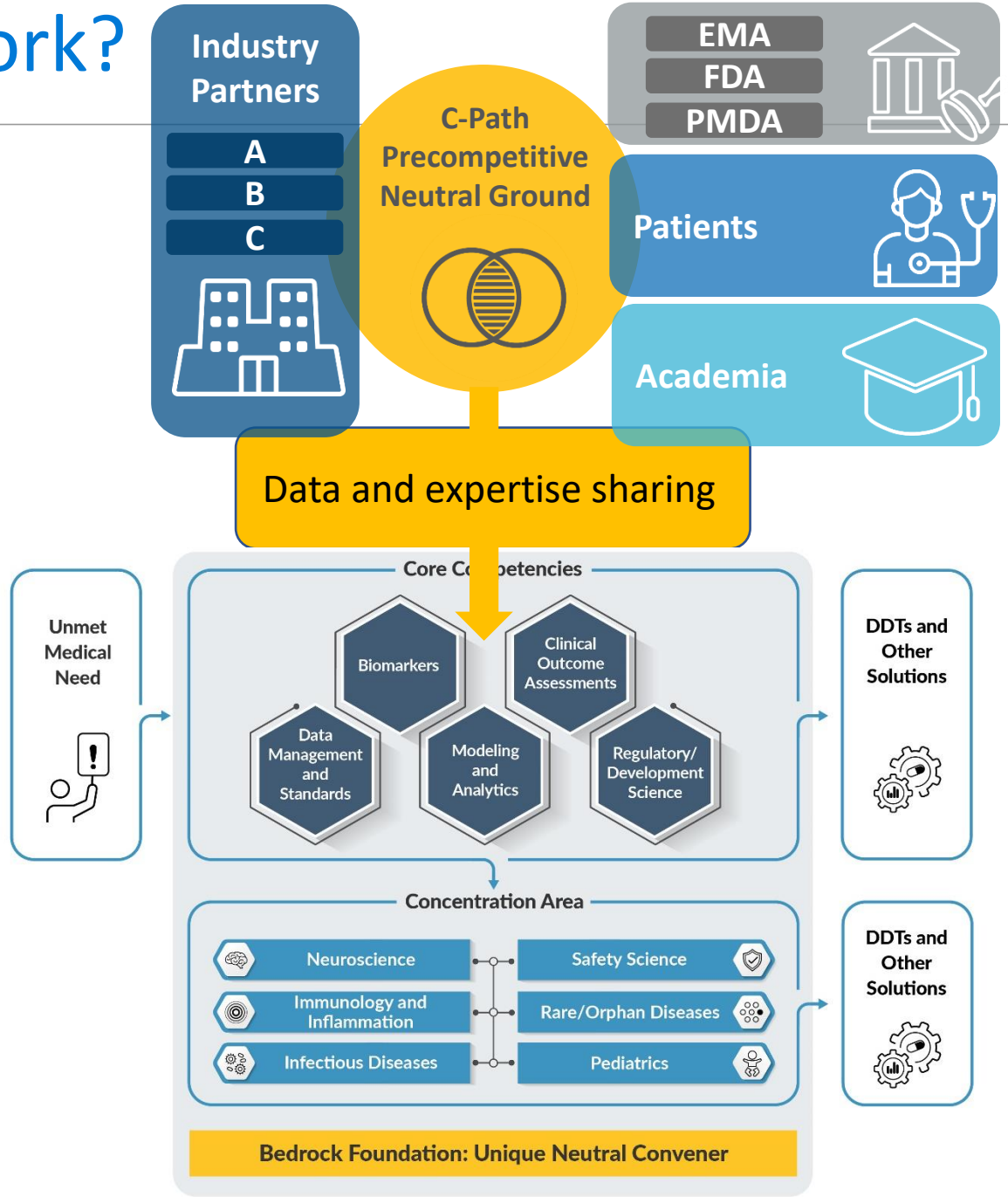
Sorin Fedeles, PhD, MBA
Executive Director, Polycystic Kidney Disease Outcomes Consortium (PKDOC)
Critical Path Institute (C-Path)

CRITICAL PATH INSTITUTE

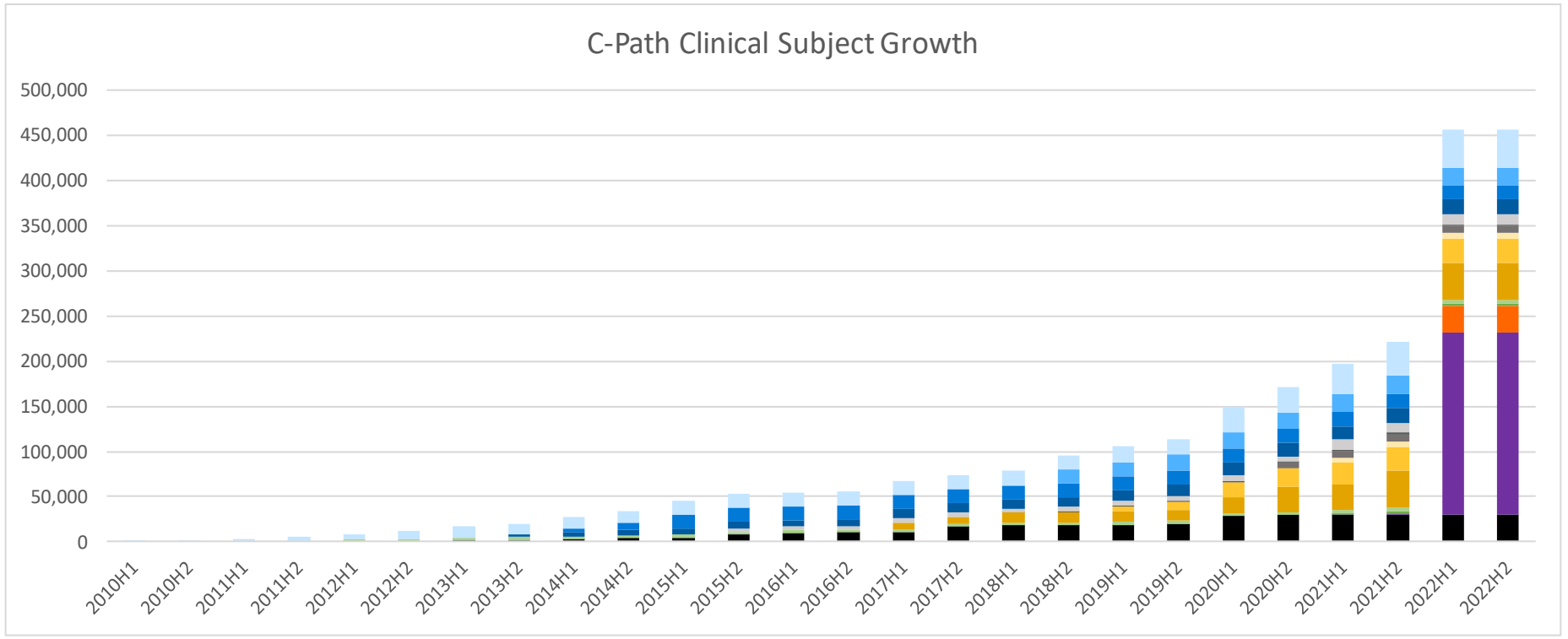
Content

- C-Path Overview
- PKDOC Background and Impact
- PKDOC 2.0

How Does it Work?



Clinical Datasets Contributed to C-Path



Clinical Data

Studies	380
Subjects	**456,443**

Nonclinical Data

Studies	148
Subjects	11,084

Neuro	
Alzheimer's Disease	42,043
Huntington's Disease	19,903
Multiple Sclerosis	15,626
Parkinson's Disease	16,120

Rare	
Duchenne's Muscular Dystrophy	11,442
Friedreich's Ataxia	1,572
Rare Diseases	8,087

IHP	
Sickle Cell Disease	6,240
Transplant Therapeutics	26,264
Type 1 Diabetes	41,096

TSSP	
Polycystic Kidney Disease	4,422
Safety Testing	2,274

CURE Drug Repurposing	29,618

Neonatal	201,277

Tuberculosis	30,459

Note: Studies currently undergoing curation are only counted in Total Studies until evaluated.

Regulatory Successes in Drug Development Tools

PKD
POLYCYSTIC KIDNEY DISEASE
OUTCOMES CONSORTIUM

FDA

- 7 Qualification Decisions
- 7 Letters of Support
- 1 Fit-For-Purpose Endorsement

EMA

- 8 Qualification Opinions
- 8 Letters of Support

PMDA

- 1 Qualification Decisions

Global endorsement of actionable solutions accelerates and de-risks medical product development.

CRITICAL PATH INSTITUTE

Content

- C-Path Overview
- PKDOC Background and Impact
- PKDOC 2.0

PKDOC Team

C-Path:

Sorin Fedeles, PhD, MBA
Executive Director

Wendy Vanasco
Senior Project Manager

Kitty Bogy
Senior Project Coordinator

Co-Directors:

Frank Czerwiec, MD, PhD
Sparrow Pharmaceuticals

Ronald Perrone, MD
Tufts University School of Medicine

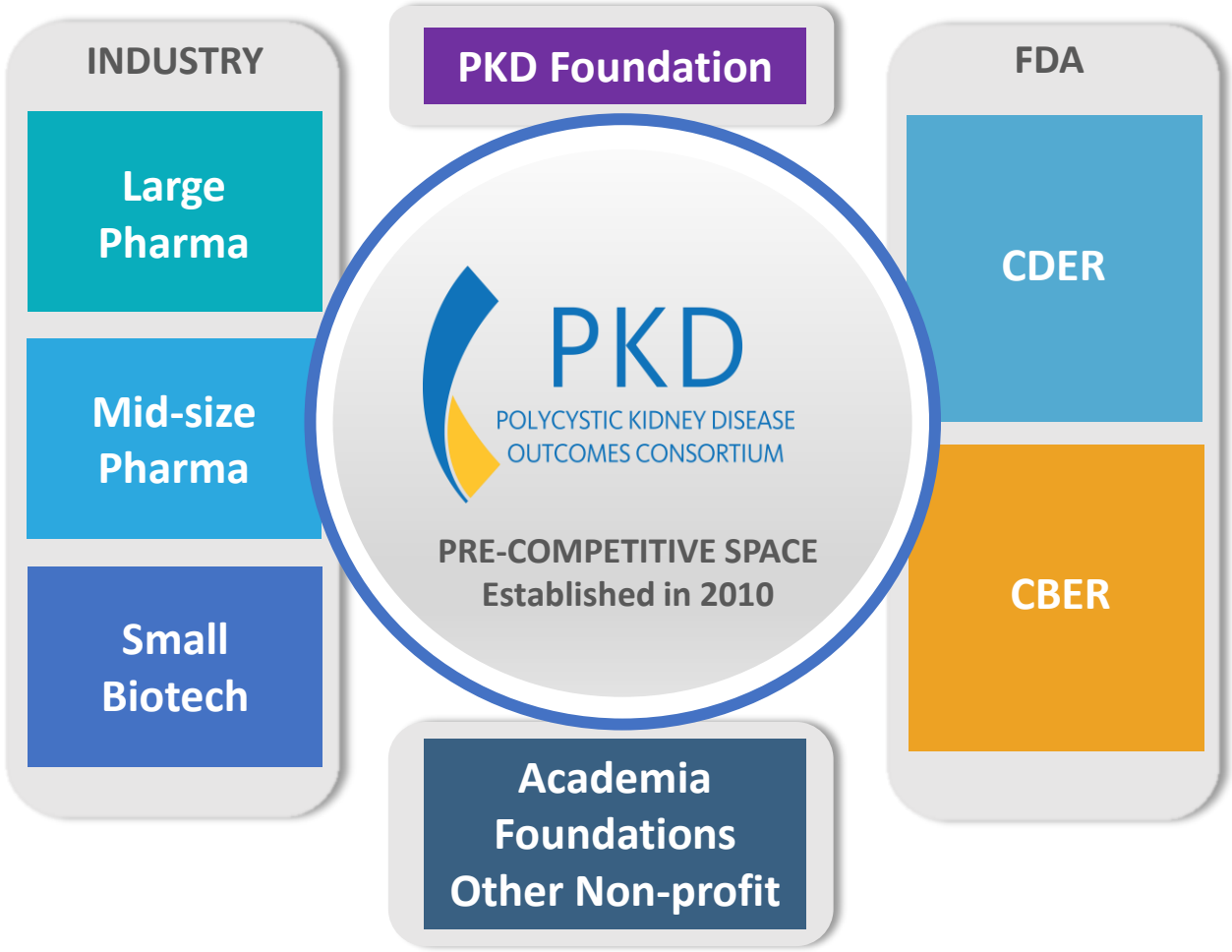
TBD
PKD Foundation

What We Do

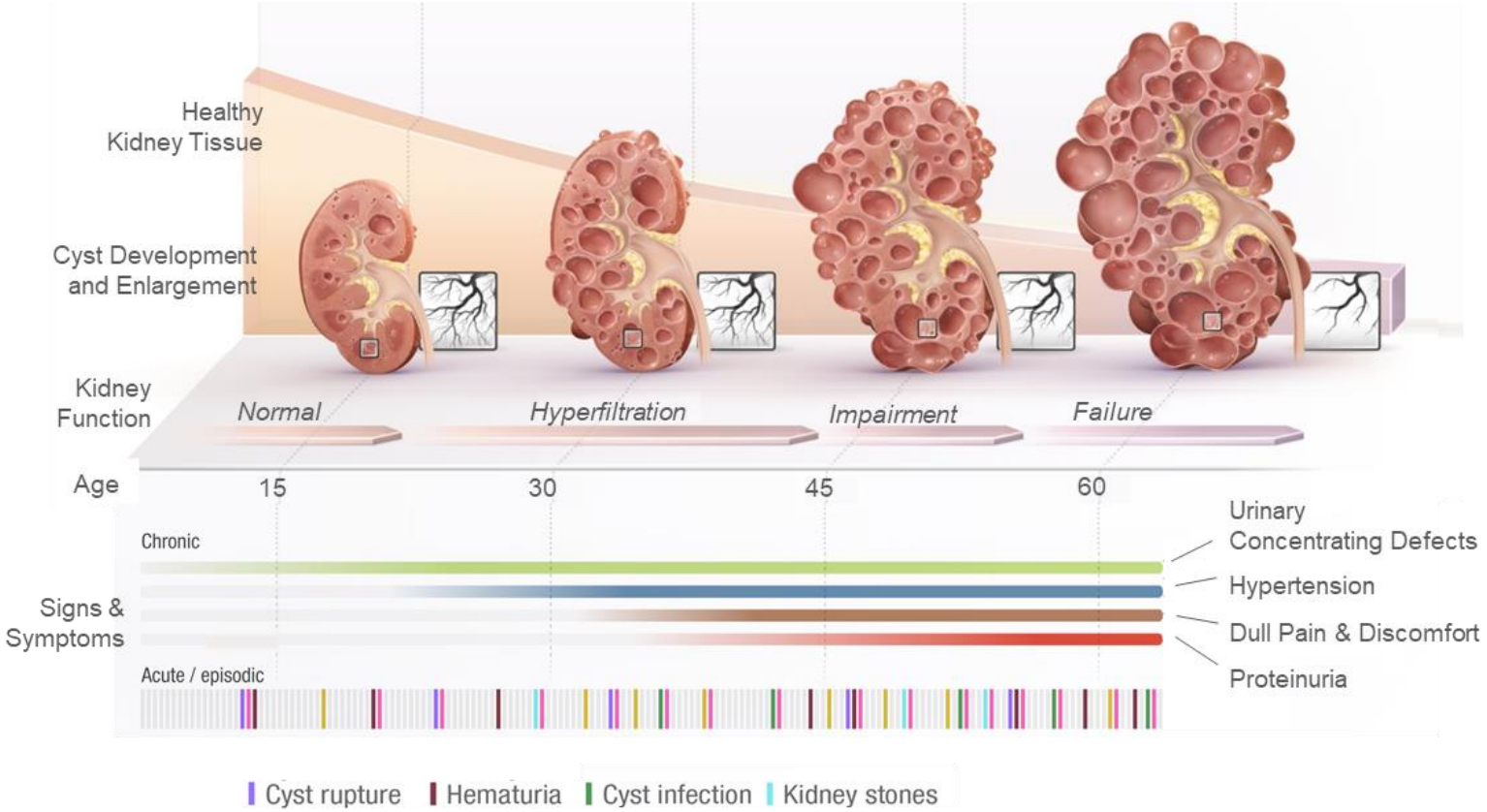
- Foster development of new evaluation tools to inform medical product development and regulatory decision-making
- Convene scientific consortia of industry, academia, and government for sharing of data/expertise

The best science
- ✓ The broadest experience
- ✓ Active consensus building
- ✓ Shared risks and costs

- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products
- Obtain official regulatory endorsement of novel methodologies and drug development tools



ADPKD: Progression of Kidney Disease



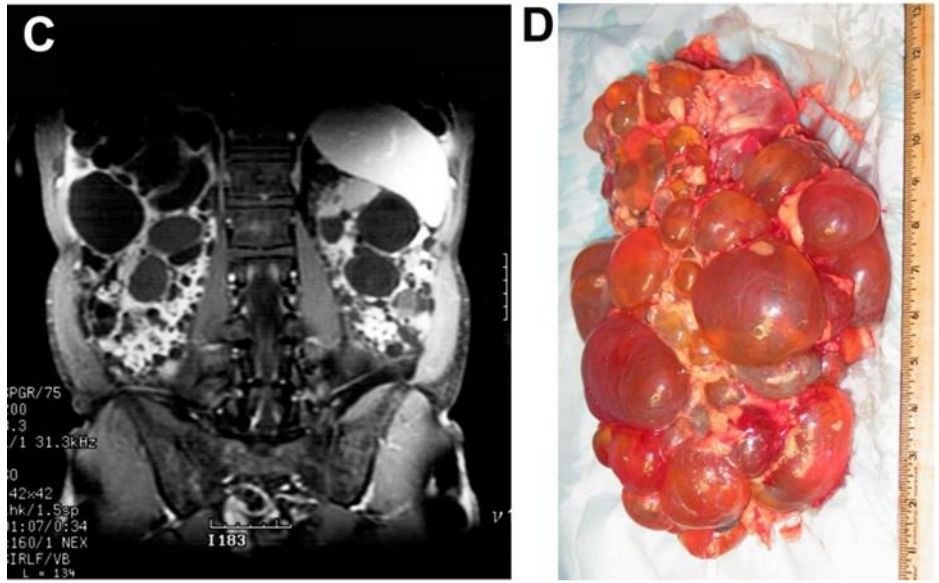
GFR = glomerular filtration rate

Adapted from Grantham JJ, *et al*. *N Eng J Med* 2006; 354(20):2122-30

ADPKD

PKD
POLYCYSTIC KIDNEY DISEASE
OUTCOMES CONSORTIUM

- Most common hereditary renal disease (1:400 to 1:1,000)
- Autosomal dominant inheritance
- Genetically heterogeneous
  - *PKD1* (16p13.3) (~77%)
  - *PKD2* (TRPP2) (4q21-23) (~15%)
  - No mutation detected (8%)
- Affects all nationalities and ethnic groups (~12.5 M worldwide)
- No common or recurrent mutations



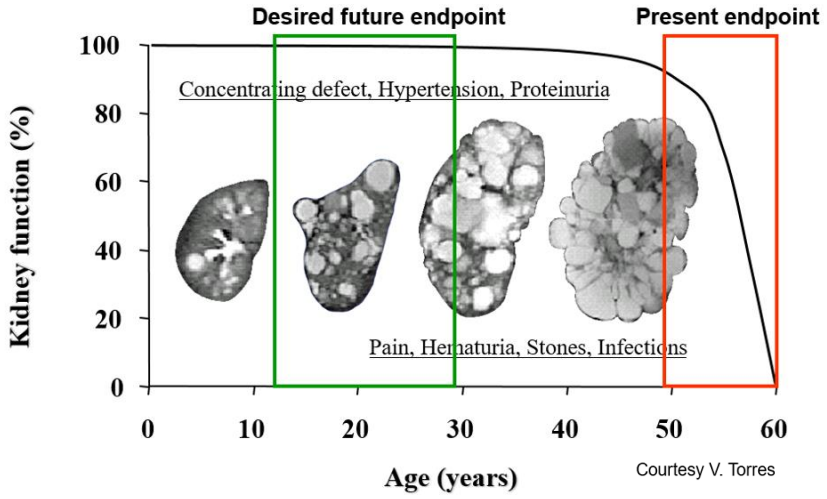
Somlo S, Torres VE, Caplan MJ. (2012). In: Seldin and Giebisch's The Kidney: Physiology and Pathophysiology, (5th Edition), Alpern RJ, Caplan MJ, Moe OW (eds.). Elsevier. Chapter 80, pp. 2645 – 2688.

CRITICAL PATH INSTITUTE

Polycystic Kidney Disease: Lack of Biomarkers Discouraged Therapeutic Development

PKD POLYCYSTIC KIDNEY DISEASE OUTCOMES CONSORTIUM

The Challenges



- Heterogeneous and slow progressing disease requires long trials and challenging endpoints
- Finding clinical endpoint(s) or an accepted surrogate for measuring disease progression early in the course of the disease where kidney function is largely preserved
- Designing a clinical trial and acceptable post marketing study to use FDAs Accelerated Approval pathway

Initial Mission of PKDOC

1. Develop standard common data elements specific to ADPKD
2. Create new integrated patient-level database from existing multiple, longitudinal, well-characterized and varied data sources
3. Develop quantitative biomarker dynamics and disease progression joint model
4. Incorporate results of contemporary trials into database
5. Generate scientific consensus on the utility and reliability of TKV as a biomarker and clinical endpoint for the progression of ADPKD
6. Submit qualification package on TKV to FDA and EMA for review and possible designation as “qualified for use” in drug development

CRITICAL PATH INSTITUTE

Data Sources

Sources of Data:	Information
University of Colorado Registry	• Time Frame: 1985 – 2004 • Number of individuals: 5,684 individuals from 1228 families with ADPKD, ≈107996 patient-years • Structure: Long-term registry funded by NIH • Process: Structured evaluation at the University of Colorado General Clinical Research Center; irregular visit and TKV measurement interval • Outcomes: Information from 1112 participants, 648 women (58.3%) and 464 men (41.7%), has been mapped to the CDISC SDTM standard. There were 165 deaths and 342 ESRD events with timing information
Mayo Clinic Registry	• Time frame: 1984 - present; analysis limited to those with electronic records, after mid-90s • Number of individuals: 2,871 patients with ADPKD, ≈34452 patient-years • Structure: Encounter for clinical care at Mayo Clinic, Rochester, MN • Process: Comprehensive data collection through clinical care; irregular visit and TKV measurement interval • Outcomes: The Mayo Clinic has supplied CDISC STDM mapped data on 1010 participants including 607 women (60.1%) and 403 men (39.9%). There were 68 deaths and 198 ESRD events with timing information
Emory University	• Time frame: 1998 - 2014 • Number of individuals: 700 individuals from approximately 400 families, ≈11200 patient-years • Structure: Two day visit at GCRC as part of longitudinal observational program supported by the Polycystic Kidney Disease Foundation (COHORT Study). • Process: Structured evaluation at Emory University General Clinical Research Center; irregular visit and TKV measurement interval • Outcomes: Information from 376 participants, 229 women (60.9%) and 147 men (39.1%), has been mapped to the CDISC SDTM standard. There were eight deaths and 121 ESRD events with timing information
Consortium for Radiologic Imaging Studies in PKD (CRISP1 and 2)	• Time frame: 2001 - 2010 • Number of individuals: 241, ≈2169 patient-years • Structure: multicenter, prospective, longitudinal study of the natural history of ADPKD • Process: Regular visits with TKV measurements yearly through first 3 years and less frequent thereafter. Comprehensive data collection • Outcomes: All data from both CRISP I and II were converted to a CDISC SDTM structure. There were no deaths or ESRD events during CRISP I. In CRISP II there were two deaths and eight ESRD events with data available regarding the start of ESRD

→Total of 2355 patients with at least one TKV measurement (all modalities) in the database were available. Overall, the analysis dataset included 1140 patients of which 361 (31.7%) patients had a 30% worsening of eGFR (two measurements 30% lower than baseline).

TKV Qualifications from FDA and EMA

Contains Nonbinding Recommendations

Qualification of Biomarker—Total Kidney Volume in Studies for Treatment of Autosomal Dominant Polycystic Kidney Disease

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration's (FDA) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (email: CDER-BiomarkerQualificationProgram@fda.hhs.gov).

Drug Development Tool (DDT) Type: Biomarker
Referenced Biomarker(s): Total Kidney Volume (TKV)

TKV is defined as the sum of the volume of the left and right kidneys.

I. SUMMARY OF GUIDANCE

A. Purpose of Guidance

This guidance provides a qualified context of use (COU) for the biomarker TKV in studies for the treatment of autosomal dominant polycystic kidney disease (ADPKD). This guidance also describes the experimental conditions and constraints for which this biomarker is qualified through the CDER Biomarker Qualification Program. This biomarker can be used by drug developers for the qualified COU in submissions of investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) without the relevant CDER review group reconsidering and reconfirming the suitability of the biomarker.

B. Application of Guidance

This guidance applies to the use of TKV in studies for the treatment of ADPKD. It does not change any regulatory status, decisions, or labeling of any medical imaging device used in the medical care of patients.

TKV use in drug development outside of the qualified COU will be considered by FDA on a case-by-case basis in regulatory submissions. In such cases, additional information relevant to the expanded use may be requested by the CDER product review team.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/CHMP/SAWP/361949/2015 CONFIDENTIAL
Procedure No.: EMEA/H/SAB/037/1/Q/2013/SME
Product Development Scientific Support Department

Qualification Opinion
Total Kidney Volume (TKV) as a prognostic biomarker for use in clinical trials evaluating patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

On 11 April 2013 the Applicant Critical Path Institute's Polycystic Kidney Disease Outcome Consortium (PKDOC) requested qualification opinion for total kidney volume (TKV) as a prognostic biomarker to enrich the ADPKD population with the aim to conduct clinical trials more efficiently.

Dr Armin Koch was appointed as coordinator. The Qualification Team comprised of: Ms Tess Harris, Dr Romaldas Maciulaitis, Prof. Dr W. Van Biesen, Dr Evi Nagler, Ms Anika Großhennig and Dr Flora Musuamba Tshinanu. The EMA Scientific Officer for the procedure was Mr Efthymios Manolis.

A formal Letter of Intent was submitted to the EMA on April 11th, 2013, followed by submission of the initial EMA Briefing Package on April 30, 2013. The procedure started during the SAWP meeting held on 06 – 08 May 2013. On 13 June 2013 a list of issues was sent to the applicant. A face-to-face meeting between the PKDOC and the EMA Qualification Team was held in London on July 9, 2013. Following questions and responses that were addressed via email during the next several months, the Agency indicated that all remaining questions could be addressed in the submission of an updated Briefing Package. The updated package was submitted on 20 March 2014. When assessing the submission, it was felt that another set of issues has to be addressed by the Applicant, before a qualification opinion can be issued. The list of issues was sent on 20 May 2014. Response has been provided on 27 June, 2014 and a teleconference was planned on the 7th of July 2014. An additional request for data has been submitted to enable re-analyses for a better understanding of the competence of the database and the model.

During its meeting held on 01 – 04 June 2015, the SAWP agreed on the opinion to be given to the Applicant. During its meeting held on 22 – 25 June 2015, the CHMP adopted the draft opinion to be given to the Applicant. The draft Opinion was published for consultation. Following consultation, during its meeting on 19-22 October 2015, the CHMP adopted the final Opinion to be given to the Applicant. This opinion is annexed to this letter.

The response given by CHMP is based on the questions and supporting documentation submitted by the Applicant, considered in the light of the current state-of-the-art in the relevant scientific fields.

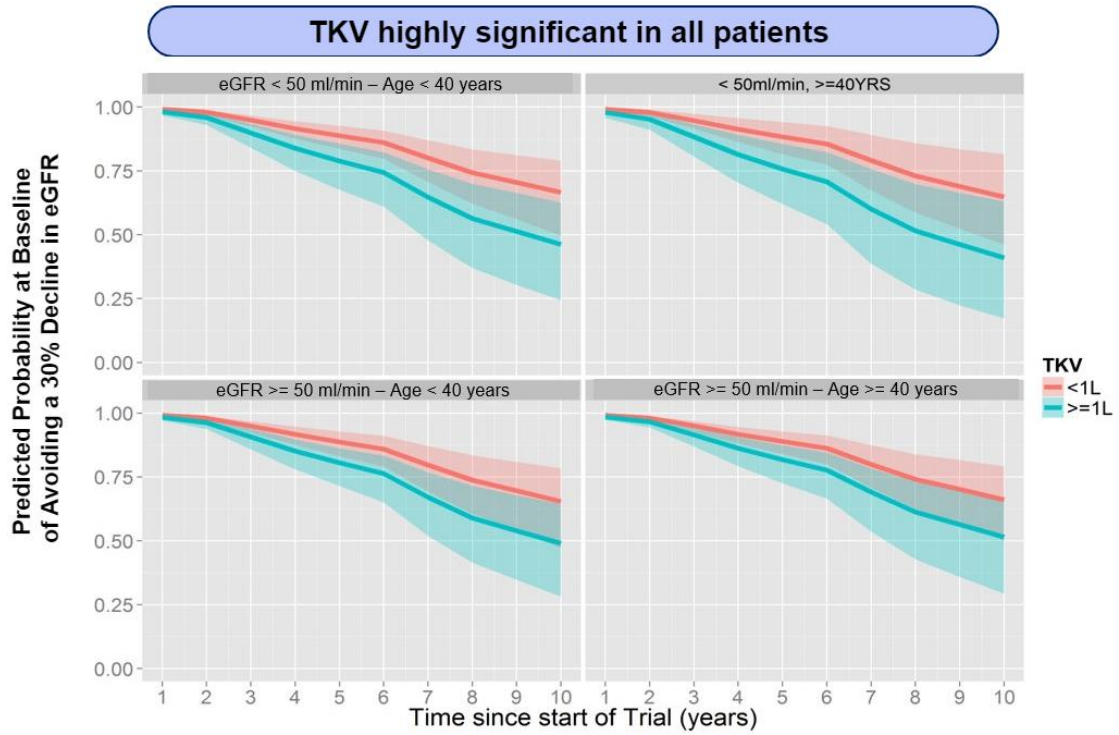
London, 22 October 2015

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5510

II. CONTEXT OF USE

A. Use Statement

This guidance provides qualification recommendations for the use of TKV, measured at baseline, as a prognostic enrichment biomarker to select patients with ADPKD at high risk for a *progressive decline* in renal function (defined as a confirmed 30% decline in the patient's estimated glomerular filtration rate (eGFR)) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient's age and baseline eGFR as an enrichment factor in these trials.



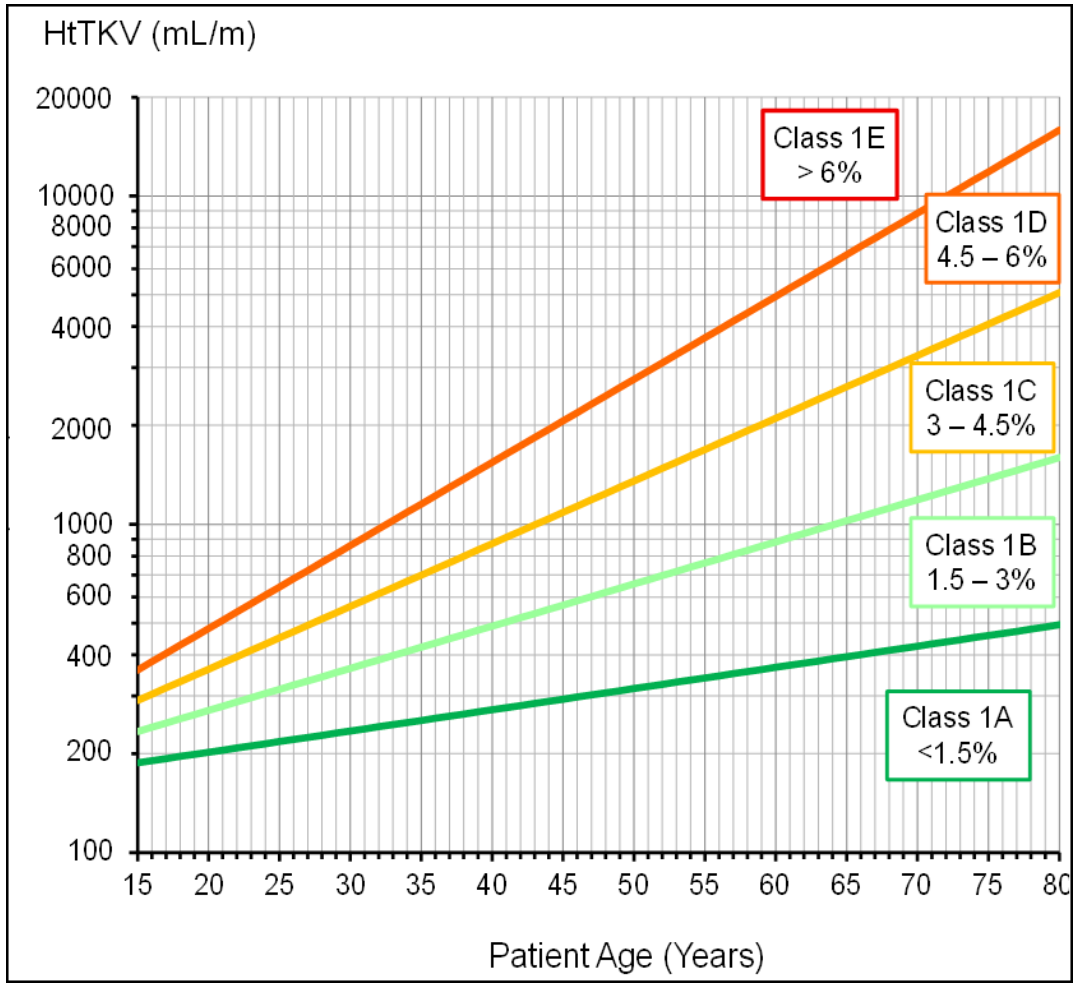
The Value of Enrichment

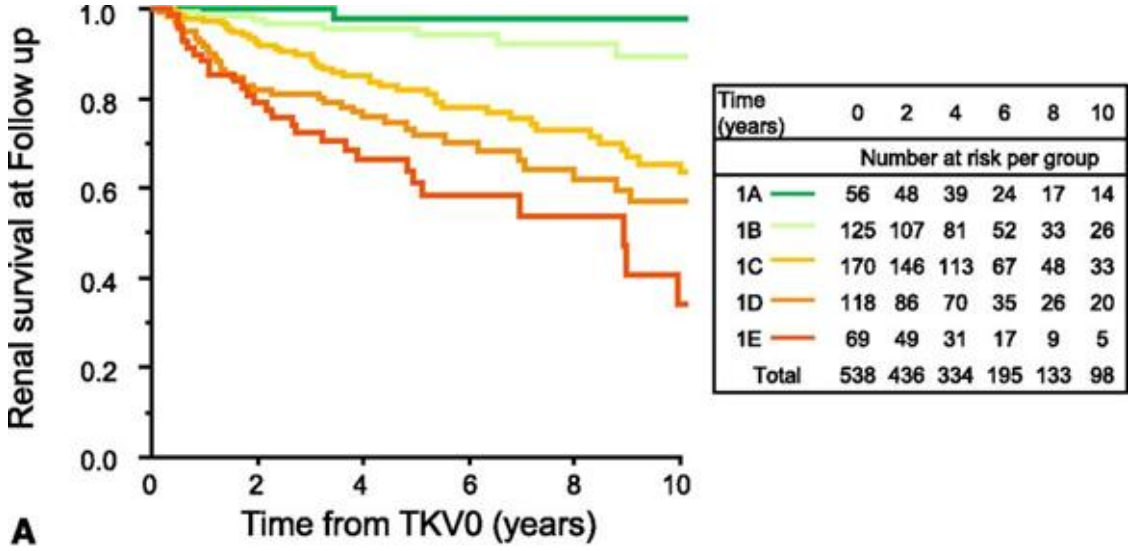
Predicted event rate in placebo arm over 3 years, **number needed to enroll and number needed to treat to get one event** using the best fit models with and without TKV.

	Model without TKV	Model with TKV, using added criterion of TKV > 1 L
Predicted event rate in placebo arm over 3 years	0.091	0.110
Number needed to enroll†	11	9
Number needed to screen	13	25

Assumes entry criteria of eGFR > 50 mL/min per 1.73 m^2 and age between 20 and 50 years.

Scoring PKD: Imaging Classification of ADPKD



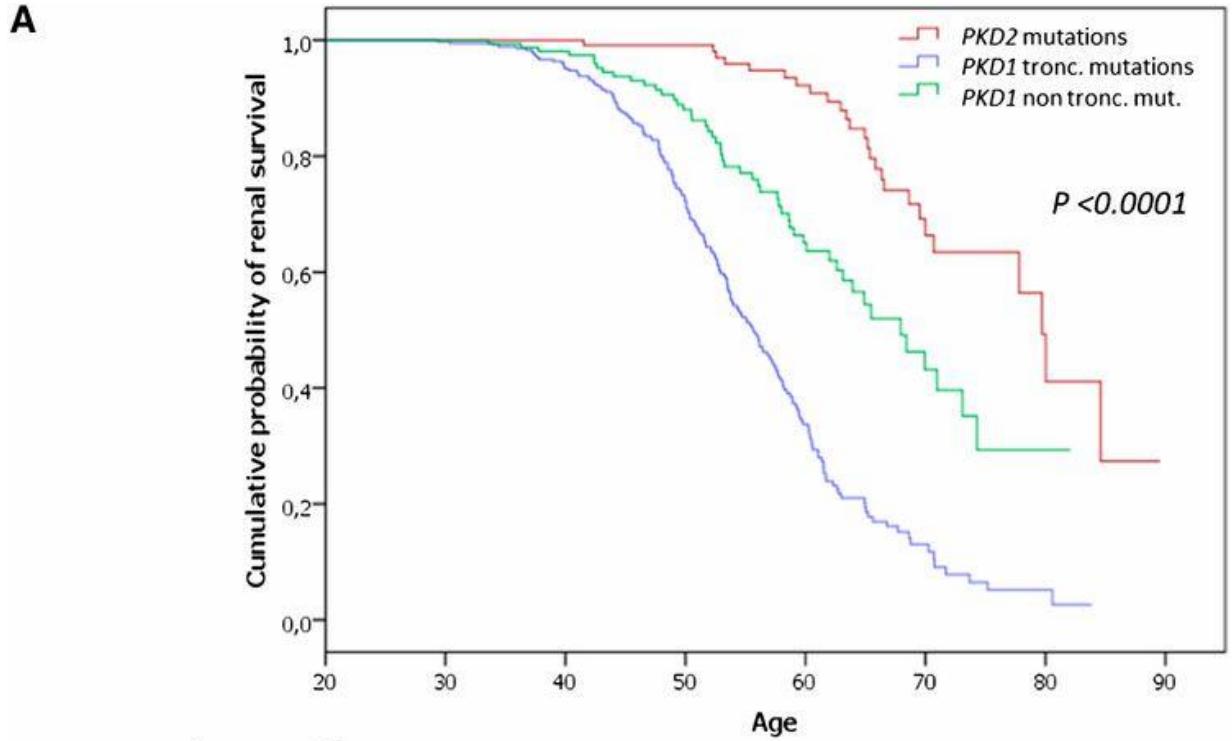


Time (years)	0	2	4	6	8	10
Number at risk per group						
1A	56	48	39	24	17	14
1B	125	107	81	52	33	26
1C	170	146	113	67	48	33
1D	118	86	70	35	26	20
1E	69	49	31	17	9	5
Total	538	436	334	195	133	98

- Tool for inputting htTKV and age to classify patients into groups A-E
- Classification predicts renal survival
- Useful to optimize patient selection for enrollment into clinical trials and for treatment

María V. Irazabal et al. JASN 2015;26:160-172

PKD1 Mutation Type Influences Renal Survival



Patients at risk :

PKD1 truncating mutations (n=387)	356	296	175	53	11	2
PKD1 non truncating mutations (n=184)	172	144	134	48	15	1
PKD2 Mutations (n=133)	127	116	99	63	23	5

Cornec-Le Gall E et al. JASN 2013;24:1006-1013

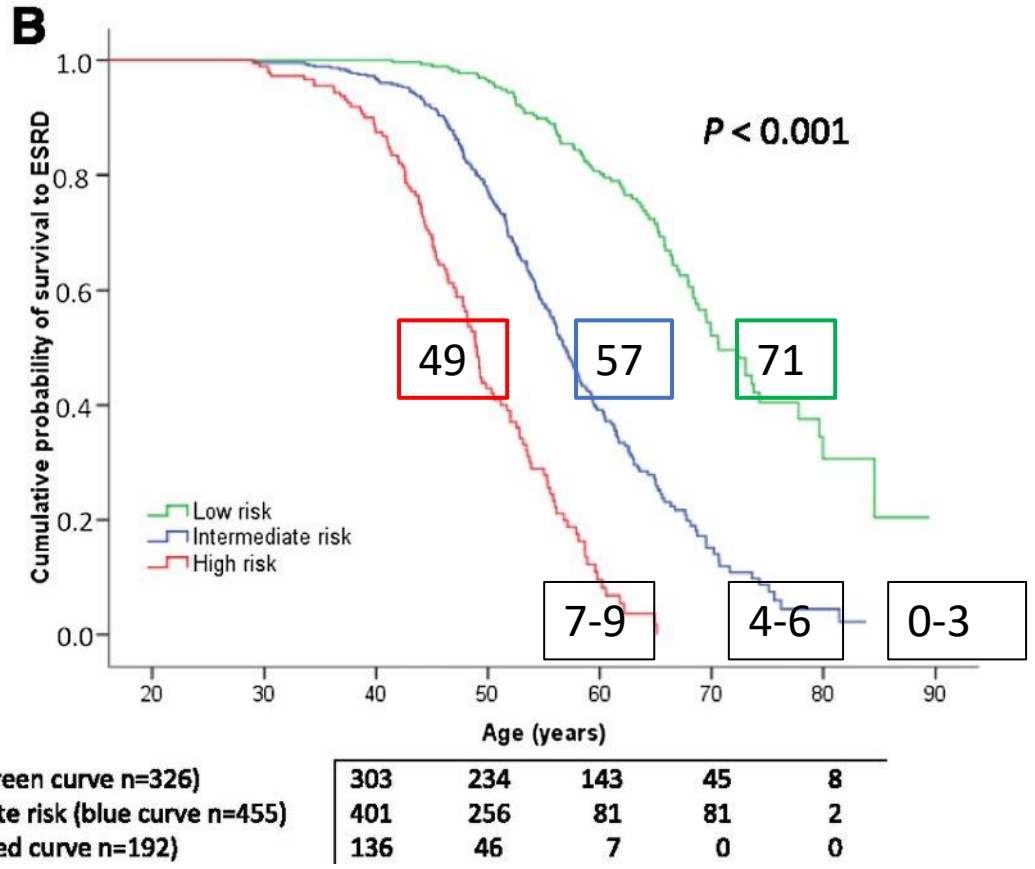
Scoring PKD: PRO-PKD

Table 3. Multivariate Cox analysis

Variable	Patients (*n*)	HR (95% CI)	95% CI from Bootstrap Analysis	*P* Value	Points for PROPKD Score
Sex					
Female	541				0
Male	432	1.55 (1.29 to 1.88)	1.27 to 1.89	<0.001	1
Hypertension before age 35 yr					
No	679				0
Yes	294	2.11 (1.71 to 2.61)	1.71 to 2.62	<0.001	2
≥1 urologic event before age 35 yr					
No	734				0
Yes	239	1.73 (1.38 to 2.18)	1.35 to 2.24	<0.001	2
Mutation					
PKD2	186				0
PKD1 nontruncating	239	2.27 (1.57 to 3.28)	1.61 to 3.18	0.002	2
PKD1 truncating	548	4.75 (3.41 to 6.60)	3.63 to 6.60	<0.001	4

95% CI, 95% confidence interval.

The AUC for the PRO-PKD score is 0.84;
It is 0.79 for the genetic score alone

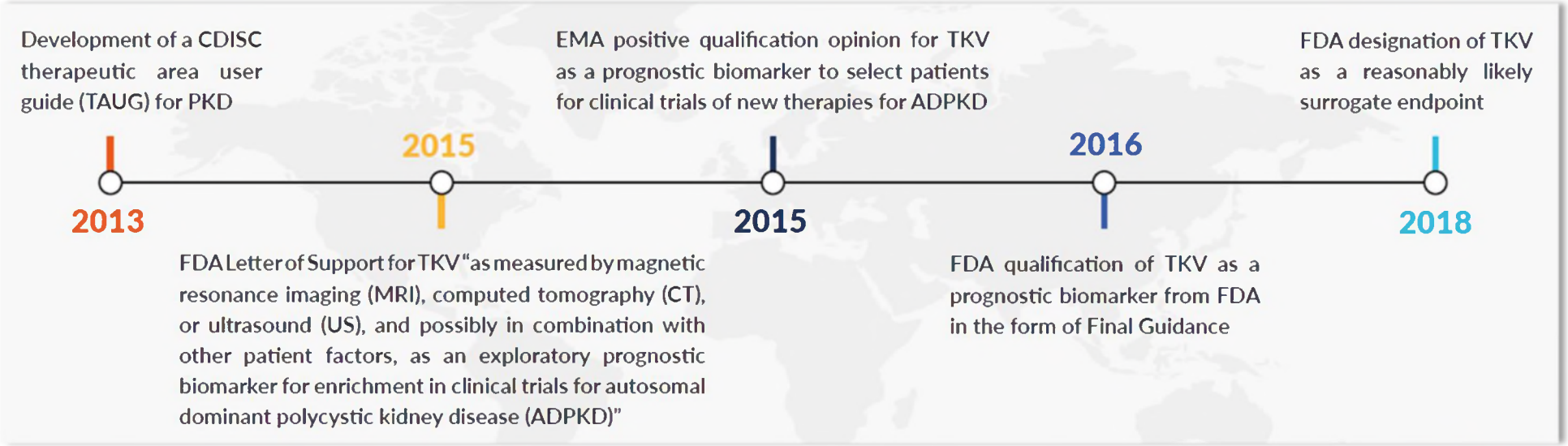


Low risk (green curve n=326)	303	234	143	45	8
Intermediate risk (blue curve n=455)	401	256	81	81	2
High risk (red curve n=192)	136	46	7	0	0

Emilie Cornec-Le Gall et al. JASN 2016;27:942-951

PKDOC Impact

- Development of a CDISC therapeutic area user guide (TAUG) for PKD to collate data from several clinical patient registries and observational studies of ADPKD patients
- Successful qualification of total kidney volume (TKV) as prognostic biomarker to select patients for clinical trials of new therapies for ADPKD is a key milestone for the consortium
- TKV has been designated as a reasonably likely surrogate endpoint and therefore could be used in an FDA accelerated approval process, but an acceptable plan for a post-marketing confirmatory trial would be required
- Otsuka's drug JYNARQUE® (Tolvaptan) was designated as the first FDA-approved treatment for PKD; Although it was not a direct output of PKDOC, the consortium was a significant positive influence over many years in this success story



Lessons Learned

- While TKV had been used as part of development programs, the TKV qualification effort quantified the amount of information that “was added” by using TKV to enrich a trial population

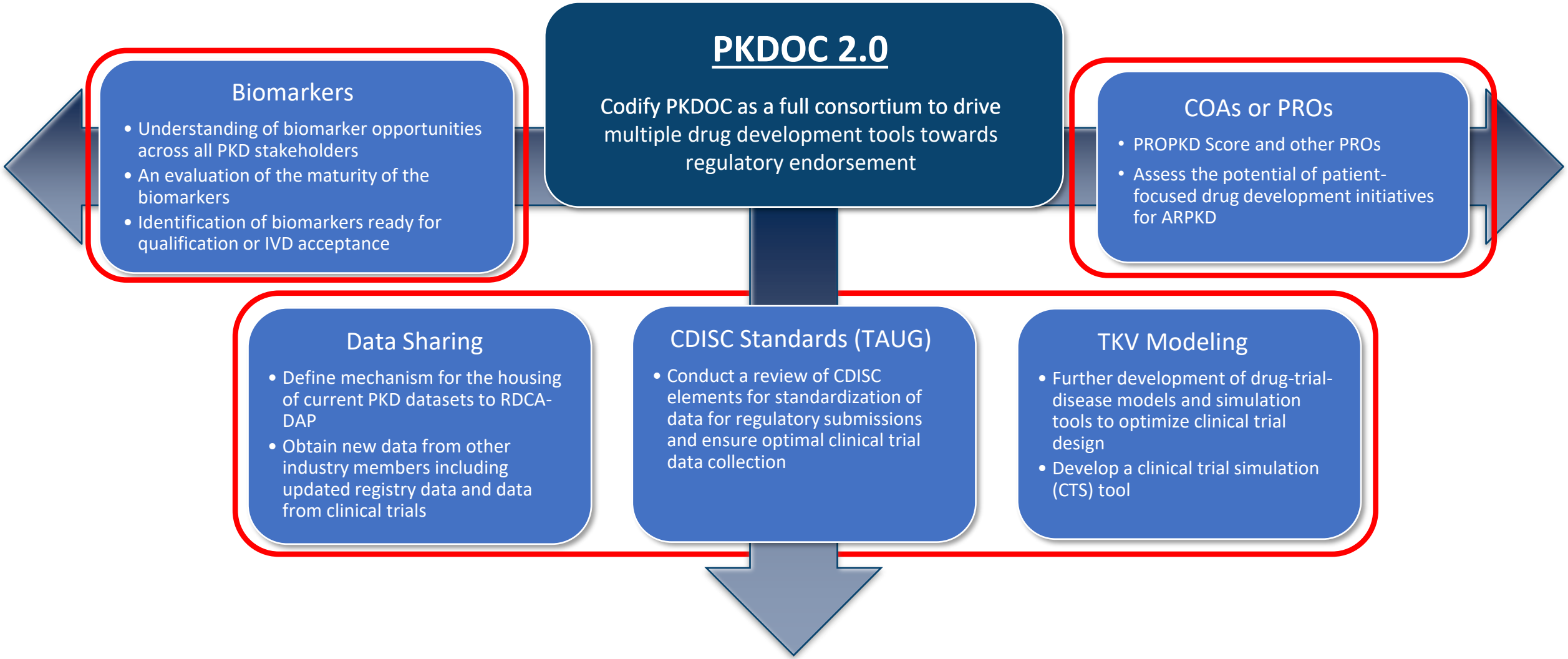
- Qualification served as a steppingstone to more meaningful discussions about the use of TKV as a reasonably likely surrogate and potential endpoints for approval

- Registry data can be critical for establishing the value of a biomarker as a tool in drug development (with inherent challenges associated with using and interpreting the data)

Content

- C-Path Overview
- PKDOC Background and Impact
- PKDOC 2.0

PKDOC 2.0 Goals and Objectives



Innovation Through Data Sharing

PKD
POLYCYSTIC KIDNEY DISEASE
OUTCOMES CONSORTIUM

Academia

- **Improves their research**
- Understand disease course/variance
- Understand/develop biomarkers/endpoints
- Visibility of data and research, collaboration
- Publish more/better papers

Industry

- **Design more effective trials**
- Understand disease course/variance
- Understand/develop biomarkers/endpoints

Patients/Patient Groups

- **Faster drug development**
- Understand disease course/variance
- Visibility to industry
- Drive collaboration

CRITICAL PATH INSTITUTE

PKD Modeling/CTS Tool Roadmap

PKD
POLYCYSTIC KIDNEY DISEASE OUTCOMES CONSORTIUM

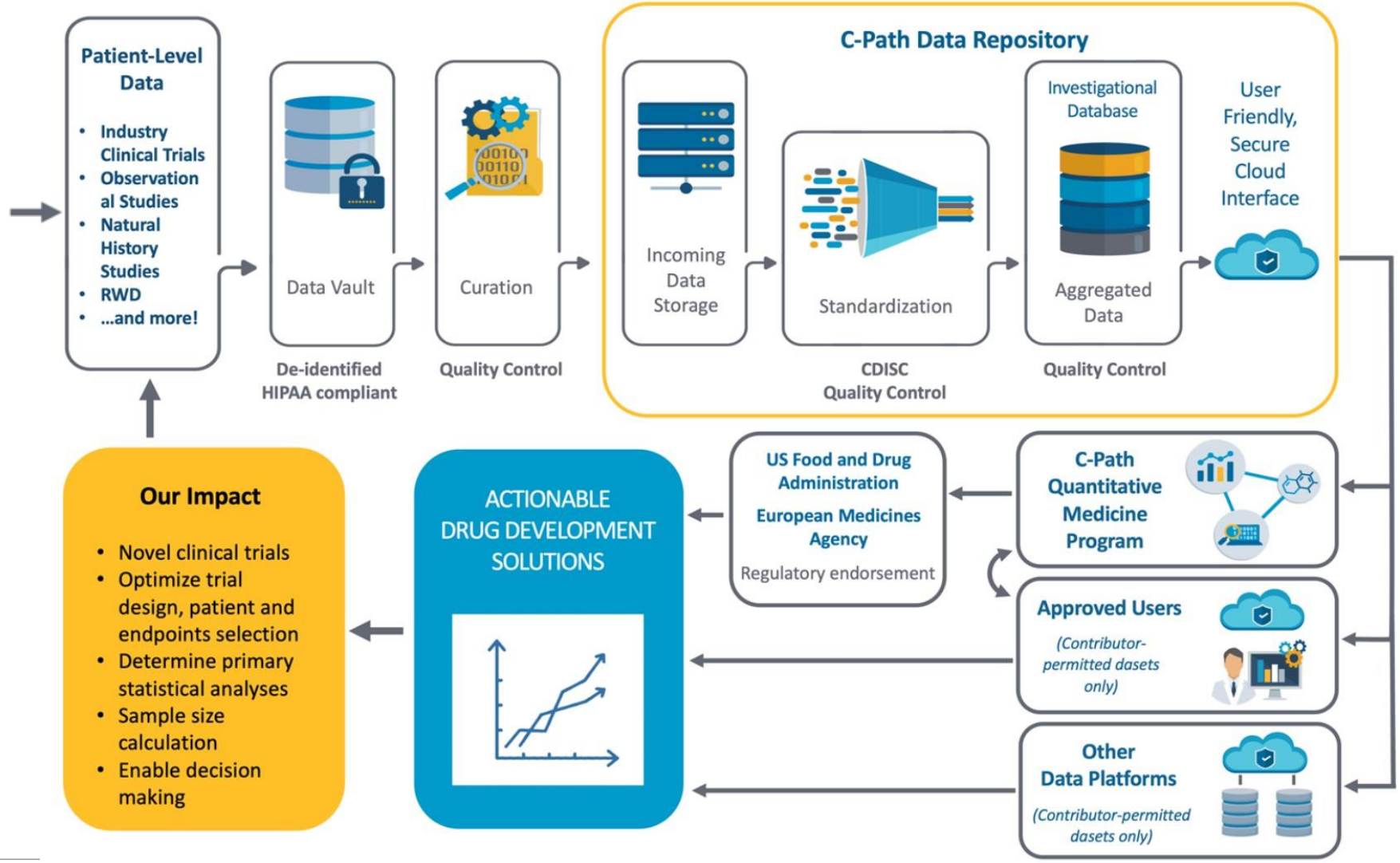
1. Current Datasets

- University of Colorado
- Emory University
- Mayo Clinic
- CRISP
- HALT

2. Incoming Datasets

- ALADIN 1
- TAME

3. Investigating strategies to leverage industry-led RCT data



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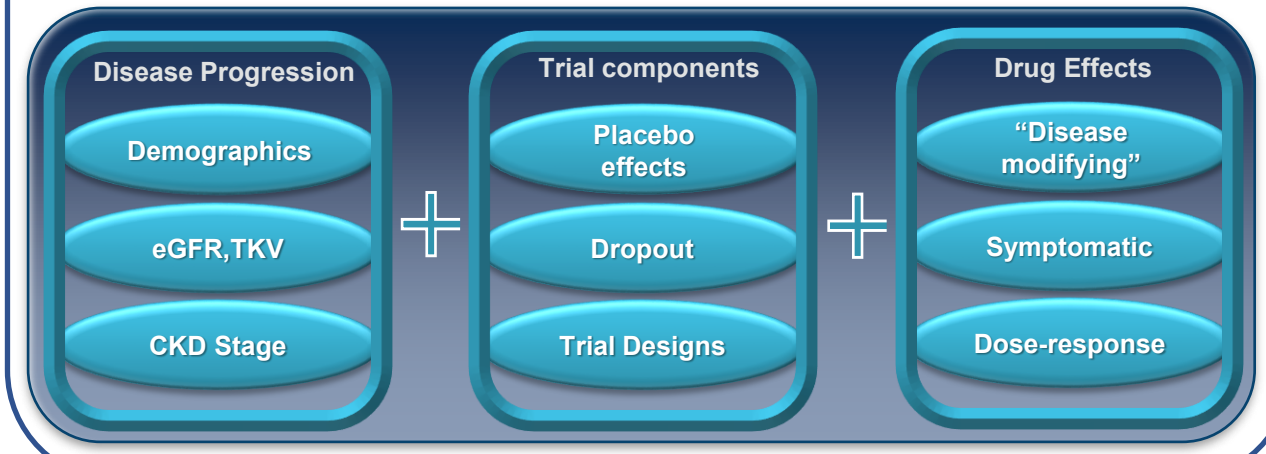
The Envisioned Outcome: Clinical Trial Simulations

The developed model is intended to be used as a basis in a **clinical trial simulation tool**

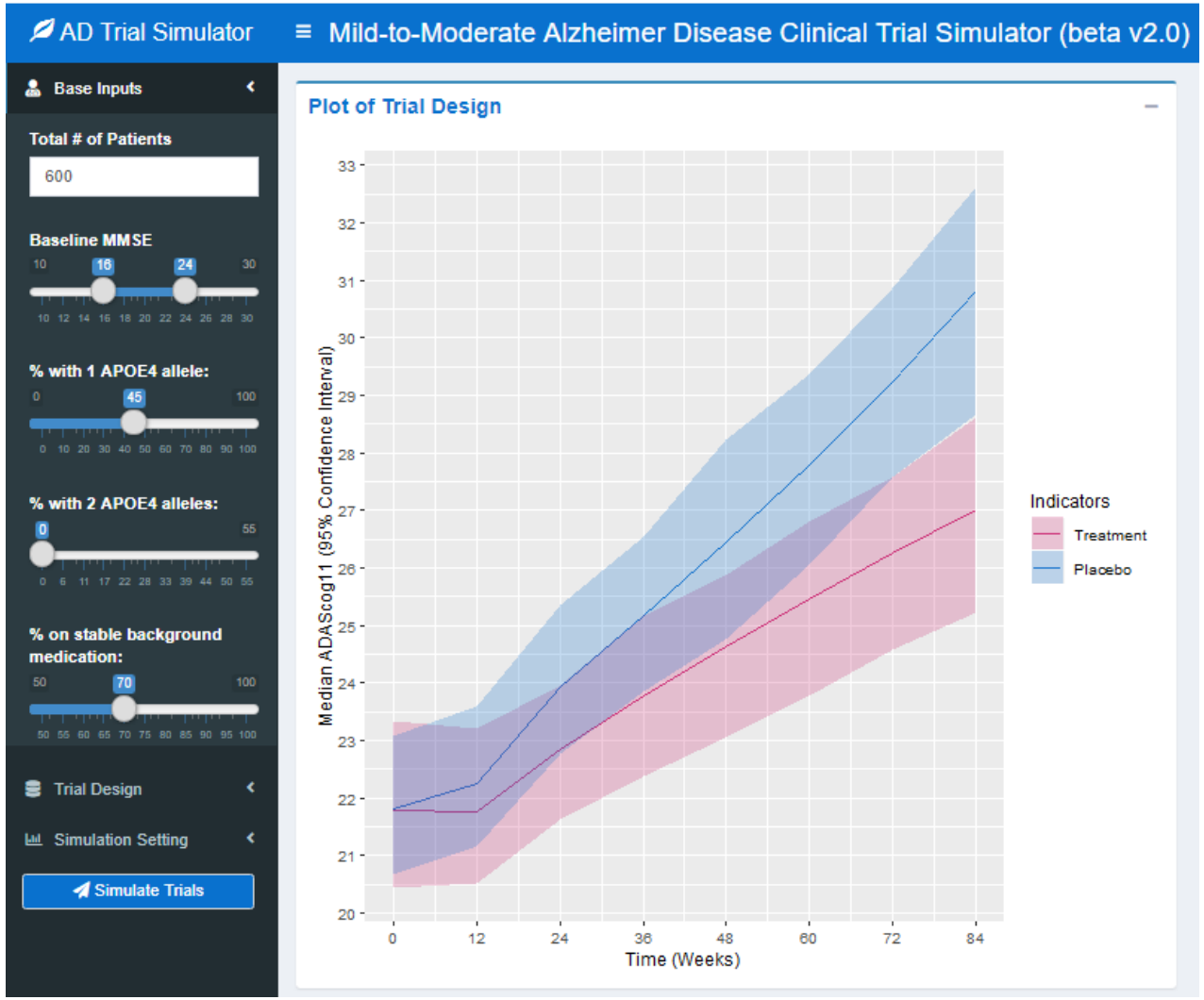


Such a tool is intended to inform clinical trial design by computing trial power based on user chosen information:

1) **Inclusion/exclusion criteria**
2) **Enrichment strategies**
3) **Trial duration and sample size**
4) **Support design of accelerated approval programs**

The Envisioned Outcome: Clinical Trial Simulations

PKD
POLYCYSTIC KIDNEY DISEASE
OUTCOMES CONSORTIUM



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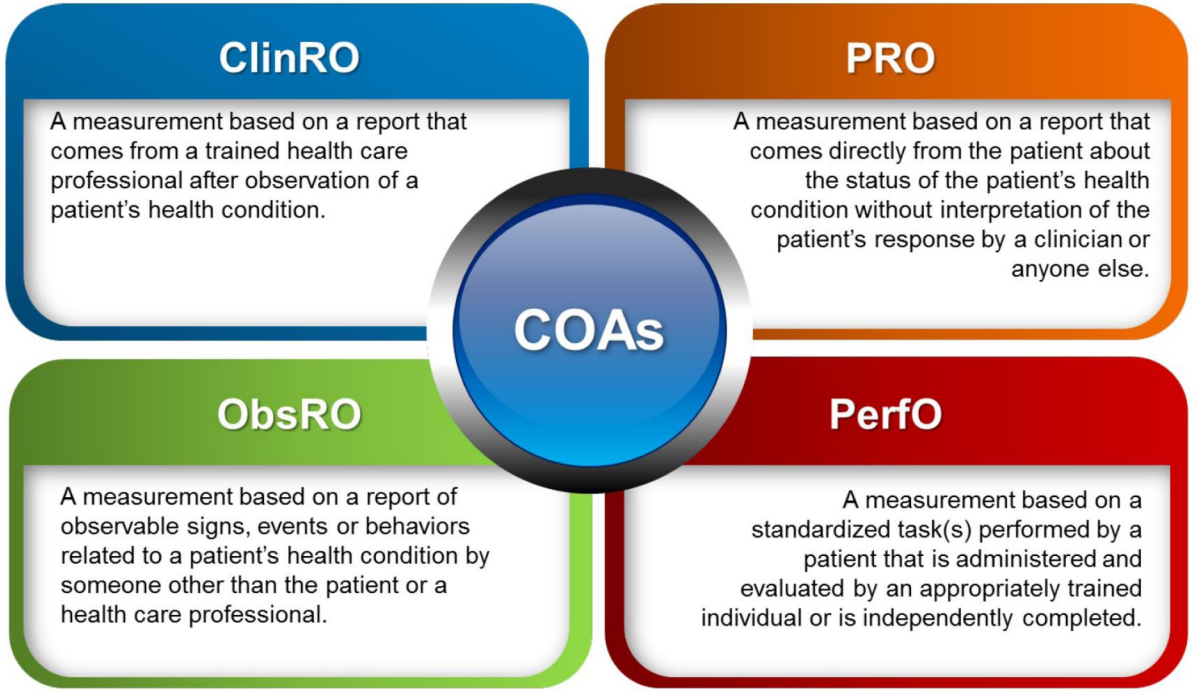
PRO-Focused Approaches

- Focus on patient-reported outcomes (PRO) as an avenue to inform medical product development
- Both ADPKD and ARPKD represent areas of unmet need for PRO development
- Use ARPKD as a case study for an externally-led patient focused drug development (EL-PFDD) project



ARPKD EL-PFDD Objectives

Broad objective of the meeting are to inform the FDA and other stakeholders (e.g., drug developers) on:

- Patients' and families' experiences and perspectives regarding symptoms and burdens of ARPKD and its impact on daily living
- Factors that may influence patients' and families' decision making on entering clinical trials, including
  - Endpoints
  - Trials conducted under Accelerated Approval Program
- Current medical management of ARPKD, patient/family experiences with treatment and their aspirations for new treatments

Who does this meeting benefit?

FDA

- Gain understanding of what it's like to live with ARPKD
- Learn about side effects and risks patients are willing to accept
- Hear patients' needs for new drugs and preferences for clinical trials

Patients

- Know that the FDA and industry stakeholders have heard their voices
- Hearing other patients' experiences and needs to validate symptoms and feelings in order to better self-advocate

Patient Advocacy Groups

- Identify additional needs for patient education and advocacy
- Increase public awareness through gained knowledge of ARPKD
- Create greater connections with patients and their peers

Industry

- Gain insights into the major concerns of patients to help develop treatments and optimize clinical trial design
- Learn about symptoms and side effects to help develop drugs that matter to patients

Value to PKDOC 2.0 Stakeholders

- Regulatory acceptance
  - Better understanding of disease and application of biomarkers across all stakeholders including health authorities
- Rapid implementation of biomarkers in clinical trials
  - Accepted under IND vs qualified
- Patient stratification and disease monitoring biomarkers lead to efficient clinical trials, faster approvals
- Change patient journey—precision medicine

Thank you!

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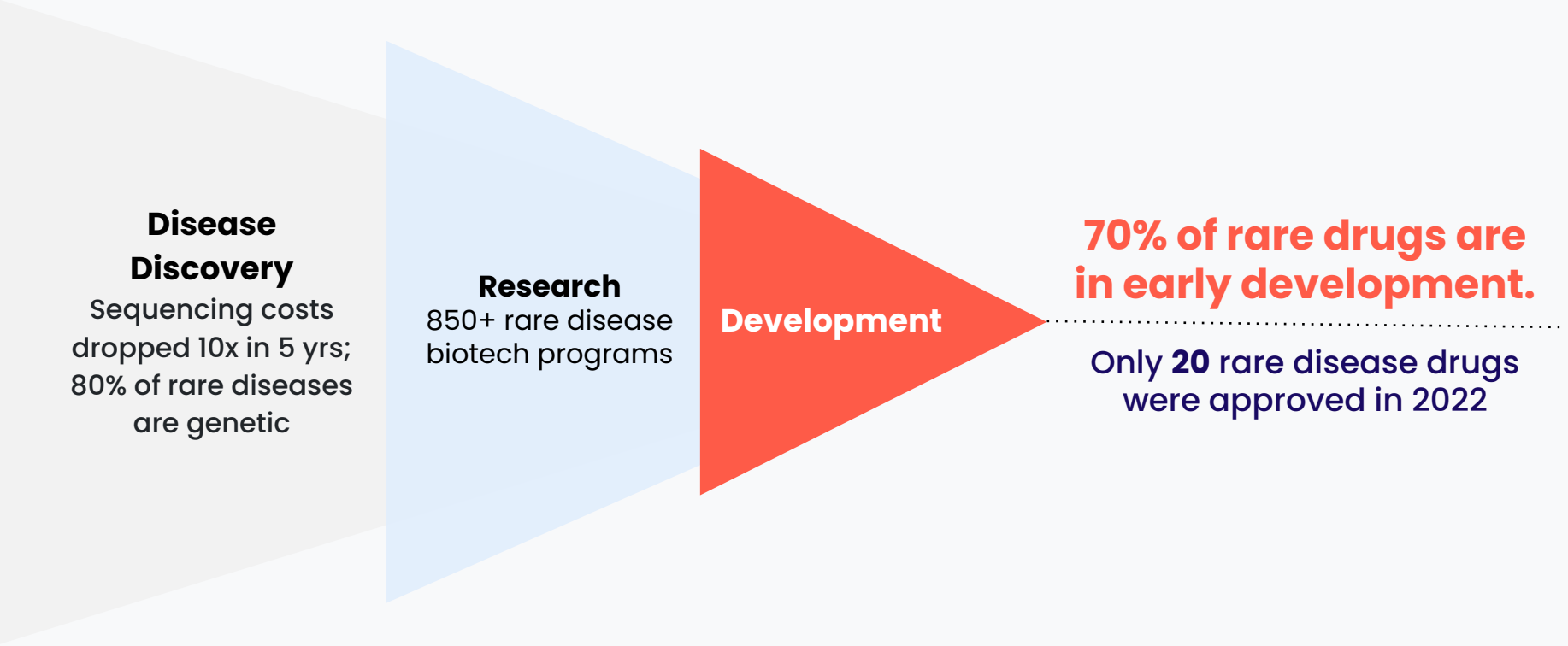
Leveraging patient engagement and real-world data to inform rare disease drug development

FDA CDER-JHU CERSI Rare Disease Workshop
2 May 2023

Despite advances in research and technology, relatively few orphan drugs are approved each year



Rare disease drug development is uniquely challenging

Small patient number geographically spread across the globe

Many specialties / institutions involved in patient care

Scarcity of high-quality data in orphan populations

Natural history rarely understood; limited longitudinal data

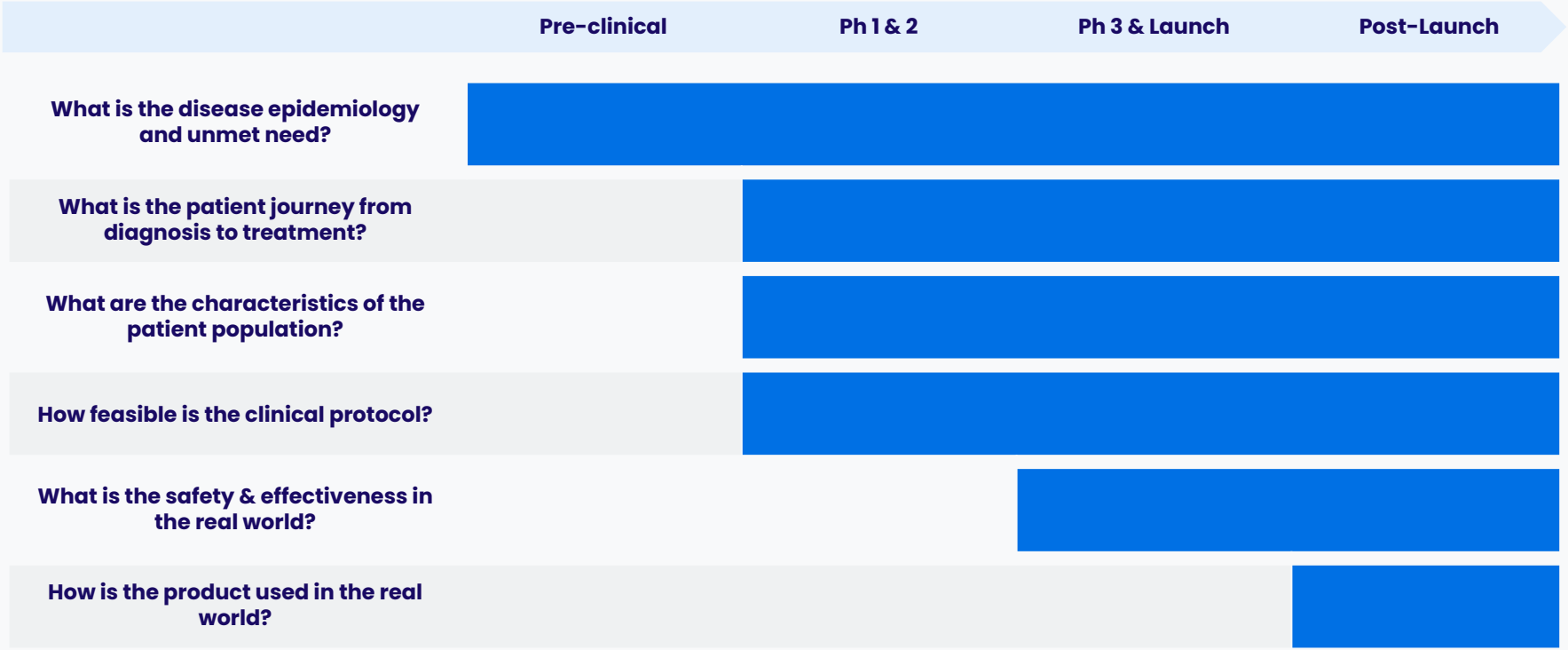
Burden of illness difficult to quantify & characterize

Appropriate clinical outcome measures are often unclear

Studies are clinically & ethically difficult to design & execute

Deep engagement of patient communities is critical

Real-world evidence has the potential to address key questions across the drug development lifecycle



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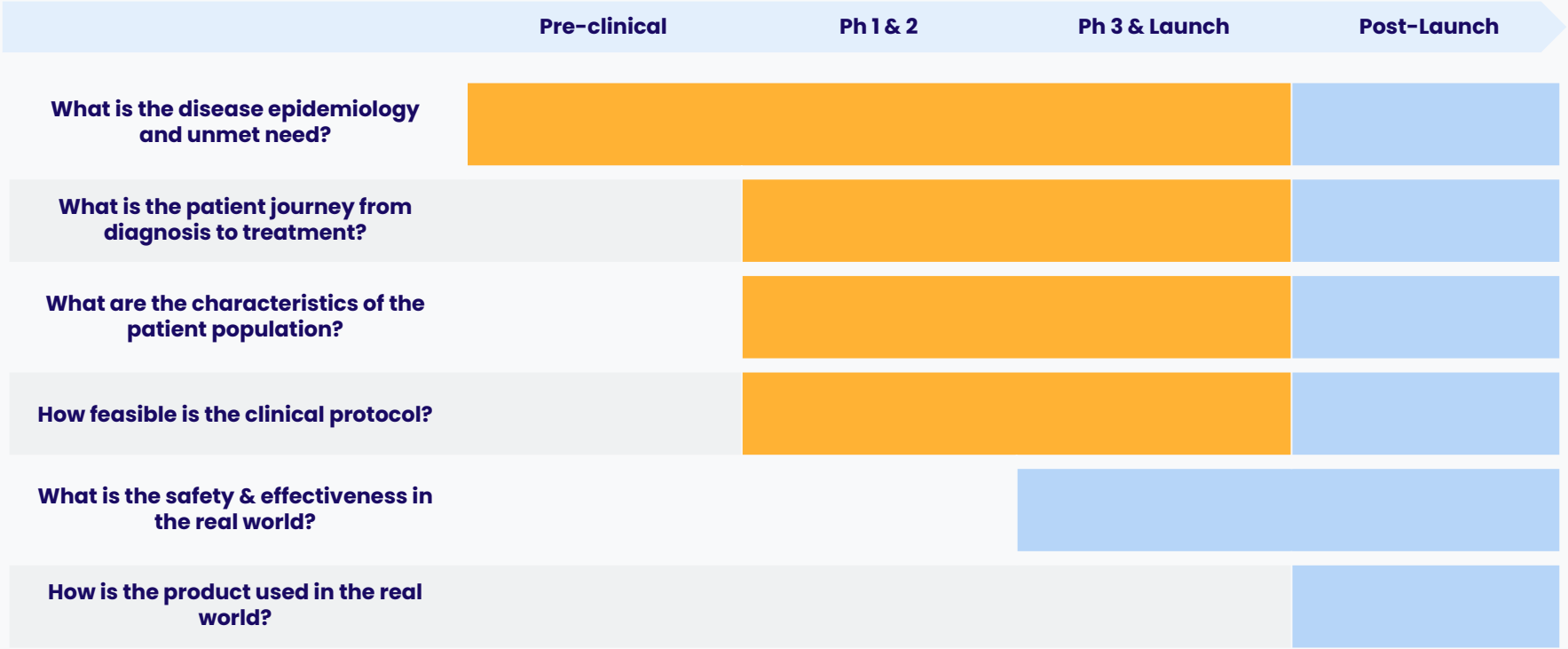
Real-world evidence has the potential to address key questions across the drug development lifecycle



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Integrating the patient voice

is critical to a robust real-world data strategy

Real-World Data Sources

Claims / Billing Data

Patient-Reported Data

Structured EHR Databases

Unstructured Clinical Notes

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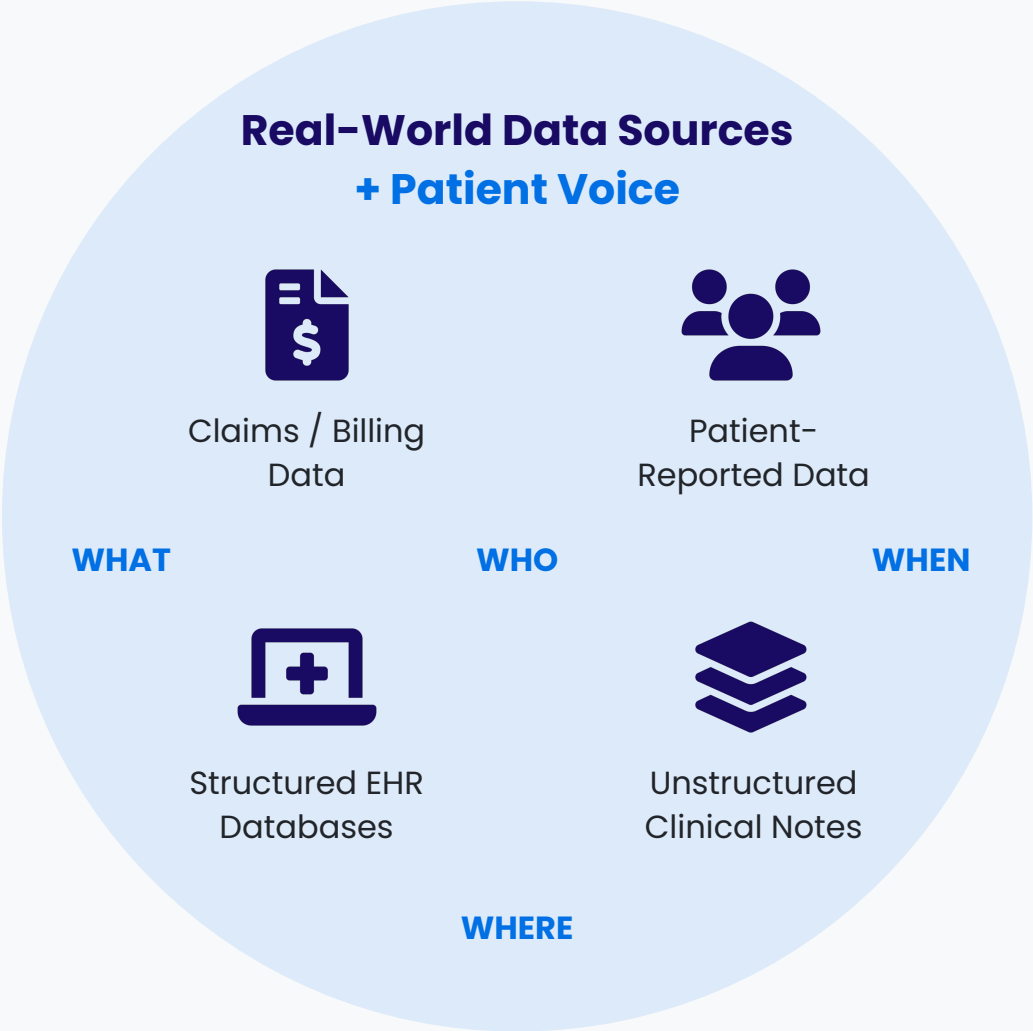
Integrating the patient voice

is critical to a robust real-world data strategy



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Integrating the patient voice is key to answering the big questions in clinical trial planning

Who?

Characterize the population

Evaluate I/E criteria feasibility

What & When?

Characterize unmet need

Determine appropriate outcomes and endpoints

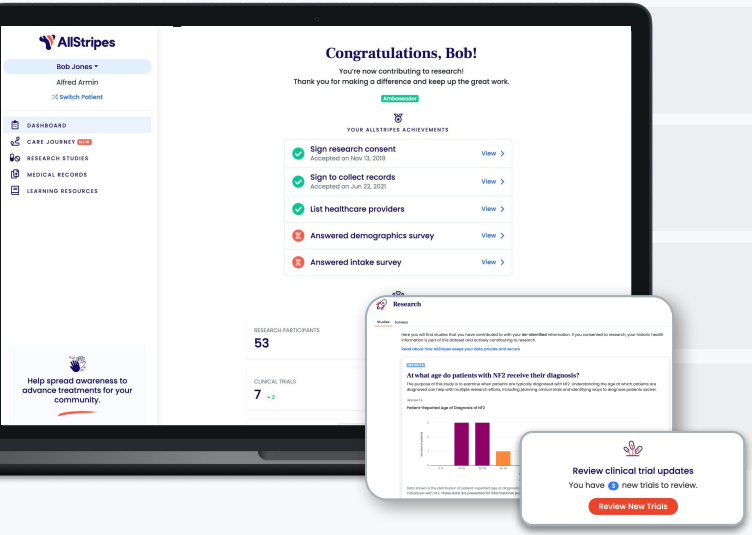
Where?

Evaluate recruitment approaches

Identify suitable trial sites

AllStripes

AllStripes serves as the nexus of patient engagement and real-world data generation



Patients and caregivers can **sign up and e-consent in minutes**; accounts may be created for deceased patients

The umbrella research consent allows use of de-identified data for **minimal risk research, survey, and recontact of patients over time**

AllStripes collects, structures, and analyzes multimodal clinical data from across the patient journey **at no cost to participants**

Ongoing engagement, insights, and communications shared about research programs

Records and data collected from over 4,000 healthcare facilities in the US, Canada, and UK

Who, What, & When: Characterizing Unmet Need and the Patient Journey

Case study: Genetic epilepsy natural history

SPONSOR: **Sponsor A**, a biopharmaceutical company

STAGE: Pre-IND

CONDITION: **Condition B**, a rare, severe epilepsy characterized by seizures that begin in infancy

CHALLENGE: Lack of understanding of natural history and progression of Condition B. Sponsor A needed to better characterize the patient journey to inform clinical trial design.

OUR SOLUTION: Natural history study to better understand needs of the patient community and **inform clinical trial outcome and endpoint selection**.

METHODS: Participant surveys & clinical data abstracted from patient medical records

RESULTS:

250+	16,200+	235+	12,600+
Medical **facilities**	Clinical **documents**	**Years** of clinical follow-up	**Data points** abstracted

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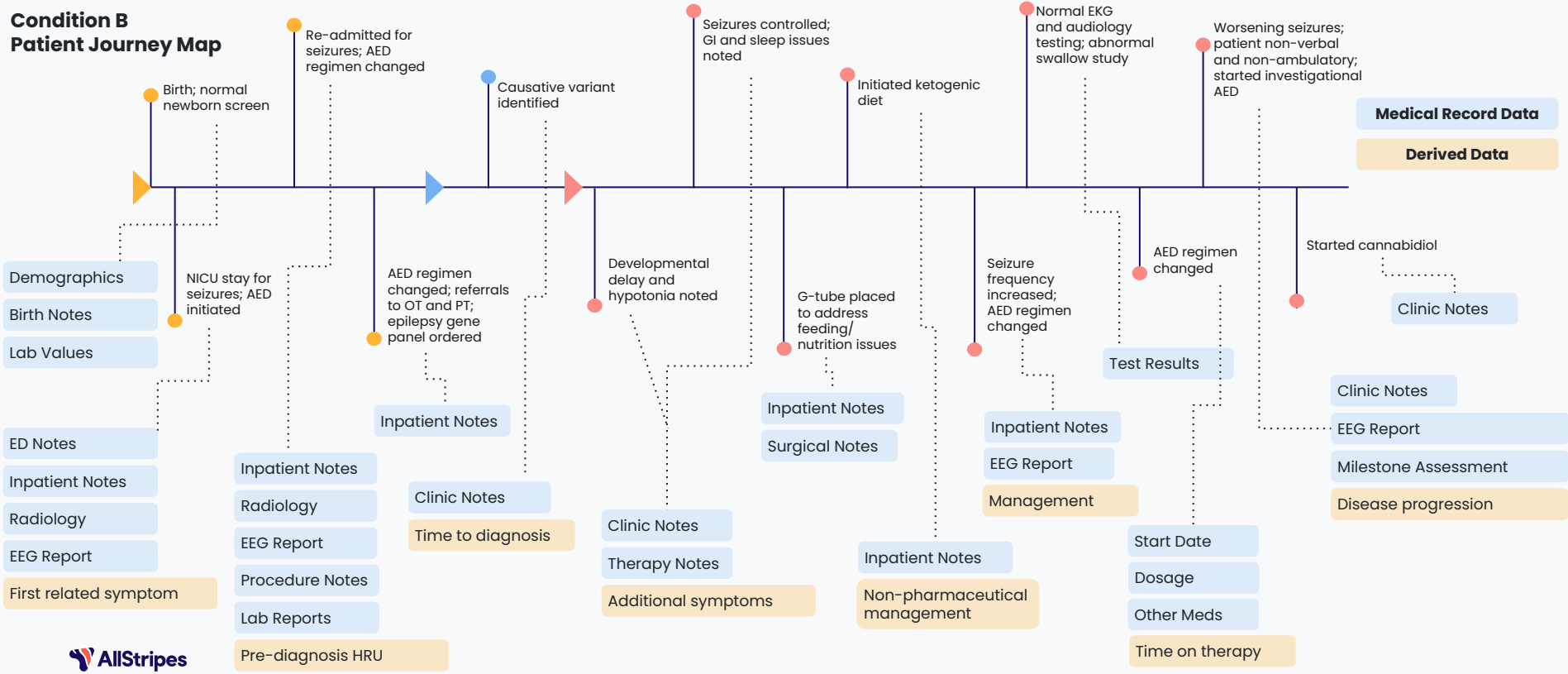
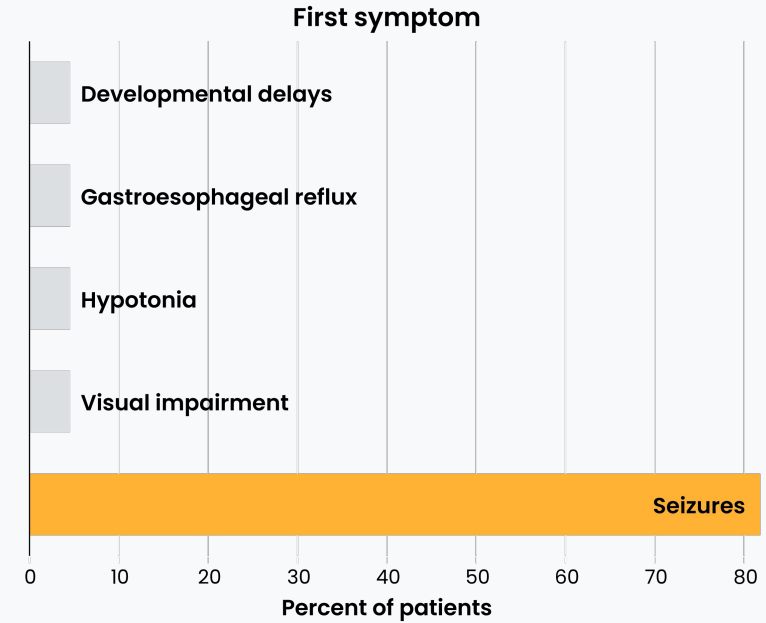
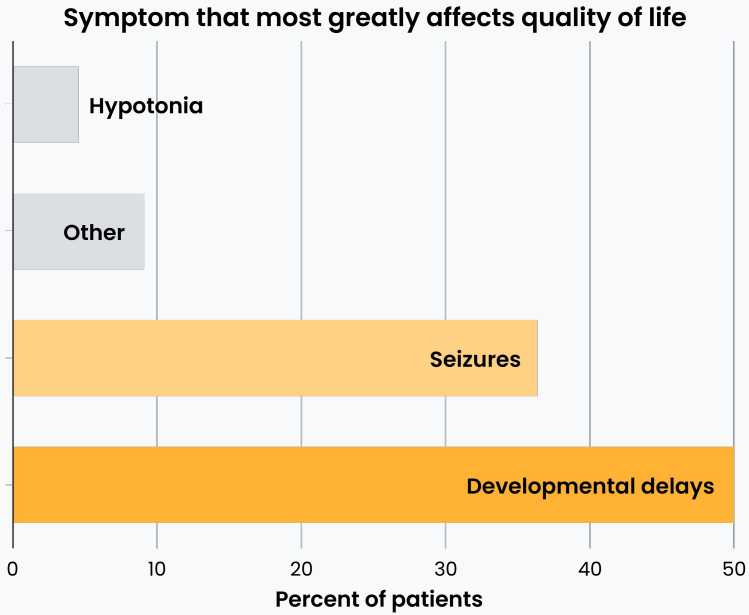
Longitudinal history with detailed context is critical to understand the complete patient journey



Partnering with families is key to understanding unmet need

Condition B, n = 22





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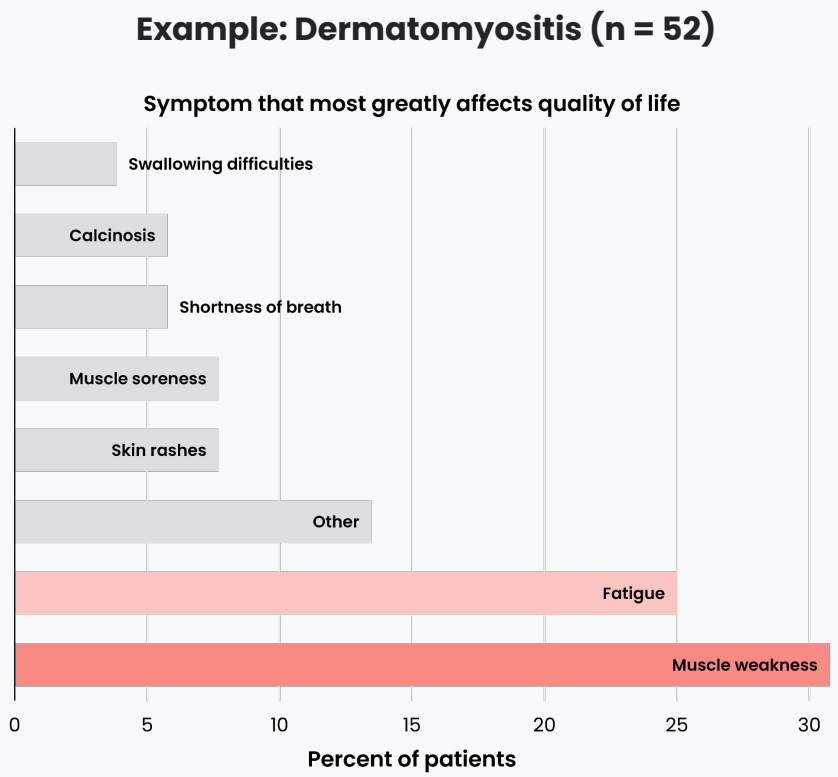
Current AllStripes symptoms database

831 completed surveys across 46 conditions



AllStripes

Who, What, & When:
Characterizing the Patient Population

Case study: Characterizing a rare metabolic syndrome

SPONSOR: **Sponsor C**, a research institution exploring commercialization

STAGE: Pre-clinical

CONDITION: **Condition D**, a rare inborn error of metabolism

CHALLENGE: Lack of understanding of Condition D manifestations, including neurological signs and behavioral symptoms beginning in childhood. **Future trials will require appropriate instruments** for measuring these symptoms.

OUR SOLUTION: Natural history study designed in partnership with Sponsor C and **Advocacy Group E**

METHODS: Surveys & clinical data abstracted from patient medical records to capture longitudinal disease manifestations.

RESULTS:

250+	13,500+	6800+	2500+
Medical **facilities**	Clinical **documents**	**Data points** abstracted	**Survey data points** collected

AllStripes

Involving all stakeholders in instrument development is key to success

Sponsor + Advocate KOL

Co-develop comprehensive list of behavioral symptoms and associated data of interest

AllStripes Research Team

Develop and test survey instrument on proprietary patient platform, with feedback from sponsor and advocate KOL

Pilot Participant Group

Complete draft instrument on AllStripes platform and provide feedback on content, language, and presentation

All Participants

Complete final instrument longitudinally to track response consistency and disease progression

Caregiver surveys collected extensive data on Condition D behavioral symptoms

Behavior Categories	# Behaviors
Physical Aggression	4
Behavior Category 2	3
Behavior Category 3	3
Behavior Category 4	11
Behavior Category 5	3
Behavior Category 6	3
Behavior Category 7	2
Behavior Category 8	2
Behavior Category 9	2
Other Behaviors (free-text)	–

Caregiver surveys collected extensive data on Condition D behavioral symptoms

Behavior Categories	# Behaviors
Physical Aggression	4
Behavior Category 2	3
Behavior Category 3	3
Behavior Category 4	11
Behavior Category 5	3
Behavior Category 6	3
Behavior Category 7	2
Behavior Category 8	2
Behavior Category 9	2
Other Behaviors (free-text)	–

Behaviors Assessed

- Hitting / kicking
- Scratching
- Biting
- Grabbing

Caregiver surveys collected extensive data on Condition D behavioral symptoms

Behavior Categories	# Behaviors
Physical Aggression	4
Behavior Category 2	3
Behavior Category 3	3
Behavior Category 4	11
Behavior Category 5	3
Behavior Category 6	3
Behavior Category 7	2
Behavior Category 8	2
Behavior Category 9	2
Other Behaviors (free-text)	–

Data Points Collected

- Age of onset
- Consistency
- Triggers
- Frequency
- Intensity
- Severity
- Mitigation strategies

Caregivers reported additional behaviors not assessed in the survey

Behavior Categories	# Behaviors	# Additional Behaviors
Physical Aggression	4	1
Behavior Category 2	3	
Behavior Category 3	3	
Behavior Category 4	11	2
Behavior Category 5	3	
Behavior Category 6	3	
Behavior Category 7	2	
Behavior Category 8	2	2
Behavior Category 9	2	
Other Behaviors (free-text)	–	

Caregivers reported additional behaviors and behavior categories not assessed in survey

Behavior Categories	# Behaviors
Physical Aggression	4
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Behavior Category 9	2
Other Behaviors (free-text)	–

“Other” Findings

- Additional behavior category involving eating / feeding identified
- 3+ additional behaviors identified that do not fit cleanly into an established category

Case study: Characterizing a rare metabolic syndrome

SPONSOR: **Sponsor C**, an academic research institution with interests in commercialization

STAGE: Pre-clinical

CONDITION: **Condition D**, a rare inborn error of metabolism

CHALLENGE: Lack of understanding of Condition C manifestations, including neurological signs and behavioral symptoms beginning in childhood. **Future trials will require appropriate instruments** for measuring these symptoms.

OUR SOLUTION: Natural history study designed in partnership with Sponsor C and **Advocacy Group E**

METHODS: Custom behavioral survey & clinical data abstracted from patient medical records to capture longitudinal disease manifestations.

RESULTS:

250+	**13,500+**	**6800+**	**2500+**
Medical **facilities**	Clinical **documents**	**Data points** abstracted	**Survey data points** collected

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Who:
Evaluating I/E Criteria

Case study: Recruiting for a pivotal trial in adult-onset autoimmune neuropathy

SPONSOR: **Sponsor F**, a biopharmaceutical company

STAGE: Pivotal trial

CONDITION: **Condition G**, a rare immune-related neurological condition that causes weakness and reduced sensation in the arms and legs

CHALLENGE: Recruiting participants for a large, multi-site pivotal trial

APPROACH: Pre-screen patients using data collected from medical records

RESULTS:

132	112	<5
Consented **participants**	Participants **pre-screened**	**Patients** connected to site

AllStripes

Sponsors should carefully consider the characteristics of a population when selecting I/E criteria

Reasons for Failing Pre-screening	# Patients (% / 112)
Diabetes diagnosis	9 (8%)
History of malignancy	8 (7%)

1 in 10 Americans

15–20% of individuals with Condition G

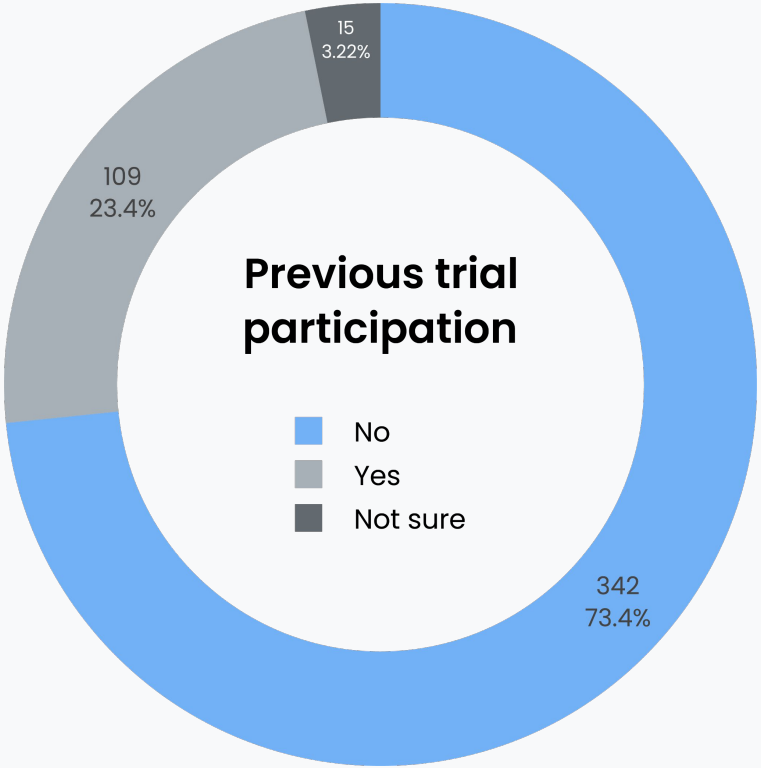
Sponsors should carefully consider the characteristics of a population when selecting I/E criteria

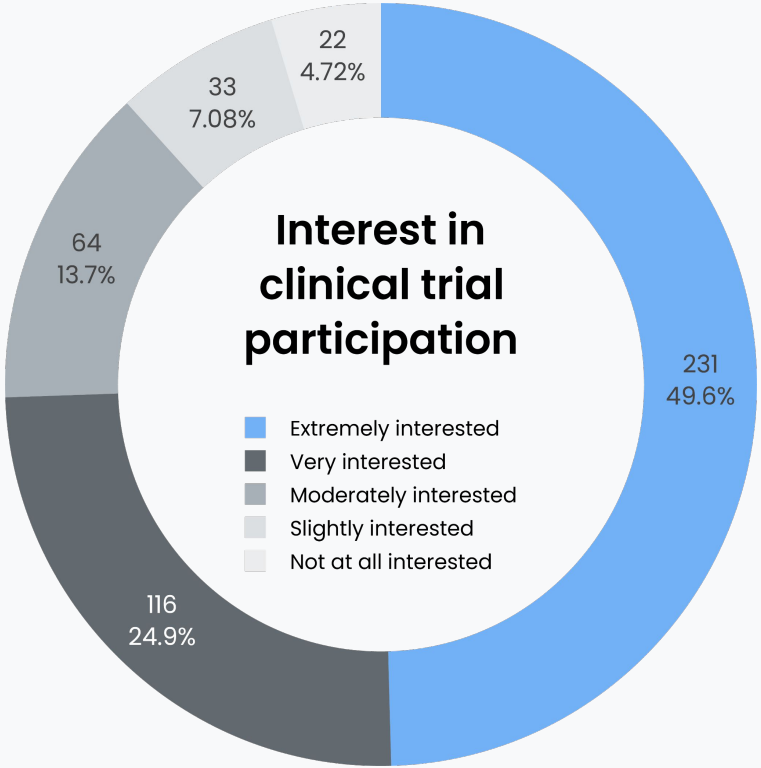
Reasons for Failing Pre-screening	# Patients (% / 112)
Diabetes diagnosis	9 (8%)
History of malignancy	8 (7%)

~ 1 in 2 people over a lifetime

Where:
Identifying trial sites

Most participants are interested in future clinical trials





n = 466

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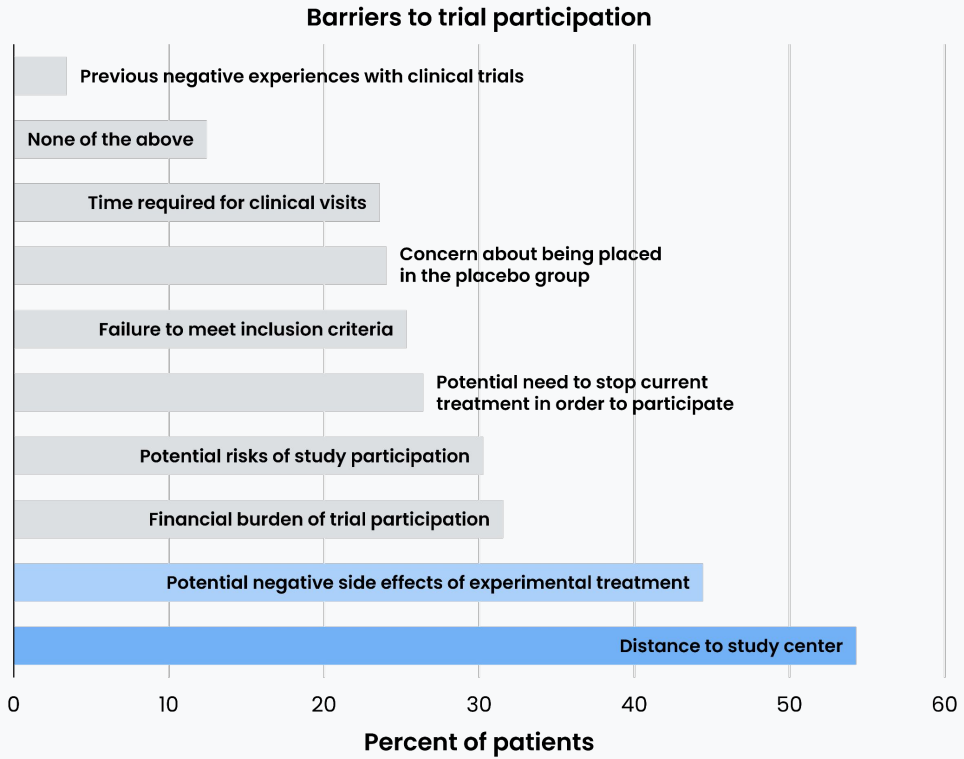
Distance to study sites is participants' most common concern about potential clinical trial enrollment



n = 466

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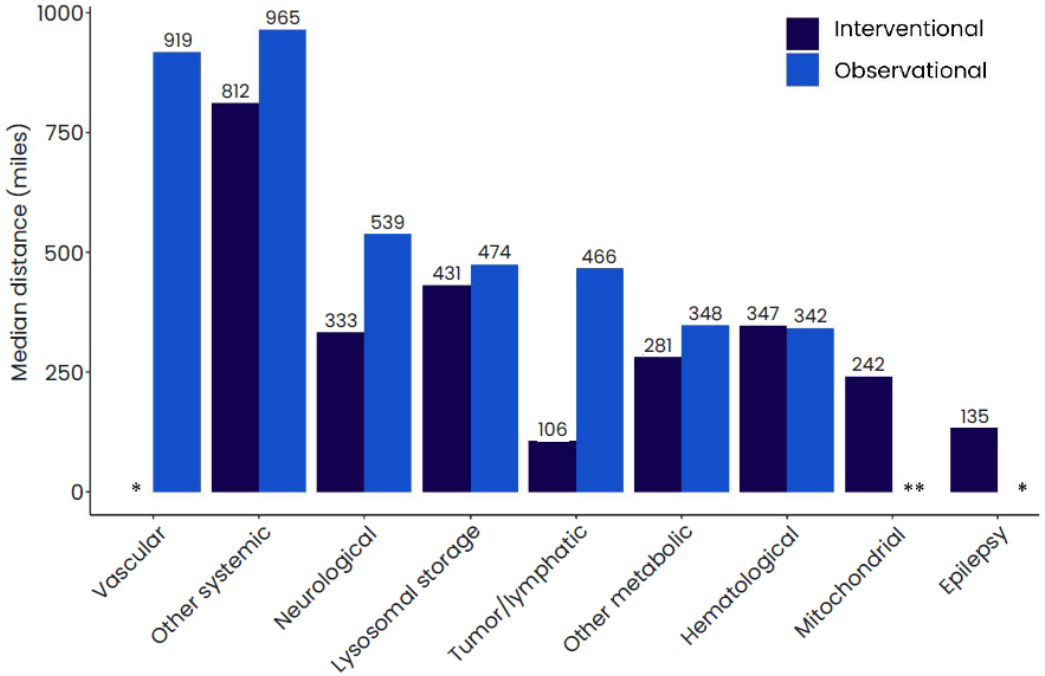
Average distance to nearest trial site illustrates potential travel burden for participants



*distance not available for condition categories with 0 interventional or observational studies
**distance not shown for categories with fewer than 10 patients with conditions covered by available studies

n = 903

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Case study: Recruiting for a pivotal trial in adult-onset autoimmune neuropathy

SPONSOR: **Sponsor F**, a biopharmaceutical company

STAGE: Pivotal trial

CONDITION: **Condition G**, a rare immune-related neurological condition that causes weakness and reduced sensation in the arms and legs

CHALLENGE: Recruiting participants for a large, 8-site pivotal trial

APPROACH: Pre-screen patients using data collected from medical records

RESULTS:

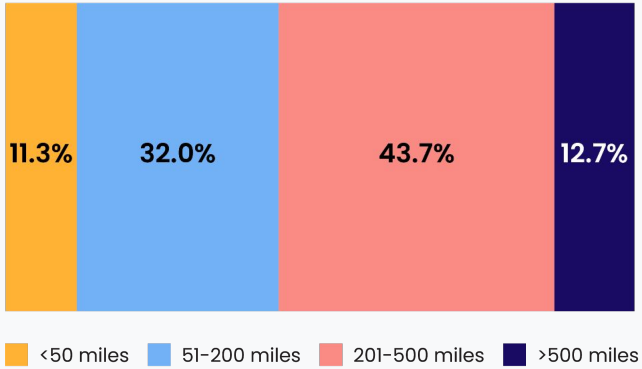
132	**112**	**<5**
Consented **participants**	Participants **pre-screened**	**Patients** connected to site

AllStripes

Sponsors should select trial sites with patient geography in mind

Minimum Distance between Participants and Any Condition G Trial Site

November 2019 71 patients, 6 trials, 15 trial sites



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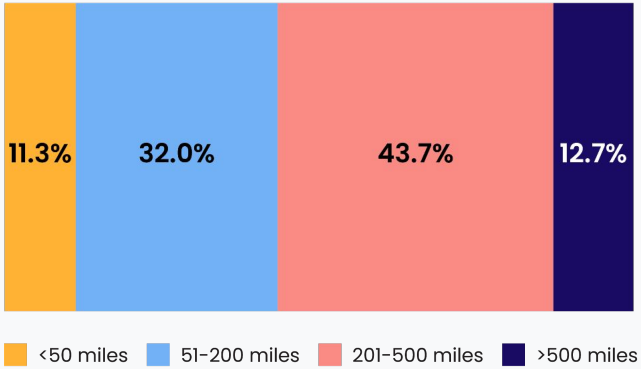


Nov 2019 – Feb 2020

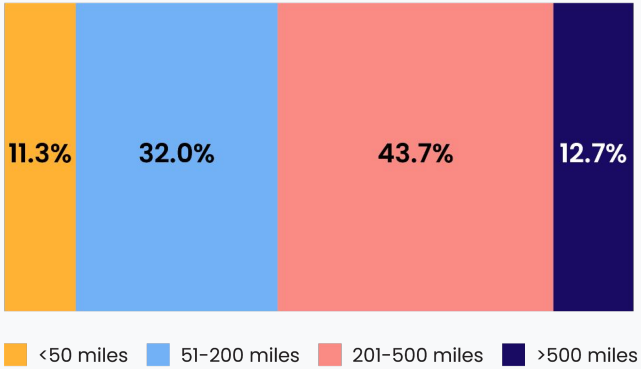
- Targeted recruitment within 200 mi of sites for large trial
- 10 trial sites added

AllStripes

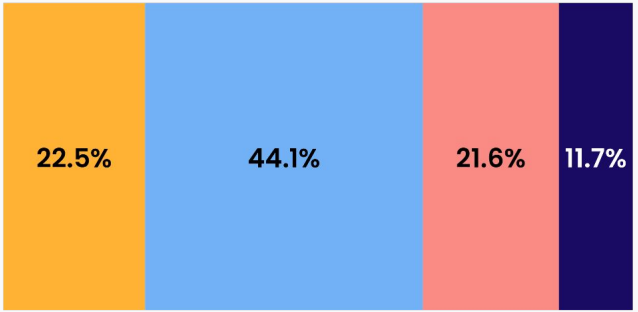
Sponsors should select trial sites with patient geography in mind

Minimum Distance between Participants and Any Condition G Trial Site

November 2019 71 patients, 6 trials, 15 trial sites



February 2020 111 patients, 6 trials, 25 sites



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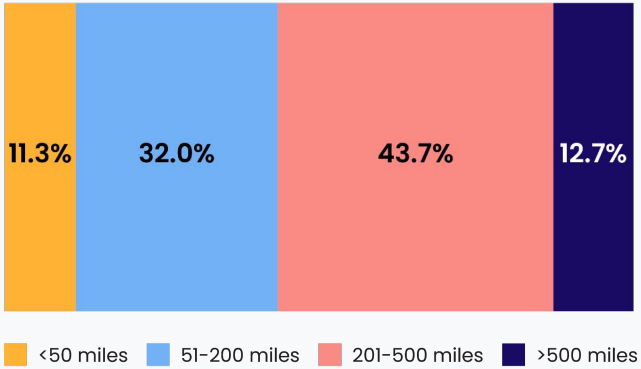

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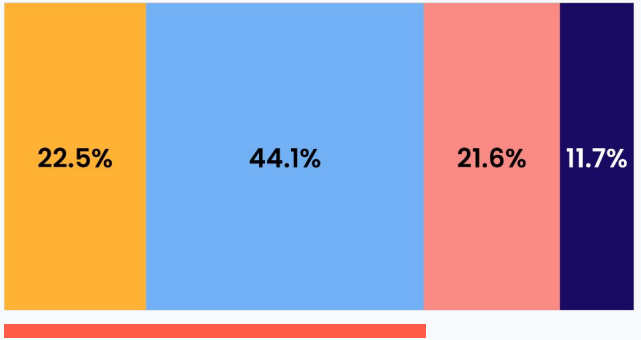

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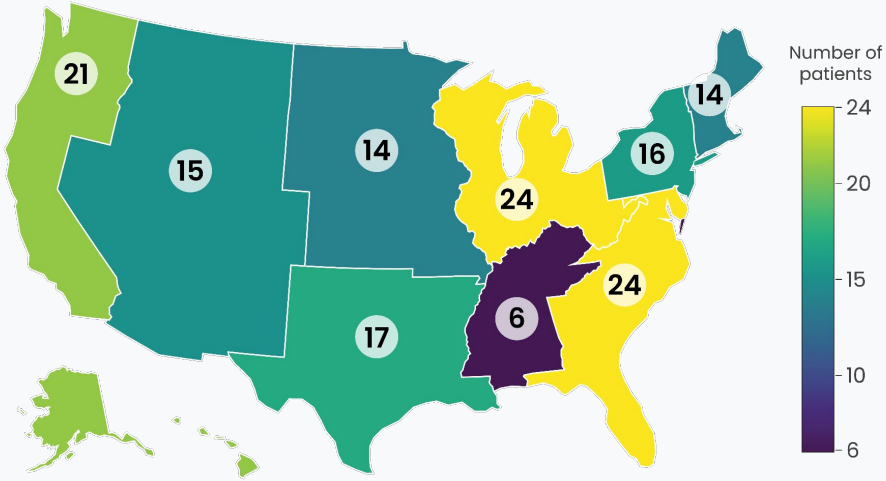
AllStripes

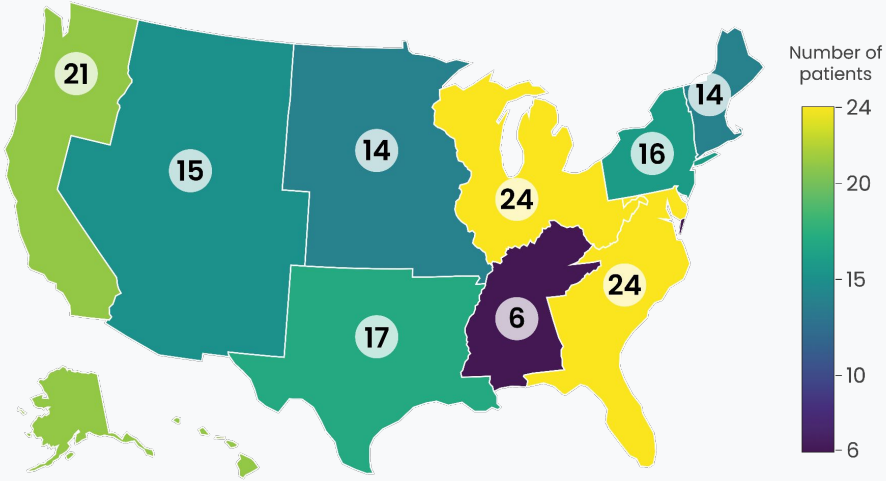
Geographic distribution of US lysosomal storage disorder (LSD) cohort vs. prospective COEs



9 LSDs, 151 participants

AllStripes

Geographic distribution of US lysosomal storage disorder (LSD) cohort vs. prospective COEs



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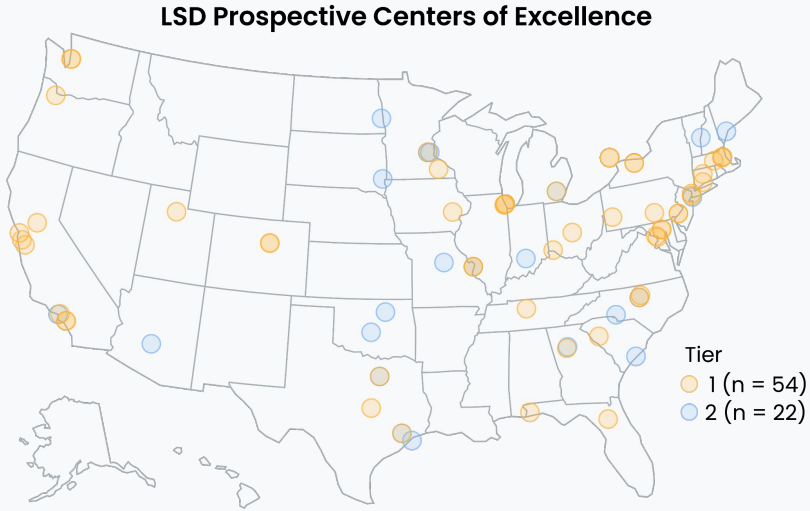

Multidisciplinary care
Peer-reviewed publications
Clinical trial participation
Presence of a metabolic genetics clinic

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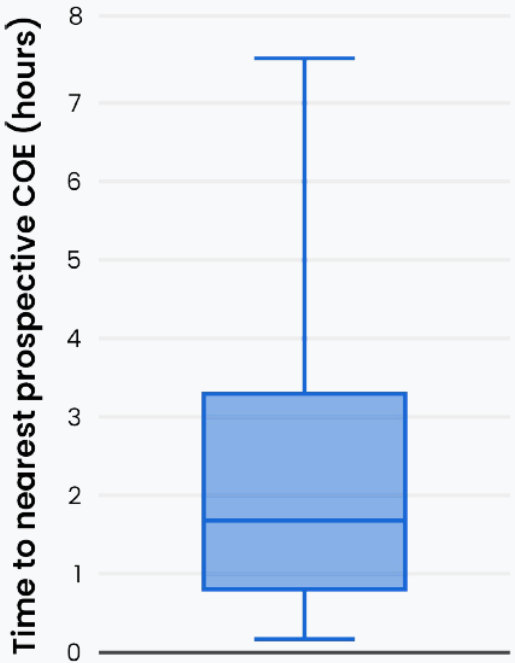
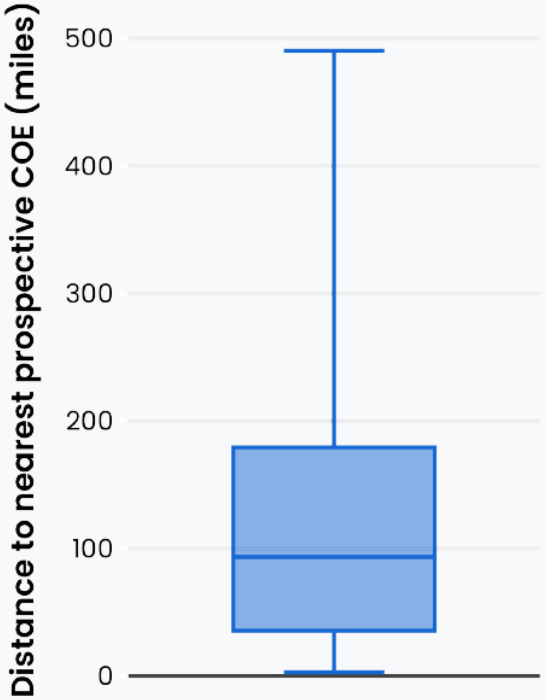
Travel to prospective COEs would entail a substantial burden

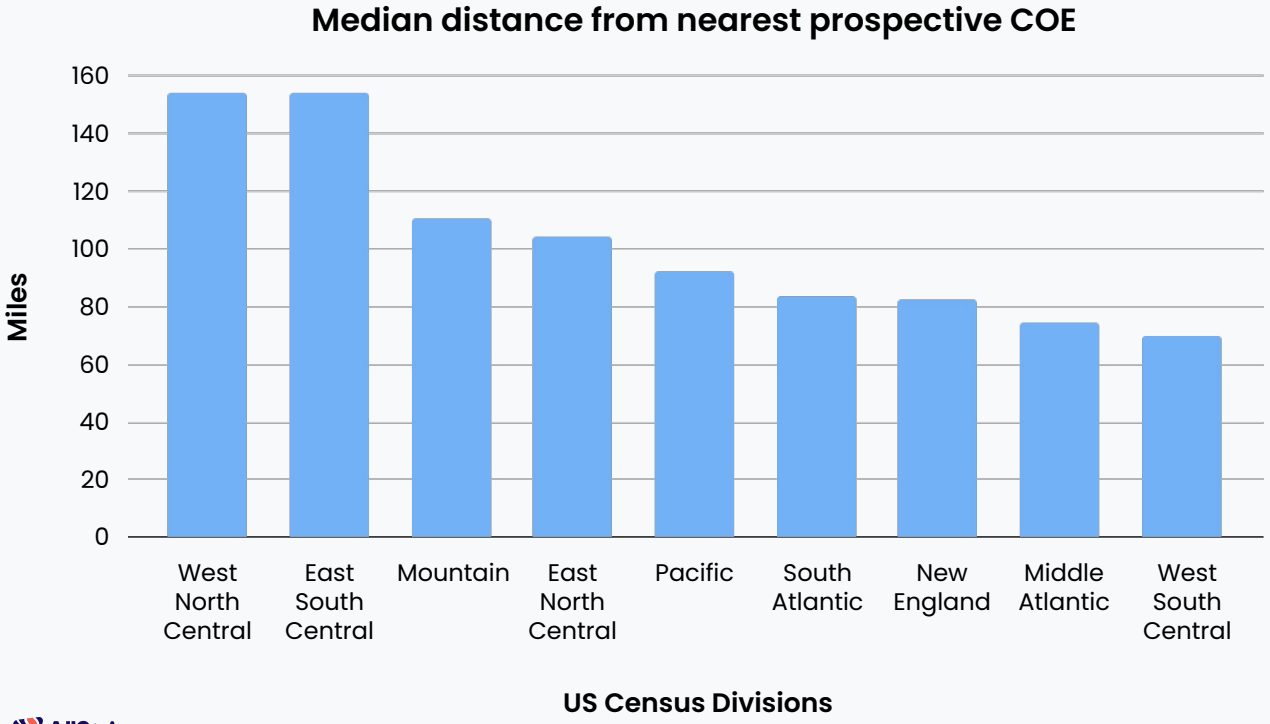


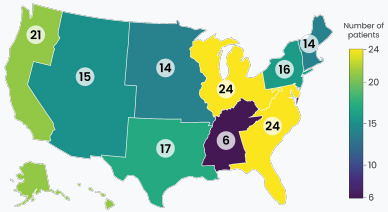
Median = 1.68 hours



Median = 93.4 miles

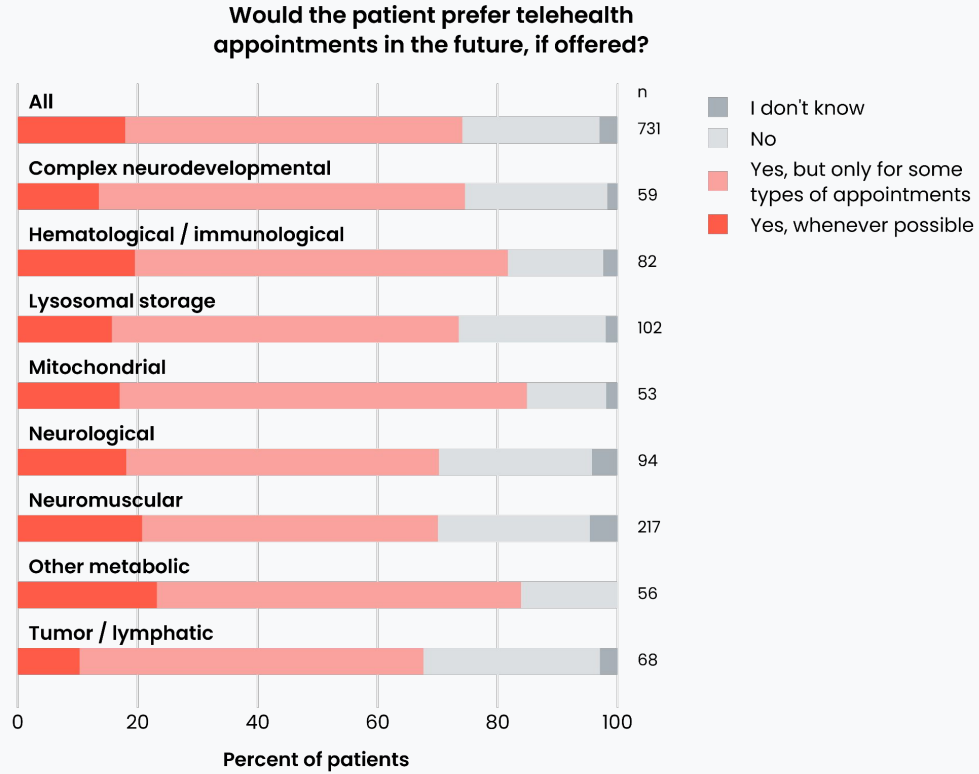
Travel time to prospective LSD COEs varies by region





AllStripes

Participants' preference for telehealth may indicate an openness to future siteless clinical trials

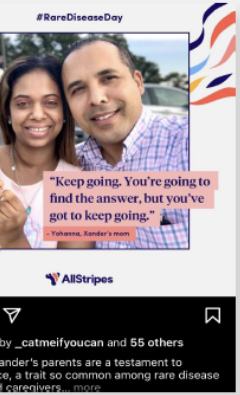


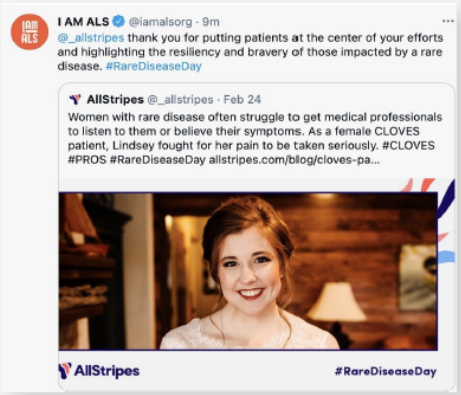
AllStripes

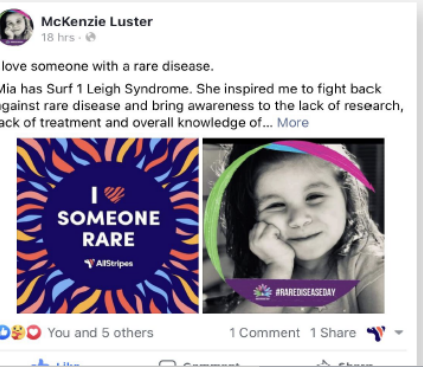
Takeaways

- Real-world data can help address the challenges inherent to orphan drug development
- Integrating the voice of the patient can help answer the big questions in clinical trial planning:
  - Who?
  - What & When?
  - Where?

Power to the patients







Thank you!

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Q&A

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Concluding Remarks

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