Strategies for Use of COAs in Rare Disease Pediatric Populations

14th Annual
Patient-Reported Outcome Consortium Workshop

April 19-20, 2023 • Silver Spring, MD

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Session Objectives

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- Provide a high-level summary of the ongoing activities and recent accomplishments within the Rare Disease COA Consortium
- Explore methodological challenges in research involving rare pediatric populations, especially in children less than 5 years of age

Session Participants

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Moderator

- *Lindsey Murray, PhD, MPH – Executive Director, Rare Disease Clinical Outcome Assessment Consortium, Critical Path Institute*

Presenters and Panelists

- *Lindsey Murray, PhD, MPH – Executive Director, Rare Disease Clinical Outcome Assessment Consortium, Critical Path Institute*
- *Dawn Phillips, PT, MS, PhD – Senior Director of Clinical Outcomes Research, REGENXBIO Inc.*
- *Ebony Dashiell-Aje, PhD – Executive Director & Head, Patient Centered Outcomes Science, BioMarin Pharmaceutical, Inc.*
- *Naomi Knoble, PhD – Associate Director of Rare Disease Measurement Science, Division of Clinical Outcome Assessment, Office of Drug Evaluation Sciences, Office of New Drugs, Center for Drug Evaluation Research, U.S. Food and Drug Administration*
- *Teresa Buracchio, MD – Director (Acting), Office of Neuroscience, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration*
- *Emily Freilich, MD – Deputy Director (Acting), Division of Neurology I, Center for Drug Evaluation and Research, U.S. Food and Drug Administration*
- *Cara O'Neill, MD – Chief Science Officer, Cure Sanfilippo Foundation*

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Introduction to the Rare Disease COA Consortium

Lindsey Murray, PhD, MPH
Executive Director, Rare Disease Clinical Outcome Assessment Consortium
Critical Path Institute

The Rare Disease Burden

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- Over 7,000 rare diseases have been recognized, affecting over 350 million people worldwide
- Most of these conditions are serious and life-altering, with many being life-threatening or fatal
- 80% of rare diseases are caused by a faulty gene
- Approximately 50% impact children
- Current estimates are that < 5% of rare diseases have approved treatments

Challenges to Rare Disease Drug Development

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Disease progression is poorly understood, which makes it difficult to measure clinical benefit

Appropriate clinical outcome assessments (COAs) to measure clinical benefit of treatment are lacking

Within and between patient heterogeneity makes documenting clinical benefit difficult

Few patients with each disease limit statistical power

There is uncertainty about which drugs are likely to work for which patients, due to variations in genotype/phenotype

Medical product developers may be hesitant to take on clinical trial design challenges in rare diseases

Establishment of Rare Disease COA Consortium

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- The FDA's Center for Drug Evaluation and Research (CDER) funded a cooperative agreement to establish the Rare Disease COA Consortium
- **Once established:**
  - *"The final outcome would be the creation of a common **resource** describing publicly available fit-for-purpose clinical outcome assessments as well as accompanying information, such as the populations for use and the strengths and limitations of each tool."*

Launch of the Rare Disease COA Consortium

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- The inaugural Rare Disease COA Consortium Coordinating Committee meeting was held on **Thursday, February 17, 2022.**
- We currently have 20 member firms!
- Coordinating Committee meetings are held monthly.

Important Initial Decisions

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- A domain approach will be used to identify COAs that could be utilized to derive primary endpoints across multiple rare diseases
  - Daily function was selected as the first domain

- Initial efforts will focus on non-oncologic, pediatric populations

Resource Development Efforts To Date

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<u>Selected COA Subdomains of Daily Function (Completed)</u>

- Self-care, gross motor function, fine motor function
  - 46 COAs included
- Communication/language
  - 8 COAs included

Rare Disease COA Resource Development Process

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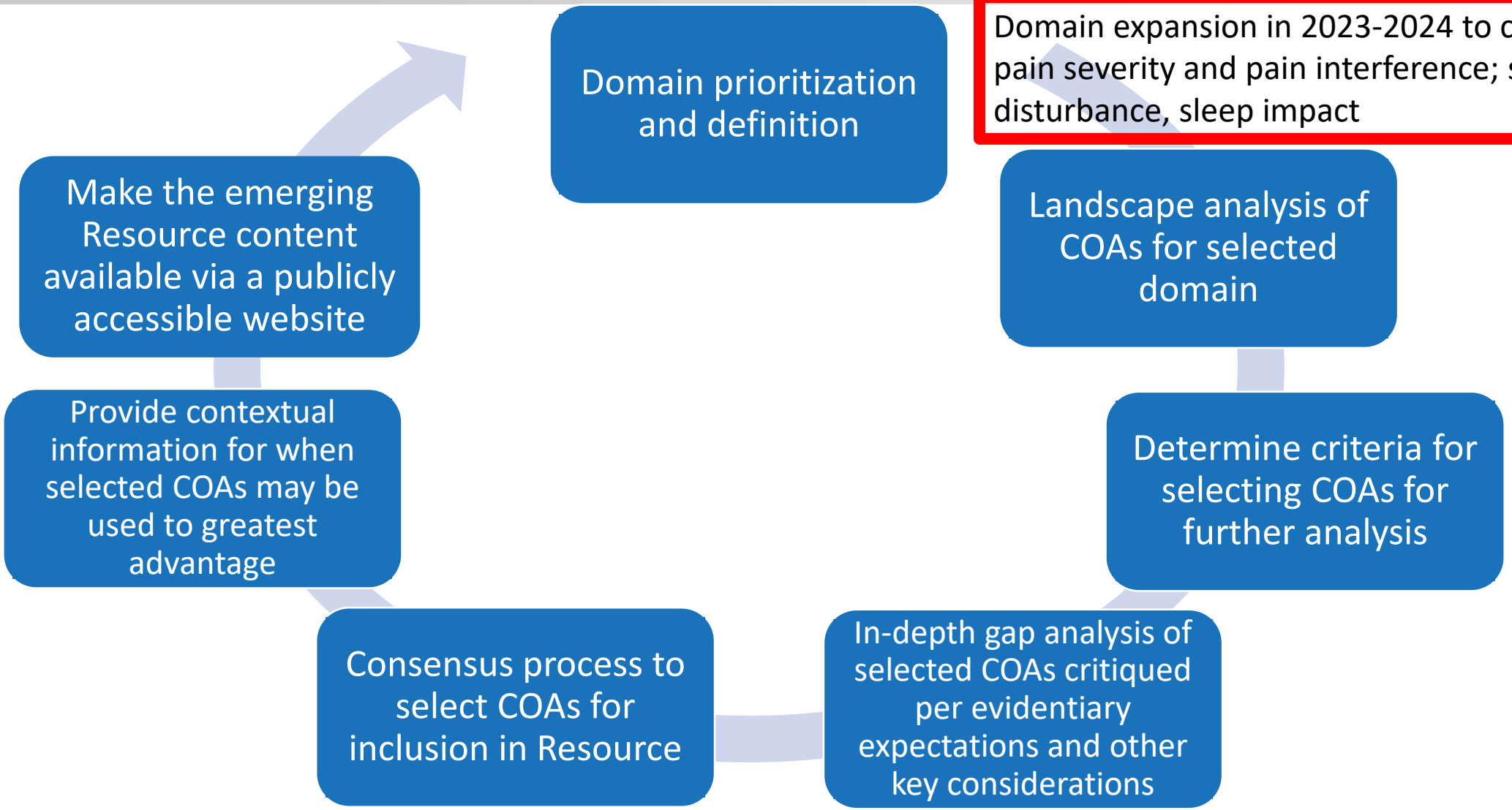

Rare Disease COA Consortium Work Structure

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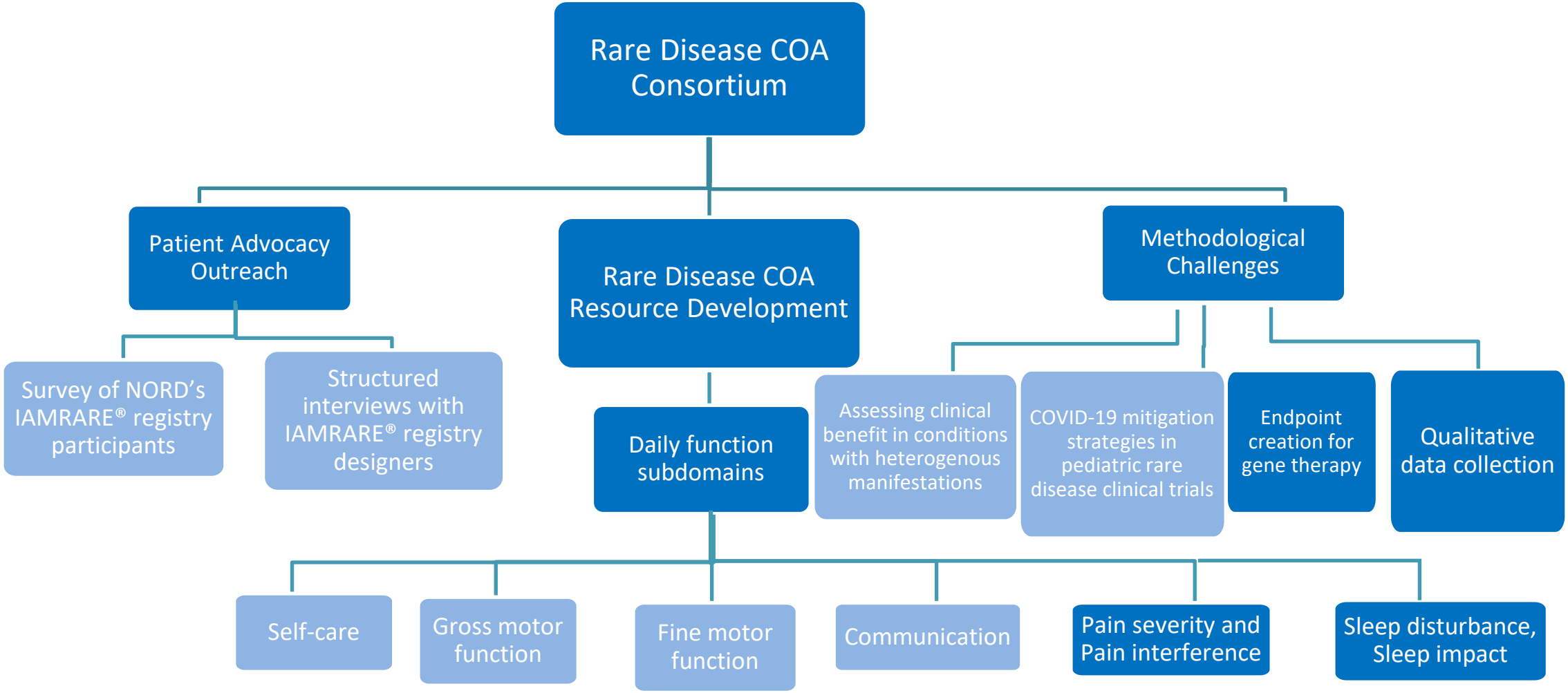
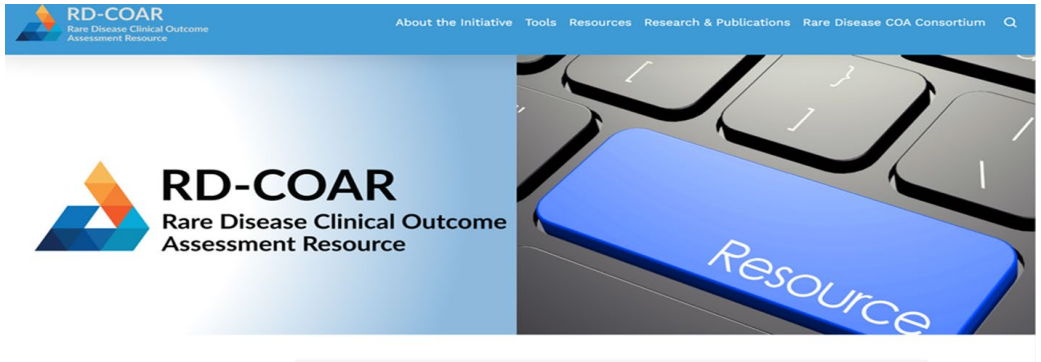


Grayed boxes indicate activity completion. Blue boxes indicate active efforts.

Next steps for the Rare Disease COA Consortium

- Launch of the Rare Disease COA Resource



- Manuscript development
  - Establishment of the Rare Disease COA Consortium

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Journal homepage: www.elsevier.com/locate/jval

Methodology

Approaches to the Assessment of Clinical Benefit of Treatments for Conditions That Have Heterogeneous Symptoms and Impacts: Potential Applications in Rare Disease

Lindsey T. Murray, PhD, Timothy A. Howell, MA, Louis S. Matza, PhD, Sonya Eremenco, MA, Heather R. Adams, PhD, Dylan Trundell, MSc, Stephen Joel Coons, PhD, on behalf of the Rare Disease Subcommittee of the Patient-Reported Outcome Consortium

ABSTRACT

Objectives: Evaluating the clinical benefit of interventions for conditions with heterogeneous symptom and impact presentations is challenging. The same condition can present differently across and within individuals over time. This occurs frequently in rare diseases. The purpose of this review was to identify (1) assessment approaches used in clinical trials to address heterogeneous manifestations that could be relevant in rare disease research and (2) US Food and Drug Administration (FDA)–approved labeling claims that used these approaches.

Methods: A targeted literature review was conducted examining peer-reviewed publications and FDA-approved labeling claims from January 2002 to July 2020, focusing on claims incorporating clinical outcome assessments. Approaches were then assessed for their potential application in rare diseases.

Results: A total of 6 assessment approaches were identified: composite or other multicomponent endpoints, multidomain responder index, most bothersome symptom (MBS), goal attainment scaling, sliding dichotomy, and adequate relief. A total of 59 FDA-approved labeling claims associated with these approaches were identified: composite or other multicomponent endpoints ($n = 49$), MBS ($n = 9$), and adequate relief ($n = 1$). A total of 10 FDA-approved labeling claims, all using multicomponent endpoints, were identified for rare diseases.

Conclusions: Multicomponent, MBS, and adequate relief have been included in FDA-approved labeling claims. Multicomponent endpoints, including composite endpoints, were the most frequent way to address heterogeneous manifestations of both common and rare diseases. MBS may be acceptable to regulators, whereas multidomain responder index is unlikely to be. The goal attainment scaling and adequate relief approaches may have potential utility in rare disease trials, assuming the theoretical and statistical challenges inherent in each approach are managed.

Keywords: clinical outcome assessment, FDA-approved product labeling, heterogeneous, rare disease.

VALUE HEALTH. 2023; 26(4):547–553

Introduction

Heterogeneous manifestations of symptoms and impacts within a condition present a significant challenge for evaluating the clinical benefit of medical interventions. Individuals with the same condition may present with different symptoms and impacts, which may change over time. Consequently, a single outcome or outcome measure may not be relevant to all participants across a clinical trial. This challenge is particularly common in rare diseases.[1]

The Orphan Drug Act of 1983 defines diseases as rare if <200 000 people in the United States are affected, whereas in the European Union, no >5 individuals per 10 000 in the European Union can be affected.[2,3] There are roughly 7000 recognized rare diseases, affecting approximately 300 million persons globally.[4]

Although the Orphan Drug Act in the United States and similar initiatives and incentives for orphan drug development in the European Union have been successful in encouraging the development of medical therapies for rare diseases,[5] <5% of rare diseases have approved treatments.[6]

Clinical benefit is defined as a "positive effect on how a patient feels, functions, or survives."[7] The uncertainty around appropriate clinical trial endpoints (eg, clinical outcome assessments [COAs] or biomarkers as validated surrogates for clinical benefit) is a substantial hurdle for determining clinical benefit in medical product development and reimbursement.[8] Indeed, the nature of many rare diseases makes the traditional recommended approaches to assessing clinical benefit challenging. Heterogeneity of disease manifestations across and within individuals can result in a poorly defined set of core symptoms or functional limitations to assess,

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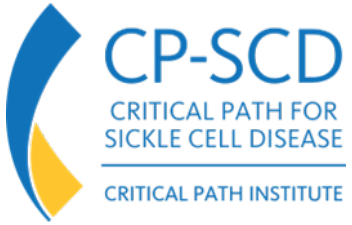
Recently published in April edition of *Value in Health*

C-Path's Active Rare Disease Programs



Pre-Consortium Efforts

Lysosomal Disorders

Alpha-1 antitrypsin

All About Collaboration

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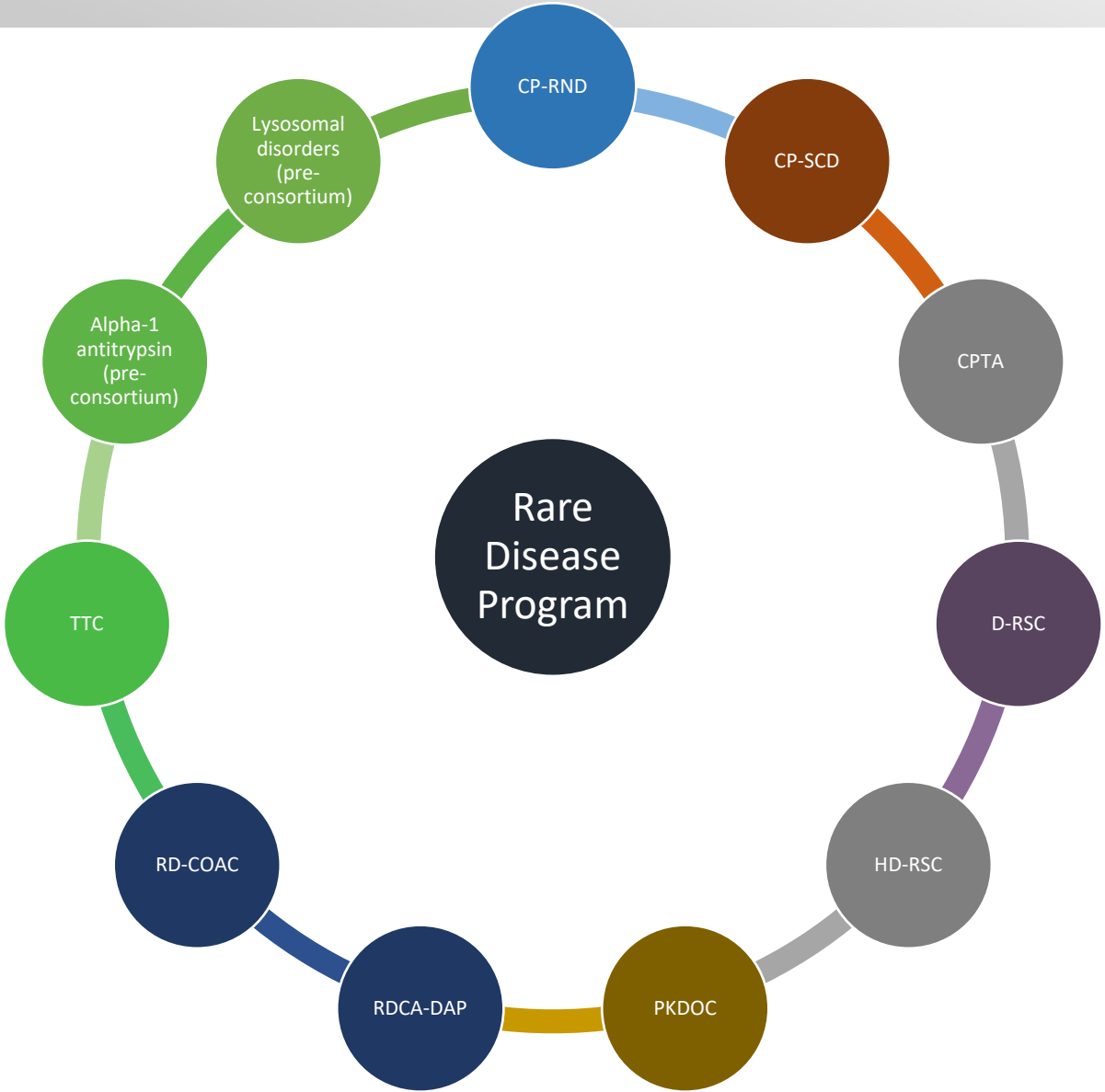

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Challenges in COA Selection and Development of an Endpoint Model in Gene Therapy Rare Disease Studies

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Roadmap for Developing a Fit-For-Purpose, Patient-Focused COA

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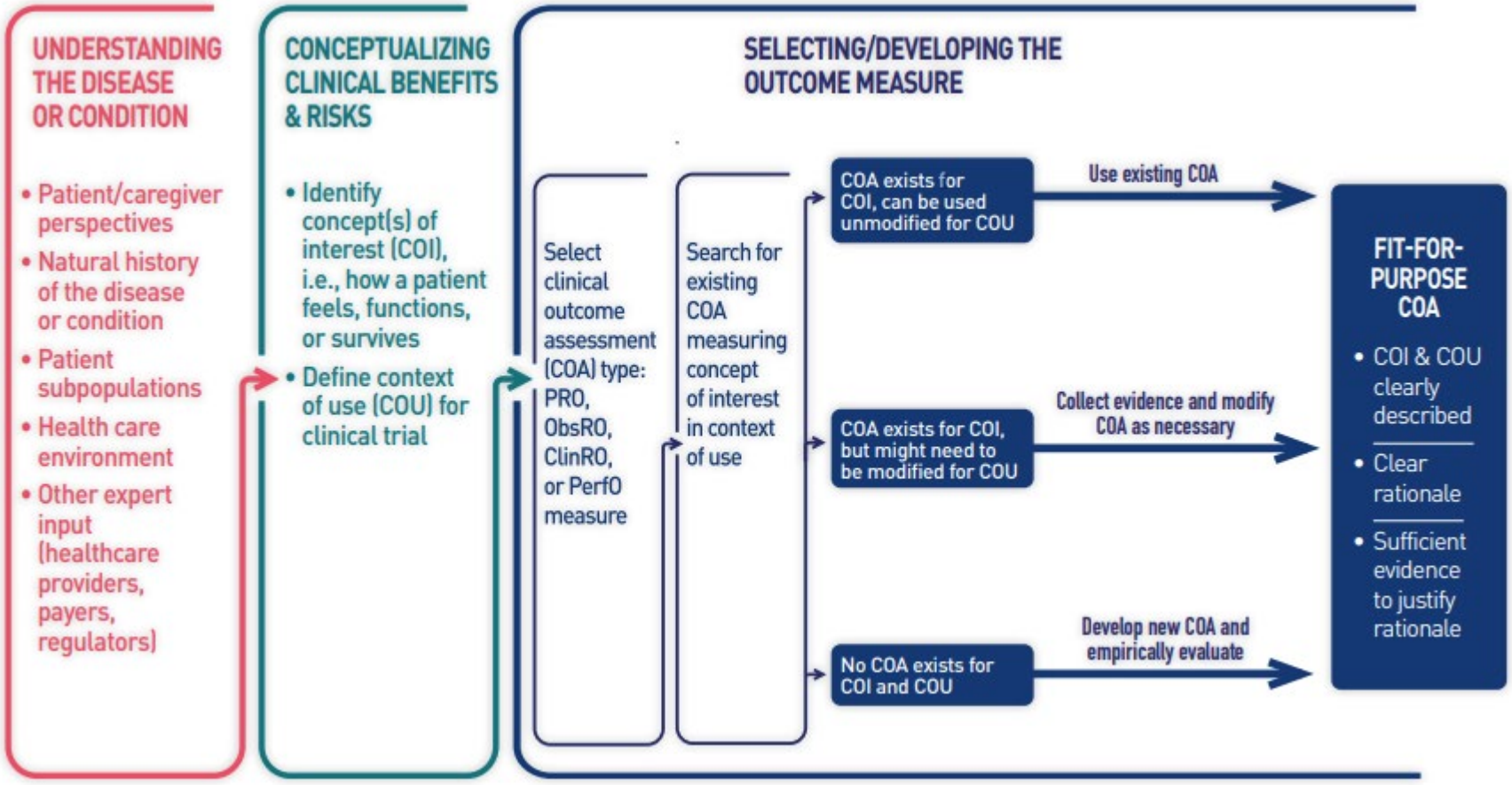
- *What are the unique considerations and challenges for developing an endpoint model and selecting or modifying COAs related to rare disease and gene therapy (GT)?*



- https://www.fda.gov/media/159516/download

Understanding the Disease or Condition

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A. Natural History
B. Patient Sub-population
C. Health Care Environment
D. Patient/Caregiver Perspective

A. Natural History

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- Complete systematic and targeted literature searches
  - Understand disease presentation for patients who are treatment naïve and on standard of care treatment
  - Define the range of impairments and the impact on health-related quality of life and age-appropriate functional skills
- How have the disease concepts been measured?
    - Gain any insights into COA performance (sensitivity, specificity) and to relationships between outcome measures
    - Include clinicaltrials.gov and regulatory application review documents
- What databases are available?
  - Desired COA data may not be included in registry
    - Neurodevelopmental or motor COAs may not be housed in main chart and therefore not extracted in some retrospective natural history studies
  - Explore data sharing resources
- Small numbers of available patients and competitive environment may limit access to patients willing to participate in a prospective natural history study, especially if disease is rapidly progressive and CNS or muscle changes are irreversible.

B. Patient subpopulation

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- Characterize disease by age, phenotype and functional level using literature, natural history data, KOLs, patient and caregiver perspectives
  - Clearly understand how infantile and juvenile/attenuated onset patients differ in disease presentation
  - Understand disease stages and inflection points (delay, plateau and decline)
  - How does COA use differ by age, phenotype, functional level, or stage of disease progression?
    - Availability of normative data comparisons?

Use of Generic Measures with Normative Data

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- **Normative Data**
  - Developmental function varies greatly by age, especially in children <5 years
  - Normative data quantifies function/development compared to mean and standard deviation (SD) of a sample of typically developing children of the same age
  - May be labelled as composite, standard or scale score or percentile rank
  - Works well to define distribution of population, to compare to rate of decline in natural history or as a component in eligibility criteria
  - Can be insensitive to change in low-functioning children because either the children fall below the test floor or the rate of change is slower than in typically developing children in the normative sample, and standard scores either plateau or decline

Standard Scores and Age Equivalent Scores

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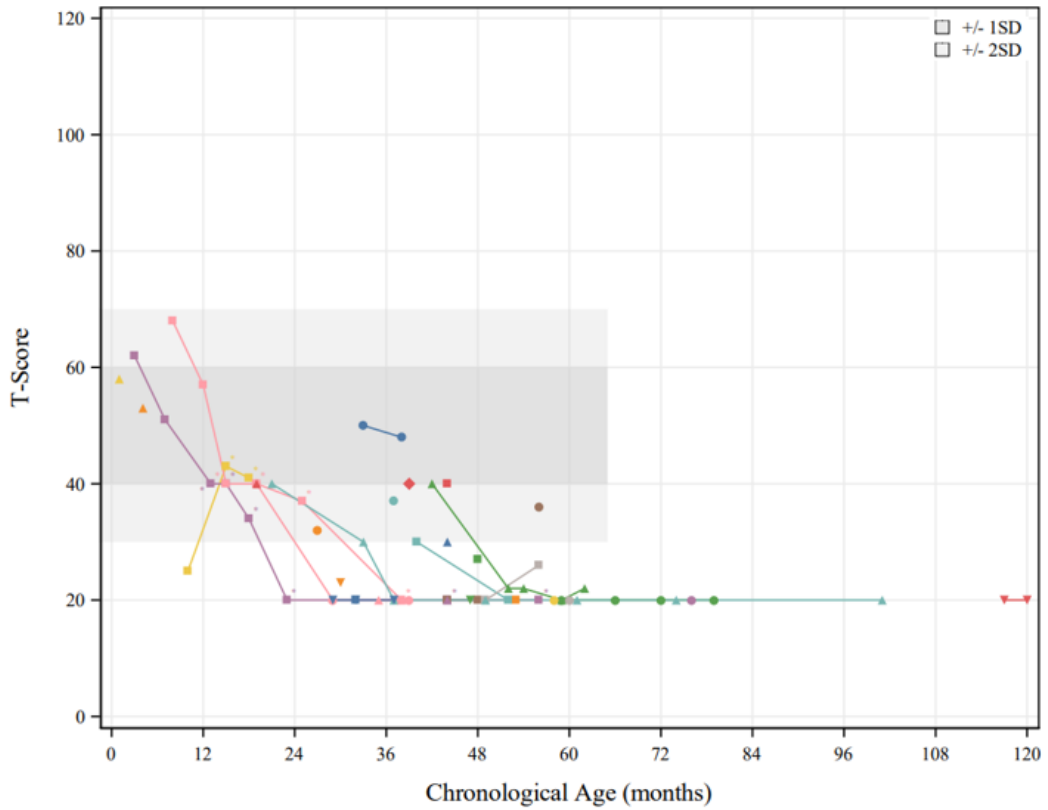
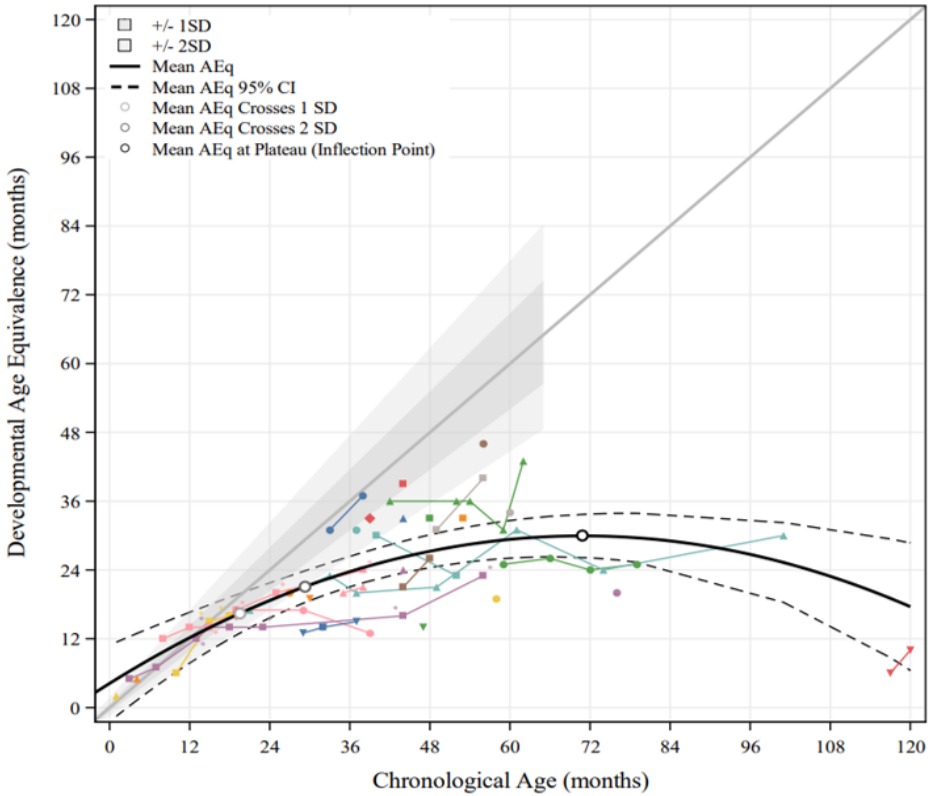
Standard Scores



Age Equivalent Scores



- Rate of skill acquisition in response to a treatment may be slower than in the normative sample and improvement may be not be reflected in normative data
- May have to pair normative data with raw, age equivalents or growth score values to better quantify skill acquisition in response to a treatment intervention

Escolar et al, 2022 SSIEM

C. Health Care Environment

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- **Current standard of care treatment**
  - Understand evolving phenotypes with new treatment options and changes in standard of care
    - May impact recruitment of naïve patients
    - May change concepts of interest for GT studies and limit duplication of endpoint model from original disease research
  - Consider regional differences in health care
- **Consult clinician experts**
  - Advisory panels
  - Delphi consensus procedures

D. Patient/Caregiver perspective

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- Define:
  - Range of signs and symptoms and impact on daily activity from the patient/caregiver perspective
  - Item relevance
  - Meaningful change in response to treatment
  - Health care utilization including therapy services, medical appointments, navigation of insurance reimbursement, and appointment scheduling
- Data collection strategies:
  - Patient Advocacy Groups (PAGs)
  - Patient Focused Drug Development (PFDD) meetings, focus groups and individual interviews, followed by qualitative data analysis
- Partner with your patient advocacy group and integrate the patient/caregiver perspective at all stages of development and study execution

Develop a Patient-Centered Disease Conceptual Model

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- Include:
  - Disease defining concepts developed from literature searches, caregiver or patient interviews, clinician expert interviews, advisory meetings and focus groups
  - Impact on daily activity, community socialization, family
  - Health care utilization patterns and burden of care
- **Use the conceptual model to define evidence gaps**
- Example:
  - Wilgoss et al., *Measuring What Matters to Individuals with Angelman Syndrome and Their Families: Development of a Patient-Centered Disease Concept Model,* Child Psychiatry & Human Development (2021)

Sample Disease Conceptual Model Content for a Pediatric Rare Disease

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Disease Defining Concepts

CNS, Musculoskeletal, GI, Cardiac, Pulmonary

Disease Impacts

Cognition, Language, Fine Motor, Gross Motor, Attentional Capacity, Behavior

Function in Age-Appropriate Daily Activity

Sleep, Feeding, Dressing, Academics, Community Mobility

Caregiver and Family Impact

Health Care Utilization, Work, Financial Burden

Conceptualizing Clinical Benefits and Risks

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A. Concepts of Interest
B. Context of Use

A. Concepts of Interest (COI)

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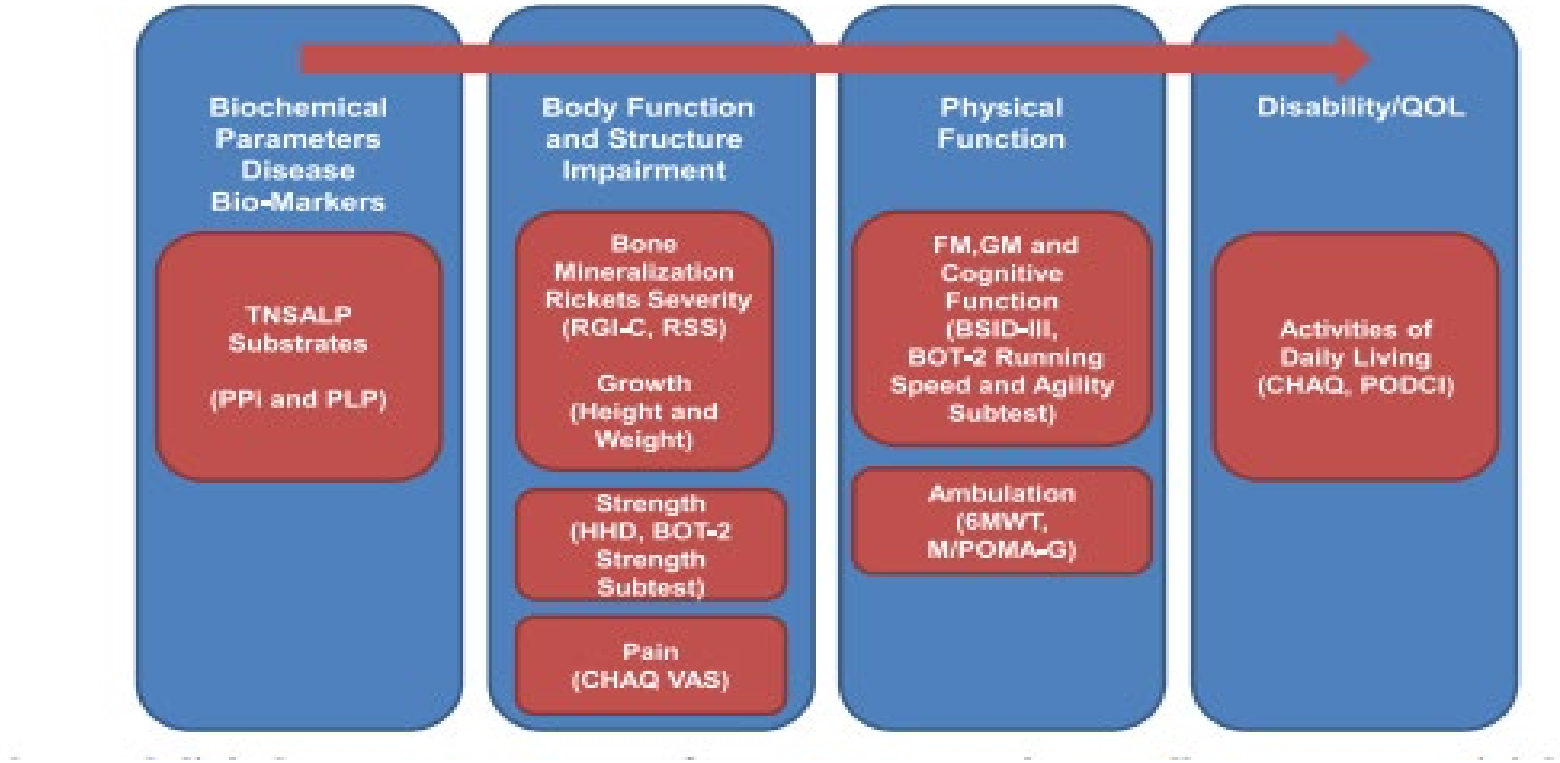
- Use disease conceptual model to define COI
- Outline the COI along a continuum that links mechanism and primary body system of treatment to function
- Create a narrative from pre-clinical to clinical to regulatory to payor strategy



Phillips D, et al. *Clinical Outcome Assessments: Use of Normative Data in a Pediatric Rare Disease, Value and Health*, 2018

A. Gene Therapy (GT) Concept of Interest Examples

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Systemic GT	Systemic GT	CNS GT
Muscle Structure/Composition	Biomarker	CNS Substrate Reduction
Strength	Motor Skill Benchmark	Brain structure/volumetrics
Ambulatory Function	Global Developmental Impact	Neurodevelopmental Function (Cognition, Language)
Community recreation and participation	Independence in age-appropriate daily activities	Adaptive Behavior (Attention, Daily Activity)

B. Context of Use (COU)

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- What COIs are unique to your GT and a well-defined sub-population of the disease?
  - What is the desired range of function that you need to capture within a COA?
  - How do the COA psychometric properties inform your endpoint model? If the measure has a ceiling or floor effect, how do you control for sample with eligibility criteria?
  - Do you need to stratify your recruitment or have an enrichment population?
    - In rare diseases with heterogeneity, functional stratification may be better than age stratification
- A broad inclusion of disease phenotypes allows better characterization for which therapy may be feasible, but adds increased design and analysis complexity
  - Have to consider disease stage to define appropriate responder definition and it may vary by baseline function

B. Context of Use (COU)

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- Early treatment desirable to minimize disease progression but need to compare to natural history
  - Endpoint model needs to reflect an understanding of inflection points where you expect a developmental plateau or decline. Use to define responder definitions
  - If you treat young patients, you may need to follow them for a long period of time to be confident that their developmental trajectory is different than the natural history.
- Impact on label and speed of development pathway
  - Determine if accelerated approval with biomarker or surrogate is possible
    - What is the relationship between the biomarker and functional measures? Is the biomarker reasonably likely to predict a clinically meaningful change?

Selecting or Developing the Outcome Measure

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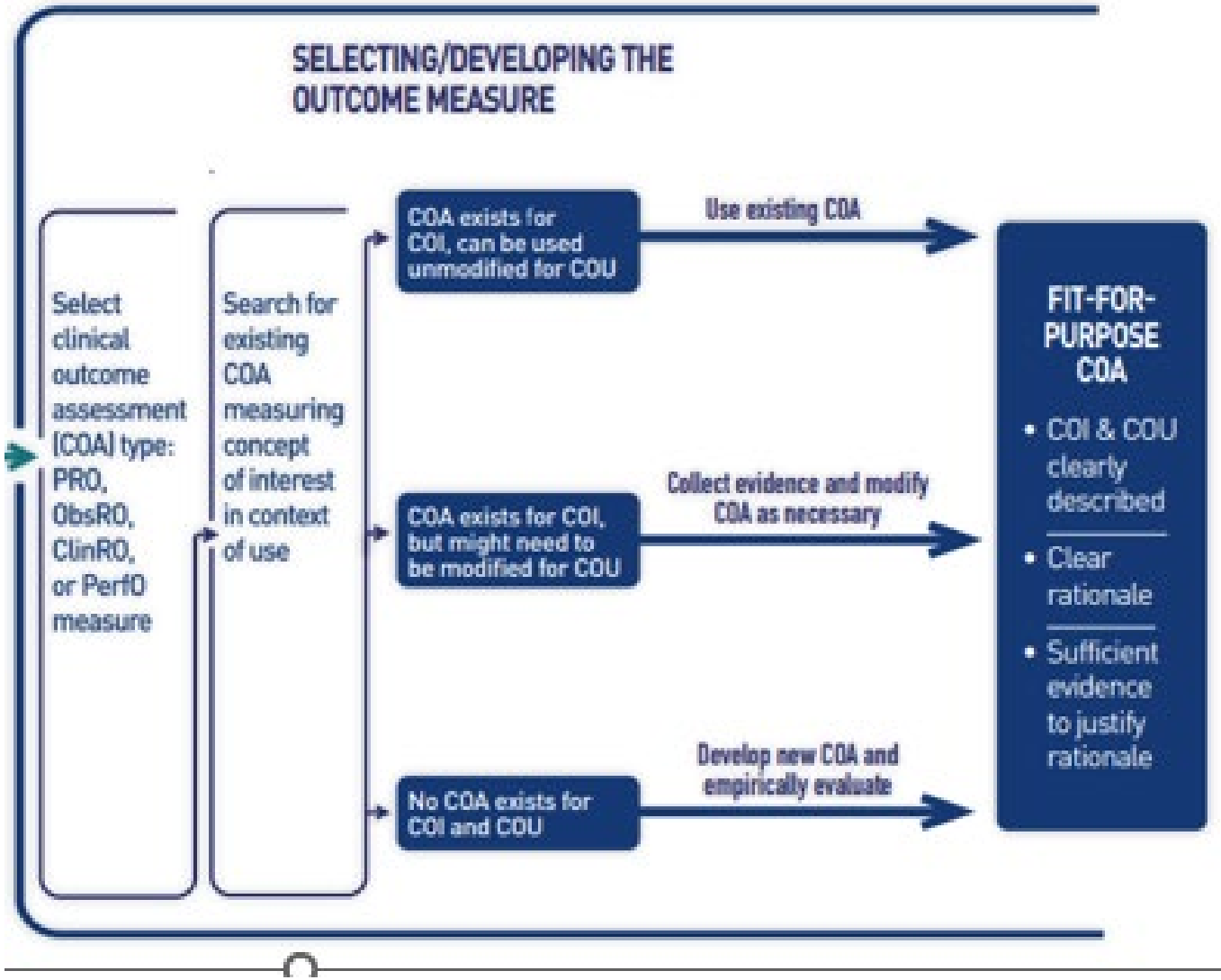

A. COA Type

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- In complex rare diseases with multi-system impairment, you will need a range of COA types.
- One measure may not be adequate to cover the disease spectrum and you may have to transition patients between measures
  - **PRO**: report from the patient or caregiver proxy about health condition without interpretation
  - **ObsRO**: observation from someone other than healthcare professional or patient. Could be caregiver, teacher etc.
  - **ClinRO**: report from trained health care professional
  - **Performance Outcome**: based on task performed according to instructions administered by a trained health care professional

https://www.fda.gov/media/159516/download

B. Search for existing COA that measures COI in COU

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- Mapping: compare disease specific COI to item content on COAs
- Caregiver/KOLs interviews to support item relevance and meaningful change indices
- Considerations for generic versus disease specific COAs
  - Developing a disease specific measure may be desirable for a rare disease, but it takes considerable time and cost and requires many layers of validation.
  - Small sample sizes in rare disease may make it challenging to divide groups by age and function
  - Existing standardized developmental assessments can provide a range of values to characterize disease presentation and to measure treatment benefits
    - Normative data can be used to classify function relative to a normative age reference
- In a one-time GT treatment, continuity in data collection can be challenging for the required long-term follow-up of 5 to 15 years. Consider retention strategies

C. Begin COA Development or Validation of an Existing Measure

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- FDA guidance documents outline measurement properties considered in review related to reliability, validity, ability to detect change and defining clinically meaningful change
  - If you are using an existing measure, you still need to document:
    - Content validity
    - Construct validity
    - Inter and intra-rater reliability
    - Ability to detect change
    - Training plan with strategies for quality review, error detection and remediation training
- Develop detailed user manuals
    - Include standardized order for all COAs; evaluate areas of overlap between multiple performance instruments to reduce redundancy and subject fatigue
    - Consider patient centric models for COA administration
- If you are developing or modifying a measure, additional content is required to support process for item generation
  - Revision history
  - Feedback from clinician experts
  - Item relevance to subpopulation

C. Complete COA Development-Clinically Meaningful Change

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- **Are scores sufficiently sensitive to reflect clinically meaningful changes within patients over time in the concept of interest within the context of use?**
- **Are differences in COA scores interpreted and communicated clearly in terms of the expected impact on the patient's experiences?**
- Challenging with rare diseases that have a small sample size and large heterogeneity.
  - Typical developmental function varies greatly by year in children, limiting your ability to define change based on the same items across your sample
  - Within person change thresholds can be difficult to develop in a heterogenous group of participants
    - Participants may have function at baseline within a normal range for age and their efficacy response is based on stability within that range
    - Stability may also be applicable to patients with a more advanced disease presentation and a chronological age that exceeds the inflection points in natural history related to plateau or loss of skill
- Relationship to claim: Targeted Product Profile
  - Targeted label claims related to all COAs

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Considerations for Use of COAs in Rare Disease Pediatric Populations: Surmounting Measurement Challenges

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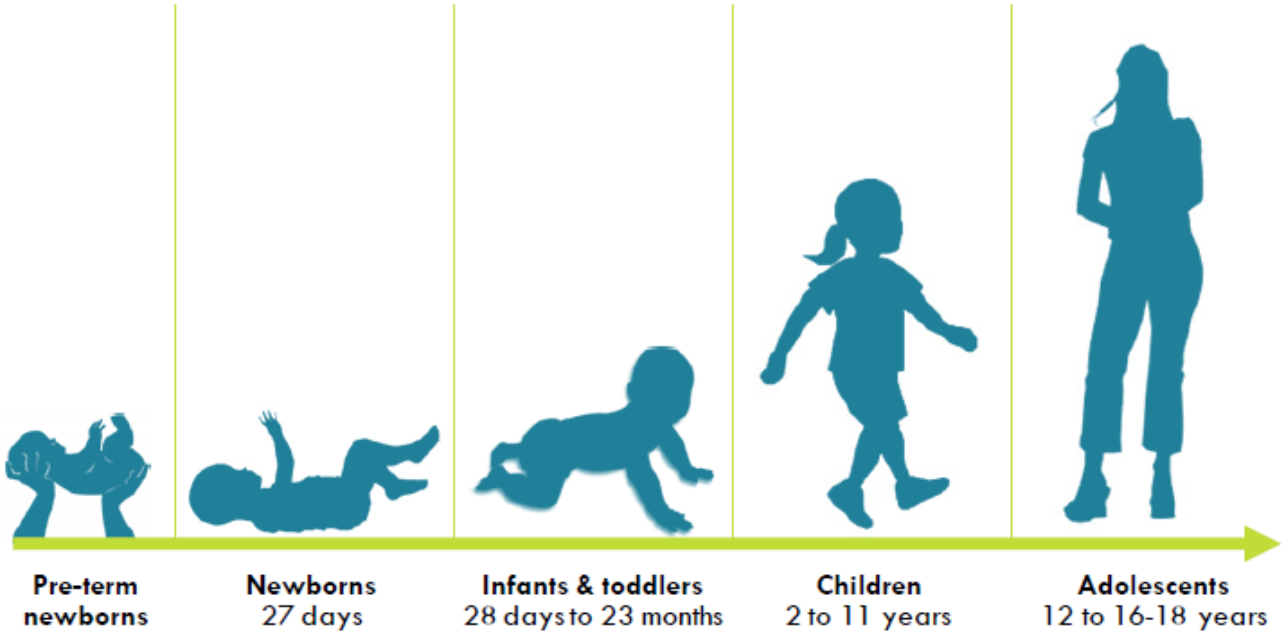
BioMarin Pharmaceutical, Inc.

Pediatric COA Development, Selection, and Implementation



Source: Kaitin KI, ed. Pediatric Oncology Drug Development: Maximizing Efficiency While Complying with FDA & EMA Regulations. Boston: Tufts CSDD R&D Management Report; October 2016;11(2).

Variability in ages, developmental stages, disease progression, and clinical manifestations make COA development, selection, and implementation challenging in rare pediatric disease

Overview of ISPOR Good Research Practices: Pediatric COA Selection and Implementation

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1. Consider Developmental Differences and Determine Age-Based Criteria for COA Administration
2. Establish Content Validity
3. Determine Whether an Observer-Reported Outcome Instrument is Necessary
4. Ensure that the Instrument is Designed and Formatted Appropriately for the Target Age Group
5. Consider Cross-Cultural Issues

[1]Matza LS, Patrick DL, Riley AW, Alexander JJ, Rajmil L, Pleil AM, Bullinger M. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. Value Health. 2013 Jun;16(4):461-79.

[2]Papadopoulos, E. J., Patrick, D. L., Tassinari, M. S., Mulberg, A. E., Epps, C., Pariser, A. R. and Burke, L. B. (2013) Clinical Outcome Assessments for Clinical Trials in Children, in Pediatric Drug Development: Concepts and Applications (eds A. E. Mulberg, D. Murphy, J. Dunne and L. L. Mathis), John Wiley & Sons Ltd., Chichester, UK. doi: 10.1002/9781118312087.ch42

Success Stories:
We Are Not Chasing a Unicorn!

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With prospective planning, scientific rigor, and regulatory collaboration, we can:

- **Use normative data** to help interpret clinical benefit within clinical trials
- **Adapt existing tools** to successfully evaluate meaningful changes over time
- **Use multiple fit-for-purpose COAs** to generate a totality of evidence
- **Leverage embedded interviews** to interpret clinically meaningful score improvements

Case Study: Use of Normative Data to Evaluate Clinical Benefit in Pediatric Trials

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VALUE IN HEALTH 21 (2018) 508–514

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Clinical Outcome Assessments: Use of Normative Data in a Pediatric Rare Disease

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Source: Phillips D and Leiro B. Value in Health. 2018. May;21(5):508-514. DOI: 10.1016/j.jval.2018.01.015.

Heterogeneity in both function and developmental/age ranges may require the use of COAs that can be interpreted against norm values

Case Study: Use of Normative Data to Evaluate Clinical Benefit in Pediatric Trials

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- **Key Learnings[1]:**
  - **Normative data can help define and interpret** functioning in a heterogeneous sample
  - **Multiple endpoints** may be required to adequately capture the impact of treatment on multiple systems
  - Variability in function by age requires that **multiple COA age versions** be developed and implemented
  - It can be difficult to distinguish between treatment effects and change due to developmental maturation – **creative analytic approaches should be explored** to control for variability

[1]Phillips D and Leiro B. Value in Health. 2018. May;21(5):508-514. DOI: 10.1016/j.jval.2018.01.015.

Case Study: COA Adaptation and Natural History Comparisons in CLN2

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Original Article

An Adapted Clinical Measurement Tool for the Key Symptoms of CLN2 Disease

Journal of Inborn Errors of Metabolism & Screening
2018, Volume 6: 1–7

DOI: 10.1177/2326409818788382
journals.sagepub.com/home/iem
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Kathleen W. Wyrwich, PhD[1], Angela Schulz, MD[2], Miriam Nickel, MD[2], Peter Slasor, ScD[3], Temitayo Ajayi, MD[3], David R. Jacoby, MD, PhD[3], and Alfried Kohlschütter, MD[2]

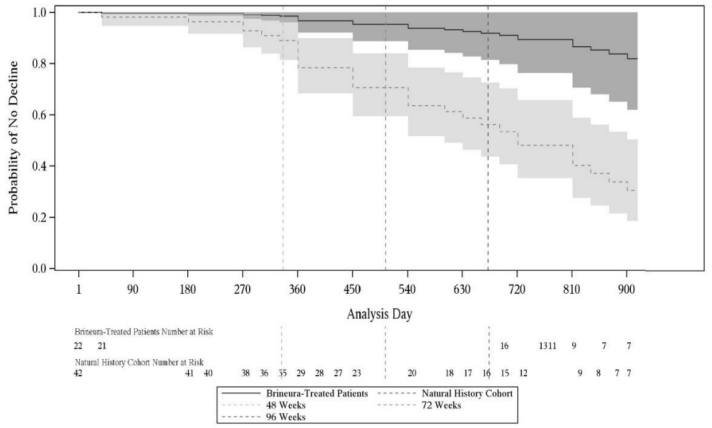
Abstract

Neuronal ceroid lipofuscinosis type-2 (CLN2) disease is a rare, autosomal recessive, pediatric-onset, neurodegenerative lysosomal storage disease caused by mutations in the *TPP1* gene. Cerliponase alfa (Brineura®), a recombinant form of human tripeptidyl peptidase-1, was recently developed as a treatment for CLN2 disease. In clinical trials, the primary end point to evaluate treatment effect was the aggregate score for the motor and language (ML) domains of the CLN2 Clinical Rating Scale, an adaptation of the Hamburg scale's component items that include anchor point definitions to allow consistent ratings in multinational, multisite, clinical efficacy studies. Psychometric analyses demonstrated that the ML score of the CLN2 Clinical Rating Scale and individual item scores are well defined and possess adequate measurement properties (reliability, validity, and responsiveness) to demonstrate a clinical benefit over time. Additionally, analyses comparing the CLN2 Clinical Rating Scale ML ratings to the Hamburg scale's ML ratings demonstrated adequate similarity.

Source: Wyrwich KW, Shulz A, Nickel M, Slasor P, Ajayi T, Jacoby DR, Kohlshutter A. Journal of Inborn Errors of Metabolism & Screening. Volume 6:1-7 2018 DOI: http://orcid.org/0000-0002-1870-1142.

Brineura®
(cerliponase alfa)

Figure 7. Estimated Time to Unreversed (Sustained) 2-Category Decline or Unreversed Score of Zero in Motor Domain for Symptomatic Pediatric Patients in the Brineura Single-Arm Clinical Study with Extension and for Patients in a Natural History Cohort (Based on the Cox Proportional Hazards Model Adjusting for Covariates)



Shading represents 95% confidence intervals.
Follow-up for the natural history cohort begins at 36 months of age or greater and at the first time a Motor plus Language CLN2 score less than 6 was recorded.
The Brineura-treated population is the full population (N=24) minus two patients with baseline Motor plus Language CLN2 score = 6.
Covariates: screening age, screening Motor score, genotype: 0 key mutations (yes/no). "Screening age" was defined in the natural history cohort as the age at the first time a Motor plus Language CLN2 score less than 6 was recorded, and no earlier than 36 months of age. The "screening Motor score" of the natural history cohort was defined as the Motor score at the screening age.
Decline is defined as an unreversed (sustained) 2-category decline or unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale.

Adaptation of existing instruments and comparisons to natural history cohorts may be useful for evaluating treatment effects in degenerative conditions

Case Study: Additional COA Adaptation in CLN2 to Increase Measurement Precision

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The Expanded Neuronal Ceroid Lipofuscinosis 2 (CLN2) Clinical Rating Scale for Motor and Language (CLN2 CRS-MX and LX): Development and Inter- Rater Reliability

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[2]Great Ormond Street National Health System Foundation Trust, London, Great Britain
[3]University Medical Center Hamburg-Eppendorf, Children's Hospital, Hamburg, Germany

Background

- CLN2 Batten disease is a rare, neurodegenerative lysosomal storage disorder.
- The rapid progression of this disease was originally quantified using the Hamburg CLN2 scale.[1]
- The Hamburg motor and language domains were subsequently adapted into the CLN2 Clinical Rating Scale Motor and Language (CLN2 CRS-M and L) and used to quantify loss of function in the natural disease course compared to the treatment response on cerliponase alfa, intraventricular enzyme replacement therapy (ERT).[2,3]
- The evolving phenotype for children on ERT with slower disease progression necessitates use of a more sensitive assessment to capture changes in motor and language function.

Methods

- An expanded CLN2 CRS for motor and language (CLN2 CRS-MX and LX) was developed to provide more granularity, improved item relevance and increased response options.
- Derivation of items was based on identification of key CLN2 disease concepts of interest from a targeted literature review, clinician expert interviews, two virtual caregiver focus groups and ongoing biweekly meetings for one year with 6 CLN2 clinician experts. Clinician experts were from Germany, the United Kingdom and the United States.
- The clinician interviews and caregiver focus groups discussed the key symptoms and impacts of CLN2 specifically related to motor and language function, differences in disease progression in ERT-treated and ERT-naïve patients and how to improve the granularity of motor and language function assessment in the CLN2 CRS to make it more useful for assessing treatment benefit in a clinical trial.
- The iterative developmental process included pilot application and numerous item revisions. Tracking matrices were used to document all scale iterations and the rationale for changes. Only the final versions are presented in this poster.
- A detailed administrative, scoring and training manual was developed for both scales. The CLN2 CRS-LX manual contains specific guidance on use of prompts to determine expressive language and non-verbal communication competencies.
- The level of agreement (inter-rater reliability) between the clinicians was calculated for the CLN2 CRS-MX and the CLN2 CRS-LX.
  - Clinician administration of the CLN2 CRS-MX and LX was performed with standardized administrative and scoring guidelines.
  - Assessments were administered and scored by a primary clinician and also independently scored by an observer clinician.
  - Each assessment was videotaped and scored independently by two additional clinicians.
  - Inter-rater reliability was calculated as percent agreement across 4 raters.

Source: Phillips D, Cho Y, Nevoret M-L, Wood M, Nickel M, Schwering C, Westermann L, Schulz A. (2022, February) *Natural History of Neurodevelopment in Neuronopathic Mucopolysaccharidosis Type II (MPS II): Mullen Scales of Early Learning (MSEL) Cognitive, Motor and Language Developmental Trajectories (Poster #238)*. Presented at the 18th Annual WorldSymposium, San Diego, CA.

Review of the most current regulatory recommendations is advised to refine COA measurement precision and increase future regulatory utility

Case Study: COA Adaptation and Natural History Comparisons in CLN2

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- **Key Learnings:**
  - **Consider multiple COAs early** in the development process to design comprehensive prospective, observational, and natural history studies
  - For clinician ratings, it is important to implement **prospective, standardized data collection and analysis** procedures including:
    - Comprehensive rating guidelines and training across studies
    - Assessing inter-rater reliability to evaluate level of concordance in ratings over time
  - **COA adaptation** may be required to make legacy tools fit-for-purpose
    - Regulatory advice should be leveraged to guide tool refinements and increase regulatory utility and data interpretation

Case Study: Caregiver Ratings to Assess Clinical Benefit

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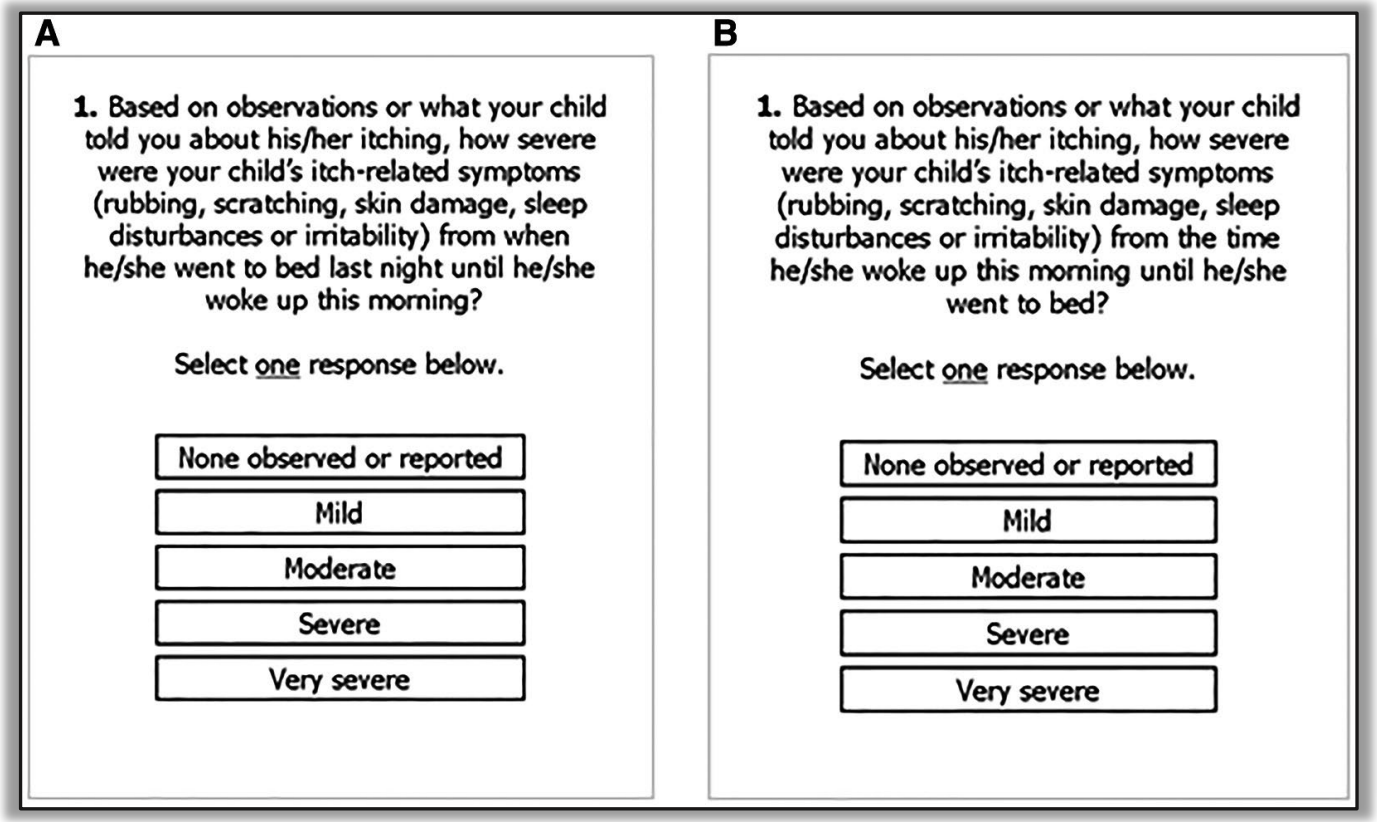

A

1. Based on observations or what your child told you about his/her itching, how severe were your child's itch-related symptoms (rubbing, scratching, skin damage, sleep disturbances or irritability) from when he/she went to bed last night until he/she woke up this morning?

Select one response below.

- None observed or reported
- Mild
- Moderate
- Severe
- Very severe

B

1. Based on observations or what your child told you about his/her itching, how severe were your child's itch-related symptoms (rubbing, scratching, skin damage, sleep disturbances or irritability) from the time he/she woke up this morning until he/she went to bed?

Select one response below.

- None observed or reported
- Mild
- Moderate
- Severe
- Very severe

Source: Kamath et al. 2020. Unraveling the Relationship Between Itching, Scratch Scales, and Biomarkers in Children With Alagille Syndrome **Hepatology Communications, Volume: 4, Issue: 7, Pages: 1012-1018, First published: 26 May 2020, DOI: (10.1002/hep4.1522)**

Livmarli™ (maralixibat) oral solution

The average of the worst daily ItchRO(Obs) pruritus scores was computed for each week. For randomized patients, the mean (SD) at baseline (pre-treatment) was 3.1 (0.5) and the mean (SD) at Week 18 (pre-randomized withdrawal period) was 1.4 (0.9). On average, patients administered LIVMARLI for 22 weeks maintained pruritus reduction whereas those in the placebo group who were withdrawn from LIVMARLI after Week 18 returned to baseline pruritus scores by Week 22. Results from the placebo-controlled period are presented in Table 3. After re-entering the open-label treatment phase, both randomized treatment groups had similar mean pruritus scores by Week 28, the first week placebo patients received the full dosage of LIVMARLI after withdrawal. These observer-rated pruritus results are supported by similar results on patient-rated pruritus in patients 5 years of age and older who were able to self-report their itching severity.

Table 3: Weekly Average of Worst Daily ItchRO(Obs) Pruritus Severity Scores in Trial 1

	Maralixibat (N=13)	Placebo (N=16)	Mean Difference
Week 22, Mean (95% CI)	1.6 (1.1, 2.1)	3.0 (2.6, 3.5)	
Change from Week 18 to Week 22, Mean (95% CI)	0.2 (-0.3, 0.7)	1.6 (1.2, 2.1)	-1.4 (-2.1, -0.8)

Results based on an analysis of covariance model with treatment group and Week 18 average worst daily pruritus score as covariates

Caregiver input is critical in defining the concepts of observable signs, within reliable observation windows, and for designing observer-reported outcome (ObsRO) measures

Case Study: Caregiver Ratings to Assess Clinical Benefit

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- **Key Learnings:**
  - **Proxy-report is discouraged** but where observable signs can be reliably assessed, caregiver-report can be useful to help interpret clinical benefit in symptomatic disease, across age ranges
  - **Patient-reported outcomes are still helpful** to assess and interpret symptomatic changes in older children and to interpret caregiver ratings
  - **Robust evidence and strong collaboration** across multiple stakeholders can lead to precedent setting approvals and COA labeling beyond PROs

Case Study: Exit Interviews to Aid Score Interpretation in Down Syndrome

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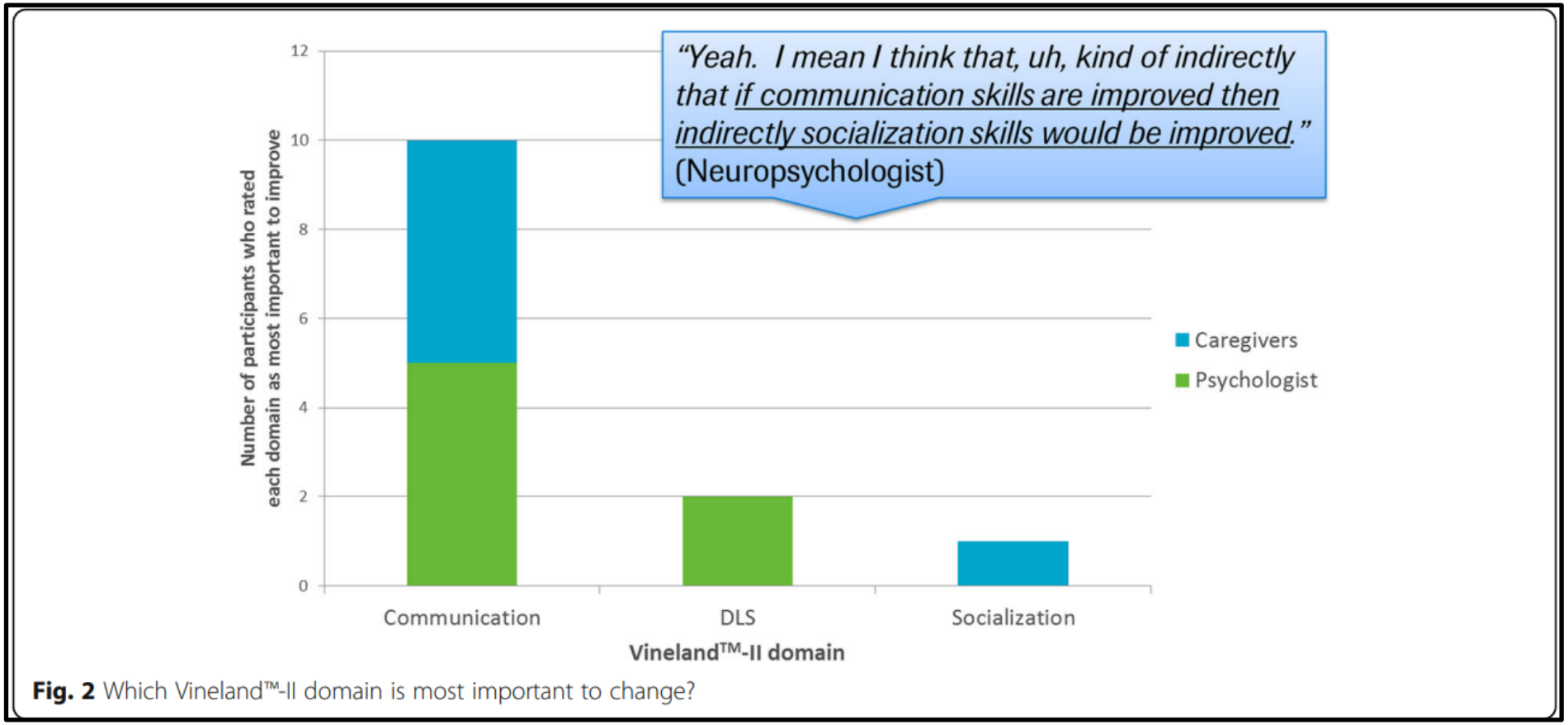

Fig. 2 Which Vineland™-II domain is most important to change?

Source: Willgoss T, Staunton H, Abetz-Webb L, Arbuckle R, Rofail, D. (2017). Qualitative exit interviews with psychologists and parents/caregivers to help inform clinically meaningful change thresholds on an observer-reported

Exit Interviews may be critical for establishing the levels of change that are clinically meaningful in rare disease populations

Case Study: Exit Interviews to Aid Score Interpretation in Down Syndrome

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- **Key Learnings[1]:**
  - **Qualitative insights** generated from caregivers, clinicians, and patients are valuable to understand the most important concepts that can improve with treatment
  - **Interview guides should use anchoring language** (e.g., vignettes, qualitative descriptors) to help respondents understand complex concepts and interpret the potential impact of conceptual changes over time

[1] Staunton H, Willgoss T, Nelson L, Burbridge C, Sully K, Rofail D, Arbuckle R. (2019). An overview of using qualitative techniques to explore and define estimates of clinically important change on clinical outcome assessments. Journal of Patient-Reported Outcomes; 3:16. https://doi.org/10.1186/s41687-019-0100-y.

Conclusions

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- Rare disease pediatric populations are often heterogenous, with the disease lifecycle spanning multiple developmental periods
- COAs used to assess clinical benefit must be deemed fit-for-purpose across all age ranges and disease severity levels
- Given variability in developmental stages and ages, more than one COA may be required to capture changes in meaningful aspects of health during a trial
- It is critical to select tools that are both sensitive and specific to ensure success
- Additional evidence (e.g., through embedded interviews) may be required to evaluate clinically meaningful change in COA scores given small sample sizes

Regulatory Perspective on Rare Disease Clinical Outcome Assessment Development

Naomi Knoble, PhD

Associate Director of Rare Disease Measurement Science

Division of Clinical Outcome Assessment | Office of Drug Evaluation Sciences

Office of New Drugs | Center for Drug Evaluation and Research

FDA

Disclosure

- This presentation is not intended to convey official FDA policy, and no official support or endorsement by the FDA is provided or should be inferred
- The opinions expressed are those of the presenter
- The materials presented are available in the public domain

Rare Disease Medical Product Development

- Rare disease medical product development is increasing
  - From 1983 to 2019 there were 5,099 orphan drug designations
  - 25% of the designations were pediatric-onset (see orphan drug database)

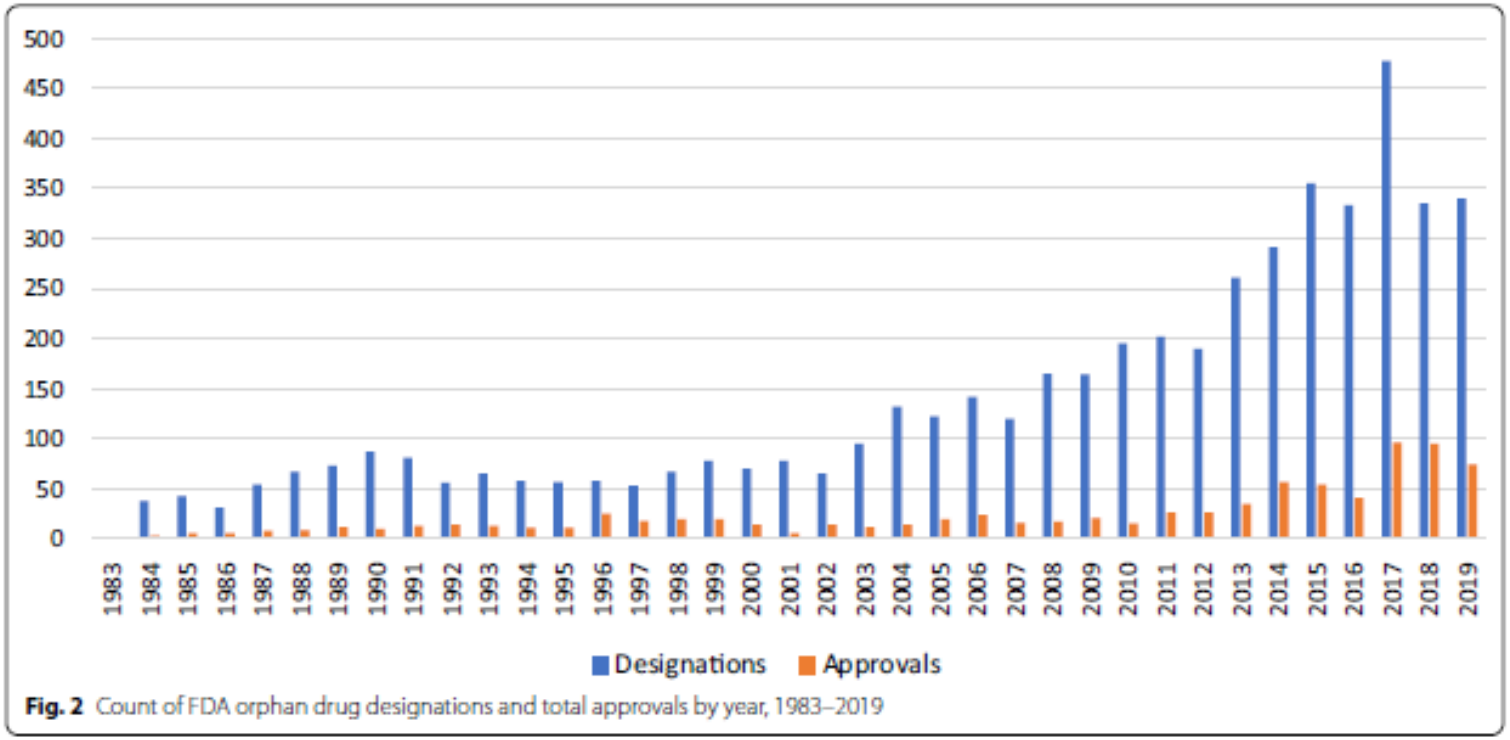


Fig. 2 Count of FDA orphan drug designations and total approvals by year, 1983–2019

- Understanding clinical trial measurement is essential for patient-centric, successful rare disease medical product development

Miller, K.L., Fermaglich, L.J. & Maynard, J. Using four decades of FDA orphan drug designations to describe trends in rare disease drug development: substantial growth seen in development of drugs for rare oncologic, neurologic, and pediatric-onset diseases. *Orphanet J Rare Dis* 16, 265 (2021).

Committed to Accelerating Rare Disease Cures (ARC)

- **ARC Vision:** Speeding and increasing the development of effective and safe treatment options addressing the unmet needs of patients with rare diseases.
- **ARC Mission:** CDER's ARC Program drives scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases.
- **CDER ARC Quarterly Newsletter:** To subscribe, U.S. Food and Drug Administration public.govdelivery.com

Upcoming Workshop: *Addressing Challenges in the Design and Analysis of Rare Disease Clinical Trials: Considerations and Tools*, May 2nd to 3rd, 2023 from 9am – 12pm EST
https://www.fda.gov/drugs/news-events-human-drugs/fda-cder-jhu-cersi-workshop-addressing-challenges-design-and-analysis-rare-disease-clinical-trials?utm_medium=email&utm_source=govdelivery

Rare Disease Endpoint Advancement (RDEA) Pilot Program

- The Rare Disease Endpoint Advancement (RDEA) pilot program will seek to advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process.
  - To learn more, visit https://www.fda.gov/drugs/development-resources/rare-disease-endpoint-advancement-pilot-program

Upcoming Workshop through Duke Margolis Center for Health Policy:

Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development

June 7th to 8th, 2023, 1-5pm EST https://healthpolicy.duke.edu/events/rare-disease-endpoint-advancement-pilot-program-workshop-novel-endpoints-rare-disease-drug

International Rare Disease Cluster

- **Participants**
  - FDA, European Medicines Agency (EMA), and Health Canada
- **Goal**
  - To conduct joint meetings that facilitate exchange between regulatory agencies about:
    - Scientific advice
    - Product licensing/marketing
    - Protocol assistance
    - Informational topics related to rare disease drug development

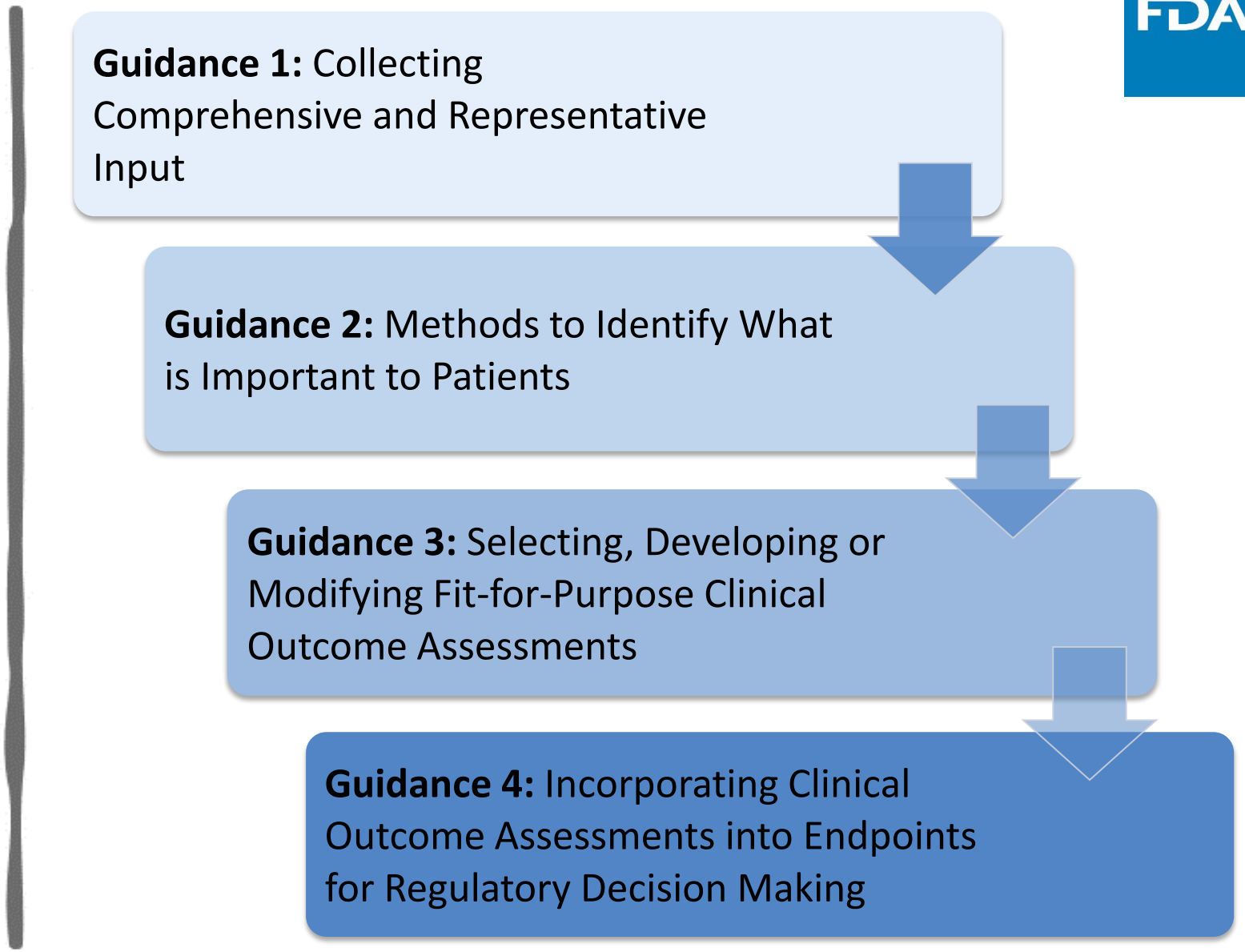
Epps et al., 2022; https://www.ema.europa.eu/en/partners-networks/international-activities/cluster-activities

Accelerating Rare Disease Medical Product Development: Collaboration

- Successful rare disease medical product development involves a high level of **stakeholder collaboration**:
  - Involving **patients as research partners**
  - Moving from exclusivity to **shared public-private resources**
  - Shifting from research silos to **collaboration**

Courbier et al., 2019; Deal et al., 2017; Denton et al., 2021; Epps et al., 2022; Larkindale et al., 2022

Patient-Focused Drug Development Guidance Series



https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

In-Trial Interview Studies

Screening and exit interview and/or survey studies can be incorporated into clinical studies to obtain patient/caregiver perspectives

- Observed changes
- Safety reports (e.g., side effects)
- Experience in the trial

See Appendix 5, Patient-Focused Drug Development Guidance: Methods to Identify What Is Important to Patients, February 2022

Pre-Competitive Consortia and Public/Private Partnerships

- **C-Path Rare Disease Clinical Outcome Assessment Consortium:** to advance COA measurement science, be a catalyst in medical product development for measuring what matters to rare disease patients

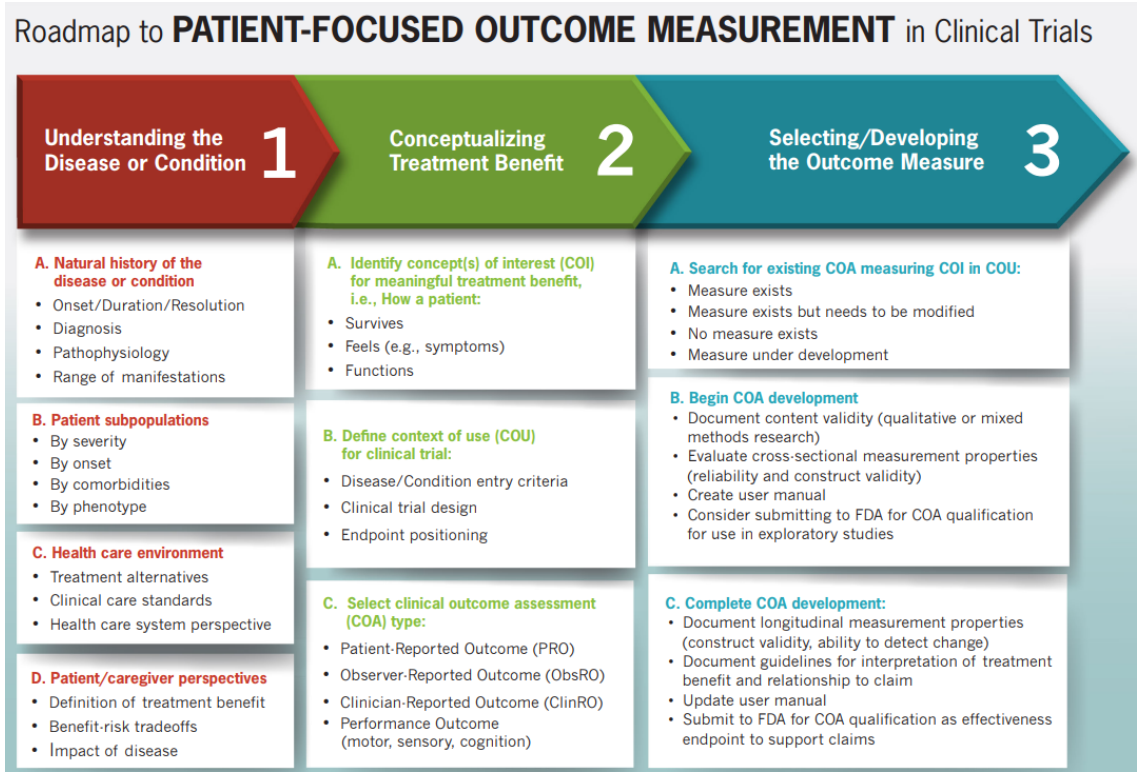
- **C-Path Rare Disease Cures Accelerator Data & Analytics Platform:** to accelerate rare disease insights and therapy developments by integrating and analyzing data from diverse sources (clinical trials, registries, RWE)

- Lysosomal Diseases Pre-Consortium in partnership with the Critical Path Institute

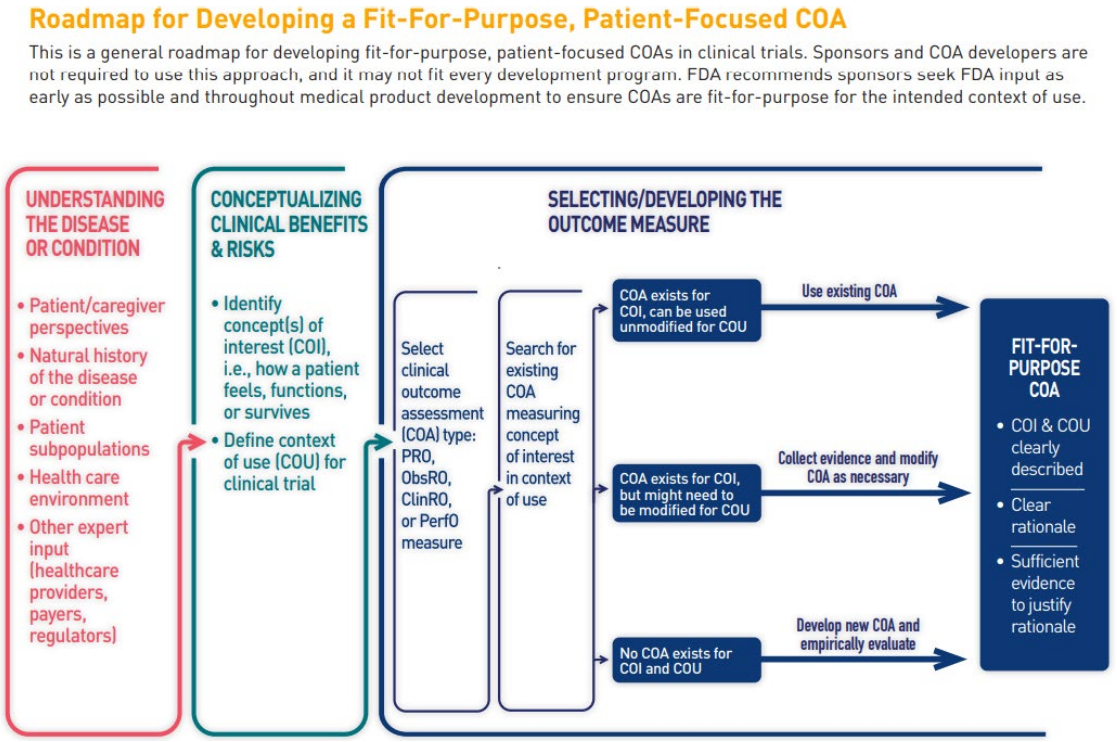
- FDA-NIH Critical Path for Rare Neurodegenerative Diseases also in partnership with the Critical Path Institute

Larkindale et al., 2022; Murray et al., 2023

Selecting Clinical Outcome Assessments for Use in Clinical Trials

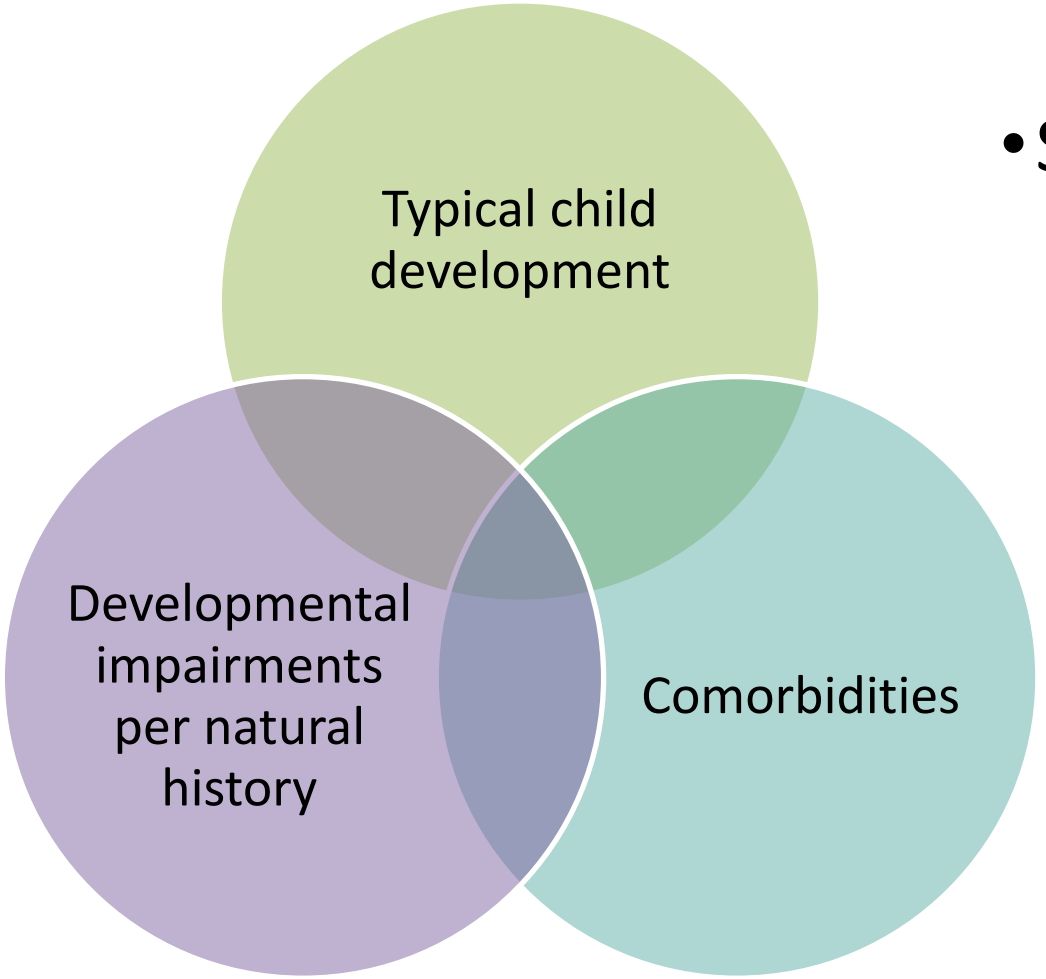


COA Roadmap Diagram: https://www.fda.gov/media/87004/download



Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-For-Purpose Clinical Outcome Assessment Guidance Snapshot: https://www.fda.gov/media/159516/download

Pediatric Developmental Measurement Considerations



- Selecting outcomes at the intersection:
  - Typical child development,
  - Developmental impairments anticipated from the known natural history/disease trajectory,
  - Additional comorbidities conferred by the disease/condition,
  - Can it be measured **validly** and **reliably implemented** within the **context** of the clinical trial?

COA Implementation

- **Implementation** of COAs in clinical trials is part of successful pediatric rare disease measurement, including:
  - **Standardization**, e.g., ensuring a COA is implemented in the same way, every time with every patient at every clinical trial site
  - **Rater training**, including ongoing administration and scoring checks to reduce administration/scoring errors (e.g., intra- and inter-rater reliability)
  - **Centralized raters**, masked to study design (e.g., treatment assignment), independent from clinical trial sites, may help mitigate forms of assessment bias and scoring errors

CNS Summit Raters, 2014; Sadler et al., 2017; Sanchez et al., 2018; Williams et al., 2015

Summary

- Rare disease medical product development is a **priority**, with multiple programs and collaborations to advance the science
- Successful pediatric rare disease measurement considers the **intersections** of child development, comorbid features of the condition, and natural history with **rigorous implementation**
- **Engage early and often** with FDA
- Outcomes in patient-focused clinical trials should reflect patient experiences and treatment priorities since patients are the primary stakeholder in medical product development

References

FDA Guidances

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FDA Patient-Focused Drug Development Guidance Series
https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

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Reviews for Approved Products are Public

Every approved medical product review is publicly available
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm


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Panel Discussion and Q&A

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Moderator

- *Lindsey Murray, PhD, MPH – Executive Director, Rare Disease Clinical Outcome Assessment Consortium, Critical Path Institute*

Presenters and Panelists

- *Lindsey Murray, PhD, MPH – Executive Director, Rare Disease Clinical Outcome Assessment Consortium, Critical Path Institute*
- *Dawn Phillips, PT, MS, PhD – Senior Director of Clinical Outcomes Research, REGENXBIO Inc.*
- *Ebony Dashiell-Aje, PhD – Executive Director & Head, Patient Centered Outcomes Science, BioMarin Pharmaceutical, Inc.*
- *Naomi Knoble, PhD – Associate Director of Rare Disease Measurement Science, Division of Clinical Outcome Assessment, Office of Drug Evaluation Sciences, Office of New Drugs, Center for Drug Evaluation Research, U.S. Food and Drug Administration*
- *Teresa Buracchio, MD – Director (Acting), Office of Neuroscience, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration*
- *Emily Freilich, MD – Deputy Director (Acting), Division of Neurology I, Center for Drug Evaluation and Research, U.S. Food and Drug Administration*
- *Cara O'Neill, MD – Chief Science Officer, Cure Sanfilippo Foundation*

Webinar

To register, visit: https://c-path-org.zoom.us/webinar/register/WN_9jBJ-ol9RWmB5zbsFuCZhA

Thank you!