Identifying COAs for Use in Rare Disease Treatment Trials

12th Annual
Patient-Reported Outcome Consortium Workshop

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Session Participants

Moderator

- *Lindsey Murray, PhD, MPH* – Associate Director, Patient-Reported Outcome Consortium, C-Path

Presenters

- *Tori Brooks, MPH* – Research Associate II, Mapi Research Trust
- *Lindsey Murray, PhD, MPH* – Associate Director, Patient-Reported Outcome Consortium, C-Path
- *Kiera Berggren, MA/CCC-SLP, MS* – Research Speech-Language Pathologist, Department of Neurology, Virginia Commonwealth University

Additional Panelists

- *Naomi Knoble, PhD* – Reviewer, Division of Clinical Outcome Assessment, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- *Dawn Phillips, PT, MS, PhD* – Director, Clinical Scientist, Outcomes Research, REGENXBIO Inc.
- *Adam Shaywitz, MD, PhD* – Chief Medical Officer, BridgeBio Gene Therapy
- *Allison Seebald* – Senior Research Program Manager, National Organization for Rare Disorders

Session Objectives

- To provide an overview of the Rare Disease COA Consortium grant activities
- To learn about the development of the Rare Disease COA Resource
- To understand how methodological challenges to rare disease are being addressed

Session Outline

- Overview of the Rare Disease COA Consortium grant
- Development of the Rare Disease COA Resource
- Methodologic challenges addressed:
  - Strategies to assess clinical benefit in conditions with heterogeneous manifestations
  - COVID-19 mitigation strategies in pediatric rare disease clinical trials

The Rare Disease Burden

- 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

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

Appropriate clinical outcome assessment tools 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 the Rare Disease COA Consortium

- The FDA's Center for Drug Evaluation and Research (CDER) funded a cooperative agreement to establish the Rare Disease COA Consortium
  - A one-year grant (U01FD006882) was awarded to Critical Path Institute (C-Path) with NORD as a sub-awardee on September 1, 2019. A no-cost extension was approved on July 17, 2019, extending funding through August 31, 2021.

Specific Aim of the FDA Grant – Establishment of the Rare Disease COA Consortium

- **As stated in FDA's Funding Opportunity Announcement:**
  - *"This cooperative agreement will provide funding to establish a rare disease consortium focusing on clinical outcome assessments appropriate for use in drug development to demonstrate clinical benefit."*

- **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."*

Establishment of the Rare Disease COA Consortium: Activities to Date

- The first step taken toward the establishment of the new consortium was the creation of the Rare Disease Subcommittee within C-Path's Patient-Reported Outcome (PRO) Consortium.

- The PRO Consortium serves as an incubator for the maturation of a pre-competitive, multi-stakeholder consortium within C-Path's COA Program

- Monthly Rare Disease Subcommittee calls have been on-going since November 2019

Rare Disease Subcommittee Participants

PRO Consortium Members	
AbbVie	Otsuka Pharmaceutical
Amgen	Sanofi
AstraZeneca	Takeda Pharmaceuticals
Daiichi Sankyo, Inc.	UCB Pharma
Genentech/Roche	
Advisory Members	
Aeglea BioTherapeutics, Inc	Horizon Therapeutics
Agios Pharmaceuticals Inc.	Ionis Pharmaceuticals, Inc.
Akcea Therapeutics	Lysogene
Apellis Pharmaceuticals, Inc.	MeiraGTx, LLC
Applied Therapeutics	Momenta Pharma
argenx US, Inc.	Neurocrine Biosciences, Inc.
Astellas Pharma Inc.	Ovid Therapeutics, Inc.
Audentes Therapeutics	PellePharm, Inc.
BioMarin Pharmaceutical	REGENXBIO Inc.
bluebird bio, Inc.	Sangamo Therapeutics
BridgeBio	Sarepta Therapeutics
Cabaletta Bio, Inc.	Ultragenyx Pharmaceutical, Inc.
Harmony Biosciences, LLC	

Grant Sub-Awardee
National Organization for Rare Disorders (NORD)
FDA Representation
Division of Clinical Outcome Assessment
Division of Neurology Products I
Office of Biostatistics
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine; Division of Rare Diseases and Medical Genetics
Office of Combination Products
Office of Strategic Programs
Patient-Focused Drug Development Program
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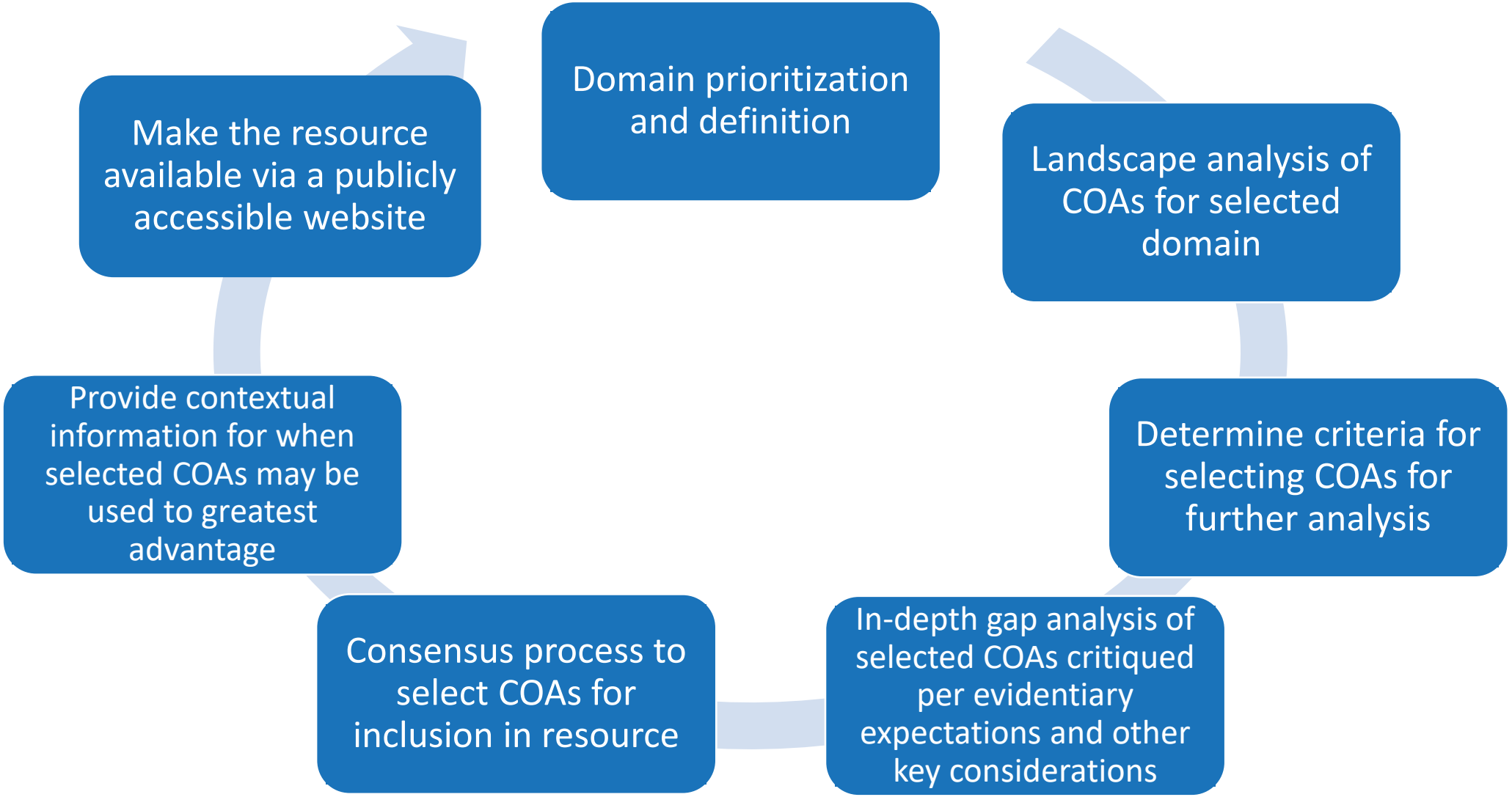
Other Representation
National Institutes of Health, National Center for Advancing Translational Sciences
Patient-Centered Outcomes Research Institute

Important Initial Decisions

- Members of the Rare Disease Subcommittee, including representatives from FDA, C-Path, NORD, the National Center for Advancing Translational Science (NCATS), the Patient-Centered Outcomes Research Institute (PCORI), and biopharmaceutical firms determined:
  - A domain approach will be used to identify COAs that might be fit-for-purpose for use as endpoint measures in treatment trials for multiple rare diseases
    - Daily function was selected as the first domain
  - Initial efforts will focus on pediatric populations
  - Oncology will be included in subsequent efforts

Rare Disease COA Resource: Development Process



Summary

- The Rare Disease Subcommittee is:
  - Utilizing a **domain approach** to identify potential COAs; **daily function** was selected as the first domain to address
  - Initially focusing on identifying COAs for **pediatric**, non-oncologic populations
- We plan to launch the Rare Disease COA Consortium in July 2021!

Member firm participation is the key to our success!

Landscape Review of Clinical Outcome Assessments Measuring Daily Function in Pediatric Populations

Tori Brooks, MPH
Research Associate II
Mapi Research Trust

Agenda

- Project objectives and overview
- Summary of findings
- Current status and next steps

Project Objectives

- **Objective:** The goals of the project are to perform a comprehensive landscape review, which will identify and summarize existing literature on clinical outcome assessments (COAs) that have been used in pediatric populations to measure the daily function subdomains of **gross motor function**, **fine motor function**, and **self-care**, and to provide a detailed gap analysis of selected candidate COAs.

Abbreviations: COA = clinical outcome assessment

Key Definitions

- **Daily function:** Common, everyday actions and behaviors involving functional ability that children display to show growing independence and mastery of skills.
- There are a number of subdomains that fall under daily function, including self-care, gross motor function, fine motor function, communication/language, cognition, emotional/behavioral function, etc.
- This landscape review covers **self-care, gross motor function, and fine motor function.**

Key Definitions, cont.

- **Self-care:** Ability to perform daily skills and adaptive behaviors involved in caring for oneself with increasing independence. Tasks may include eating or drinking, dressing, bathing, toileting, disease management, and general mobility in the home, community, and school environment.
- **Gross motor function:** Gross motor (physical) skills are those which require whole body movement, and which involve the large (core stabilizing) muscles of the body to perform everyday functions, such as standing and walking, running and jumping, and sitting upright at the table. They also include eye-hand coordination skills such as ball skills (throwing, catching, kicking) as well as riding a bike or a scooter and swimming.
- **Fine motor function:** Fine motor skills are involved in smaller movements that occur in the wrists, hands, fingers, feet, and toes. They involve smaller actions such as picking up objects between the thumb and finger, writing carefully, and even blinking.

Project Overview

The project is divided in the following steps:

- **Step 1: Review of published studies**
  - To identify COAs measuring the daily function subdomains of gross motor function, fine motor function, and self-care in international studies published in pediatric populations (ages 0 through 17) within the last 10 years. Patient-reported outcome (PRO) measures, clinician-reported outcome (ClinRO) measures, performance outcome (PerfO) measures and observer-reported outcome (ObsRO) measures were assessed.
- **Step 2: Selection of COAs* for Gap Analysis**
  - To provide guidance to the C-Path team in the selection of candidate COAs for inclusion in a detailed gap analysis.
- **Step 3: Gap Analysis**
  - To provide for each selected COA the documented development history, psychometric validation data, conditions of use, availability of languages and the review copy.

*The review and selection of COA for this project were not influenced by Mapi Research Trust's management of any of these COA licenses

Abbreviations: COA = clinical outcome assessment; PRO = patient-reported outcome; ClinRO = clinician-reported outcome; ObsRO = observer-reported outcome; PerfO = performance outcome

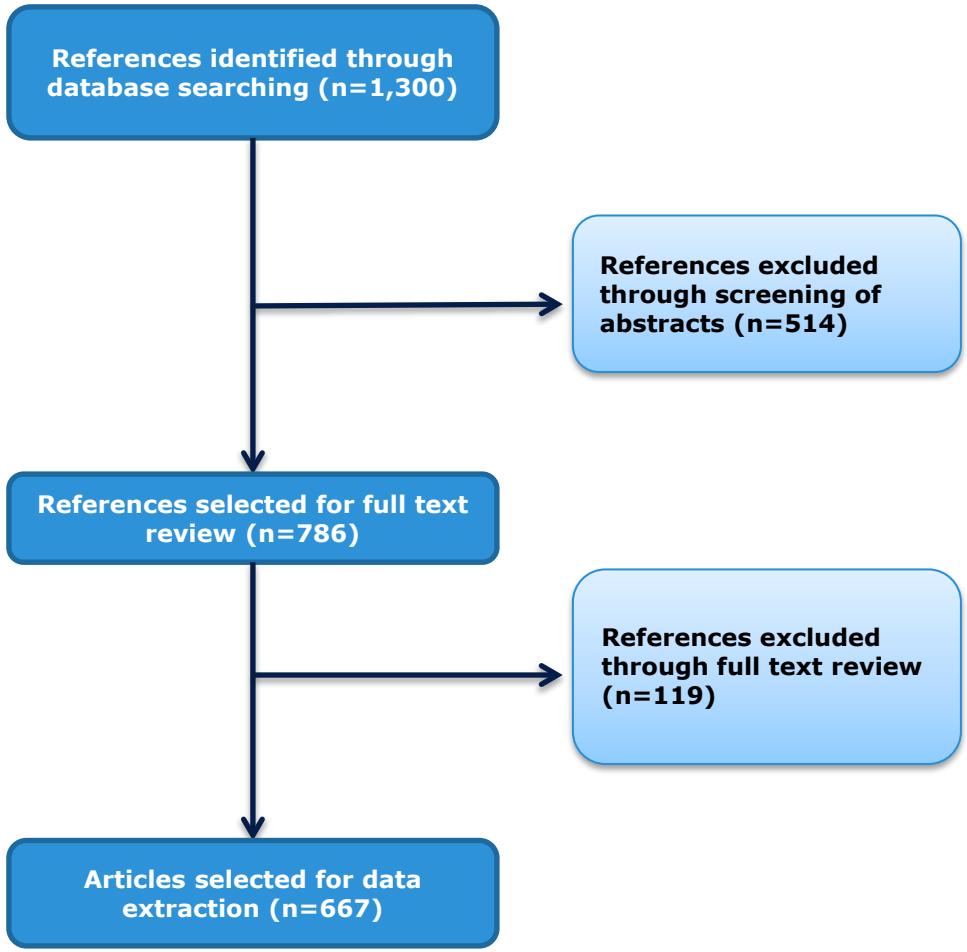
Step 1: Landscape Review – Methodology

- The following search was conducted on June 12th, 2020 in Medline and Embase databases (through Ovid platform):
    1. **Pediatric population terms**
    2. **Concept (gross motor, fine motor, self-care) terms**
    3. **COA terms**
    4. **Study type terms**
    5. **#1 AND #2 AND #3 AND #4**
    6. **#5 AND Limits: Abstracts, English language, Humans and last 10 years ("2010-Current")**
- Search strategy was developed and revised based on input from the Rare Disease Subcommittee
- 1,300 abstracts to be screened
- An additional search was performed using the search engine of the PROQOLID database to identify additional COAs measuring daily function and not retrieved in the above literature review search

Abbreviations: COA = clinical outcome assessment

Step 1: Landscape Review – Selection Process

- Reference screening and exclusion process:



Step 1: Landscape Review – Selection Process

- Inclusion criteria for COAs:
  - Developed in pediatric population or assessed in pediatric population
  - Assessing daily function subdomains of gross motor function, fine motor function, and/or self-care in entirety or with a validated subscale score
  - Can be used in generic population

- *Proxy-reported PRO measures for children were excluded*

Abbreviations: COA = clinical outcome assessment; PRO = patient-reported outcome

Step 1: Landscape Review – Data Extraction

- **278 total unique COAs identified**
  - **262** identified in the literature
  - **3** identified in PROQOLID database
  - **13** additional COAs included upon C-Path request
- **Characteristics reported for each COA:**
  - Type of COA (PRO, ClinRO, ObsRO, or PerfO measure)
  - Main concept measured
  - Daily function subdomain covered
  - Domains, number of items
  - Response scale description
  - Scoring information
  - Availability of publications of validation
  - Disease indication of COA development
  - Age range of COA development
  - Reference of development
  - Corresponding adult measure (if any)
  - Use in label claim

Abbreviations: COA = clinical outcome assessment; PRO = patient-reported outcome; ClinRO = clinician-reported outcome; ObsRO = observer-reported outcome; PerfO = performance outcome

Step 2: Selection of COAs for Gap Analysis – Summary of Findings

- A myriad of COAs (n=278) that have been used in pediatric studies to measure gross motor function, fine motor function, and self-care including:
  - Disease specific and generic instruments
  - Adult measures used in pediatrics
  - Age-specific measures
  - 'Large spectrum' tools vs single item/single concept tools
  - Various parameters of daily functioning: ability, performance, participation, dependence,…
  - Often vs. rarely used
  - Different types of COAs found (PRO, ObsRO, ClinRO, or PerfO measure)

Abbreviations: COA = clinical outcome assessment; PRO = patient-reported outcome; ClinRO = clinician-reported outcome; ObsRO = observer-reported outcome; PerfO = performance outcome

Step 2: Selection of COAs for Gap Analysis – Selection Process

- Criteria considered to narrow down the selection of COAs:
  - Frequency of use in PubMed/Embase
  - Population of development (age range, adult versus child, rare disease or common disease)
  - Gross motor function, fine motor function, self-care specific concept coverage against COA coverage
  - Review of scoring rules
  - Published data available providing evidence of content validity, psychometric properties, and responder thresholds
  - Availability (if any) on success in obtaining a COA label claim

Abbreviations: COA = clinical outcome assessment

Step 3: Gap Analysis

- List of 278 COAs and recommendations circulated among the Rare Disease Subcommittee
- 49 unique COAs with several additional versions for a total of 53 measures were selected for gap analysis
  - In-depth information to be reported for each COA: development history, psychometric validation data, conditions of use, availability of languages and the review copy

Abbreviations: COA = clinical outcome assessment

Status and Next Steps

- Gap analysis underway for 49 unique COAs with several additional versions for a total of 53 measures in gross motor function/fine motor function/self-care
  - To be delivered in 3 stages with all COA descriptions completed by June 25th, 2021

- Next subdomain of focus: Communication/language
  - Landscape review completed
  - Next step: selection of COAs for gap analysis

Abbreviations: COA = clinical outcome assessment

Closing

Thank you!

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Approaches to the Assessment of Clinical Benefit of Treatments for Conditions with Heterogeneous Manifestations

Lindsey Murray, PhD, MPH
Associate Director, PRO Consortium
C-Path

Agenda

- Overview of challenges assessing conditions with heterogenous manifestations
- Literature Review Methods
- Individualized Outcome Strategies Identified
- Special Considerations
- Applications in Rare Disease

Background

- Conditions with heterogeneous sign and symptom presentations are often difficult to assess in a clinical trial setting.
- People with the same condition may present with different symptom and impact profiles. Therefore, it can be difficult to identify a single outcome or outcome measure that is relevant to every study participant.
- This challenge commonly occurs with rare diseases.
- The combination of rarity and heterogeneity can make it difficult to recruit a study population that is sufficiently large for adequate statistical power.
- To address this challenge, researchers have used a variety of approaches involving **individualized outcomes** in an attempt to focus on the symptoms, signs, and/or impacts that are relevant to each participant.
- C-Path and Evidera conducted a literature search to identify measurement approaches for addressing heterogeneous manifestations that could be relevant in rare diseases.

Objectives of This Literature Search

1. Identify types of individualized assessments used to evaluate clinical benefit in conditions with heterogeneous manifestations

2. Determine which of these measurement methods have been included in FDA-approved label claims

3. Highlight measurement approaches that have been used specifically in rare diseases

Literature Search Methods

1. C-Path and Evidera discussed various search terms, strategies, and disease areas likely to use individualized outcomes.
2. After generating a list of likely terms with which to begin, Evidera staff searched PubMed and Google Scholar for articles reporting trials where these individualized outcomes were used.
    - If a trial was found that used an individualized outcome, Evidera examined the label for the associated product to determine whether the individualized outcome was included in the label language.
3. New approaches were uncovered while searching for known outcomes (e.g., searching for general terms like “composite endpoint” revealed more specialized terms like “sliding dichotomy”).

Individualized Outcome Terms Identified

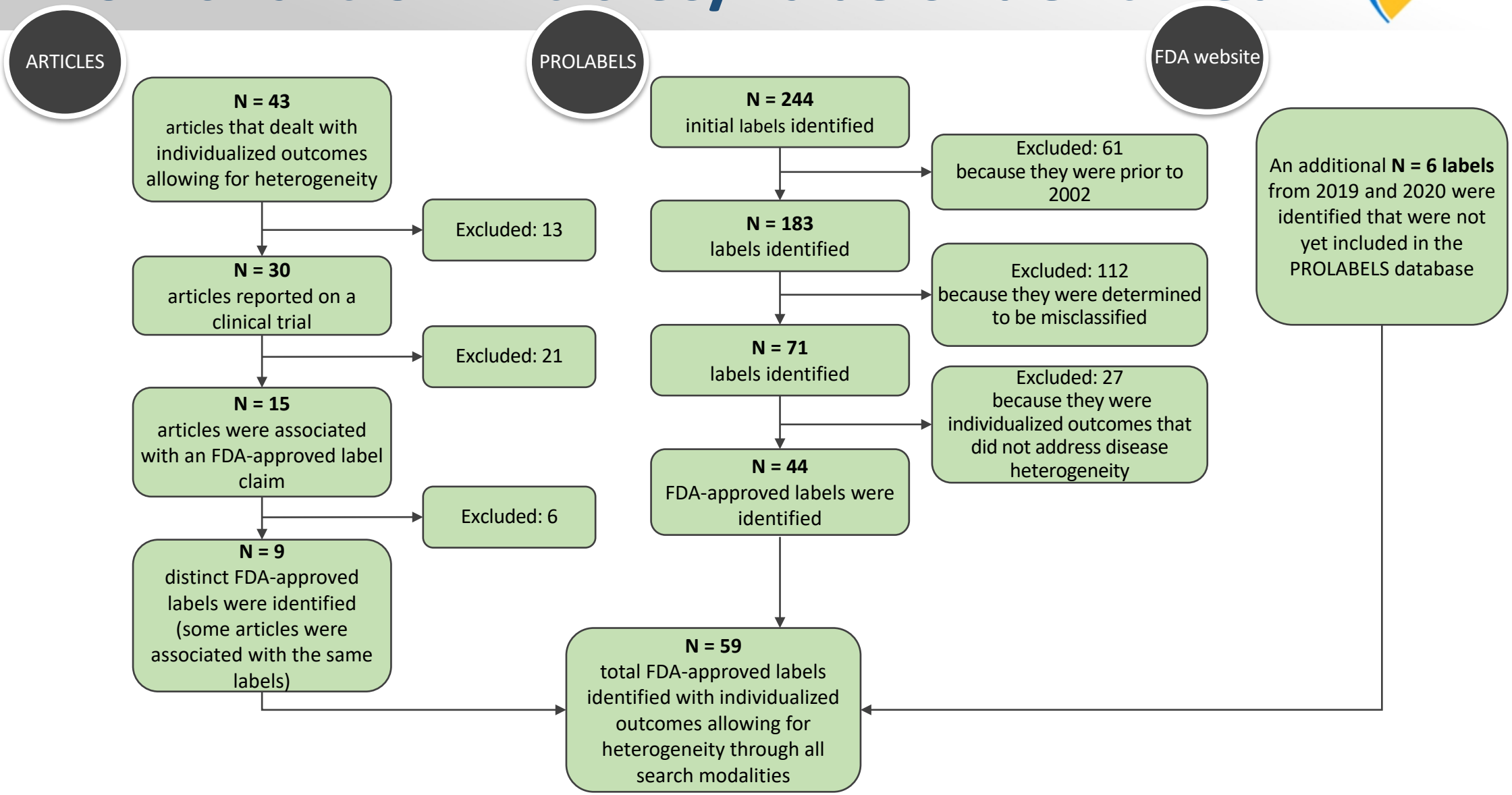
Individualized Outcomes	Definition
Multi-component endpoints, including composite	Combines multiple outcomes into a single composite measure
Multi-domain responder index	Combines multiple individual domains or endpoints by transforming them into -1, 0, or +1 points using established MID thresholds
Most bothersome symptom	Patients report improvement on their self-identified most bothersome symptom
Goal attainment scaling	Quantifies the achievement of goals unique to each person in trial
Sliding dichotomy	Point of dichotomy (acceptable vs. unacceptable outcome) on the scale is different for each person in trial with respect to baseline status
Adequate relief	Individual determines if relief from medication is “adequate” based on person’s own reference system

Abbreviations: MID = minimally important difference

PROLABELS™ Database and FDA Website

- Evidera team searched the PROLABELS™ database, focusing on FDA labels from 2002 to July 2020.
- All FDA-approved labels from 2019 to July 2020 were searched on the FDA website directly, as well.
- All FDA-approved product labels were reviewed by looking up the most recent version of each label on the FDA website.

Results:
Flowchart of Articles/Labels Identified



Multi-component Endpoints Sub-types

Multi-Component sub-type	Definition
Time-to-event[1]	Time-to-event endpoints are looking for the amount of time from beginning intervention/treatment to the prespecified event
Rate of given events after a certain period of treatment or follow-up[1]	The rate of given events is quantified after a period of time following treatment or follow-up
Total score[2]	Total score outcomes are based on rating scales in which multiple sub-scores can stand alone or be combined into a single score
Dichotomous (event) [2]	Individual patient achieving specified criteria on each of the multiple components

[1] This is classified as a composite endpoint in the FDA 2017 guidance.

[2] This would be classified as a **multi-component endpoint** in the FDA 2017 guidance but is frequently referenced as a composite endpoint in the literature.

Multi-component Endpoints in FDA-Approved Labels

49 FDA-approved labels identified in this search contained composite or other multi-component endpoints, of which 13 were for rare diseases.

MBS Outcomes in FDA-Approved Labels

9 product labels with MBS endpoints were identified, including 6 for treatments of post-menopausal vulvovaginal symptoms and 3 for migraine treatments. No MBS endpoints were found in rare diseases.

Abbreviations: MBS = most bothersome symptom

Adequate Relief Use in FDA-Approved Labels

FDA accepted adequate relief as an endpoint in the approval of the IBS product Lotronex (alosetron; initial approval in 2000), but FDA no longer recommends its use in IBS. No adequate relief endpoints were found in rare diseases.

MDRI, GAS, and Sliding Endpoints in FDA-Approved Labels

MDRI based endpoints have not been included in any FDA-approved labels for either non-rare or rare diseases.

GAS based endpoints have not been included in any FDA-approved labels for either non-rare or rare diseases.

Sliding dichotomy endpoints have not been included in any FDA-approved labels for either non-rare or rare diseases.

Abbreviations: MDRI = multi-domain responder index; GAS = goal attainment scaling

Considerations

- Although several of these approaches have not been included in FDA-approved label claims, it is important to note that this may not be driven by the approach methodology itself.
- Reasons approaches might not be in FDA-approved label claims include a clinical trial program's:
  - Failure to achieve efficacy or safety endpoints
  - Lack of funding to complete trial
  - Protocol violations
  - Poor recruitment, enrollment, and/or retention

Applications in Rare Disease

- Multi-component endpoint sub-types that may be particularly useful:
  - rate of given events after a certain period of treatment or follow-up
  - time-to-event endpoint
- These endpoints do not require that all components of the endpoint occur for each participant
  - Allow for variability in the specific component used to signal an event
  - All components of the endpoint need to be measured for each participant

Applications in Rare Disease, cont.

- MDRI, MBS, GAS, and adequate relief may be applicable to rare disease clinical trial programs
  - FDA has stated concerns related to practical application of MDRI
  - MBS can be challenging to clearly define core set of meaningful symptoms and requires larger sample sizes which can be problematic in rare diseases; additionally, the most bothersome symptom may change over time, or a new most bothersome symptom may develop
  - GAS can be time-consuming and difficult to manage; frequency of open-label, single-arm trials in rare disease increase the likelihood of expectancy bias
- Early interaction with FDA to discuss endpoint selection is key!

Abbreviations: MBS = most bothersome symptom, MDRI = multidomain responder index, GAS = goal attainment scaling

Conclusions and Next Steps

- 6 types of measurement approaches were identified to quantify clinical benefit for conditions with heterogeneous manifestations.
- Multi-component, MBS, and adequate relief have been included in FDA-approved label claims.
- The MBS, GAS, MDRI, and adequate relief measurement approaches may have potential applications in rare disease trials.
- A manuscript is under development.

COVID-19 Mitigation Strategies for Studies in Pediatric Rare Diseases

Kiera Berggren, MA/CCC-SLP, MS
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Virginia Commonwealth University

Outline for the Presentation

- Objectives of the team
- Current status
  - Workshop development
- Summary of team findings

Objectives of the Team

- Identify challenges associated with pediatric rare disease clinical trials in pandemic environment
    - Broad concerns
    - Trial specific concerns
        - At trial start up
        - For currently enrolling trials
            - In-person vs remote assessments
        - At study conclusion
        - Analysis of data
        - Regulatory challenges

Objectives of the Team

- Identify mitigation strategies

- Develop a means to share and foster an in-depth discussion among sites facing these challenges
    - Workshop to disseminate findings with open discussion for collaboration
        - COVID-19 Mitigation Strategies in Pediatric Rare Disease Clinical Trials Virtual Workshop: Friday May 7, 2021 12:00 – 1:30 pm Eastern (US)

Current Status

- Workshop learning objectives
  - Identify COVID-19 challenges to pediatric rare disease clinical trials
  - Present a range of mitigation strategies for the conduct of pediatric rare disease clinical trials under pandemic conditions
  - Present a range of mitigation strategies for conducting in-person and remote assessments under pandemic conditions
  - Provide an interactive forum for idea sharing related to COVID-19 impact and mitigation strategies across a range of stakeholders

Workshop Development – Trial Initiation Challenges

- Vulnerable populations limiting exposure
    - Reduced enrollment for populations already understudied
- Socio-political factors exacerbated by COVID-19
- Participant/family readiness to participate
    - Additional burdens to families already stressed during the pandemic
- Funding challenges in light of decreased philanthropy

Workshop Development – Trial Conduct

- Study personnel
  - Training – remote/in-person for flexibility
  - Extended time for all aspects of study visits
  - Personal protective equipment (PPE) and related limitations
- Increased documentation needs
  - Missed visits or visits outside windows
  - Protocol deviations
- Are endpoints still reasonable in a currently enrolling study?

Workshop Development – Assessments

- In-person
    - Physical space limitations
    - Effect of PPE

- Remote
    - Technical concerns
        - Access to internet
        - Caregivers assisting in data collection and how to standardize this
        - Compliance of electronic data capture systems for some assessments

Workshop Development – Assessments

- Documentation
    - Deviations
    - PPE in use
    - Site-specific requirements around COVID-19
    - Variations across sites for multi-site studies

Workshop Development – Regulatory

- Institutional Review Board (IRB)-related concerns
  - Reprioritization for evaluation of studies
  - Protocol deviations
  - Document modifications

Workshop Development – Data Analysis

- How to handle missed visits or visits out of window
- How to handle missing data unable to be captured remotely or due to site-specific health protocols
- How to treat pooled data collected in-person and remotely
    - Can these be compared?
- Developmental/educational/mental health impacts
- Natural history studies with missing or limited data

Summary of Team Findings

- Creation of a workshop for initial dissemination of information
  - Encourage continued discussion among stakeholders to crowdsource ideas around mitigation strategies
  - COVID-19 Mitigation Strategies in Pediatric Rare Disease Clinical Trials Virtual Workshop: Friday May 7, 2021 12:00 – 1:30 pm Eastern (US)

- Possible avenues for future work
  - Document summarizing identified challenges and mitigation strategies in pediatric rare disease trials under pandemic conditions will be hosted on the PRO Consortium website for reference

Panel Discussion

Moderator

- *Lindsey Murray, PhD, MPH* – Associate Director, Patient-Reported Outcome Consortium, C-Path

Presenters

- *Tori Brooks, MPH* – Research Associate II, Mapi Research Trust
- *Lindsey Murray, PhD, MPH* – Associate Director, Patient-Reported Outcome Consortium, Critical Path Institute
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