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Navigating Methodological Challenges in Rare Disease Clinical Trials: Lessons from Real-World Case Studies

Clinical Outcome Assessment Program Annual Meeting

April 16-17, 2026

Washington, D.C.

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Session Agenda

- Introduction (5 minutes)
- Presentations (25 minutes)
- Panel discussion (20 minutes)
- Open discussion and Q&A (10 minutes)

Session Objectives

- Present case studies illustrating approaches to navigating methodological challenges in rare disease research using patient-centered methods.
- Describe how qualitative and quantitative research methods support rare disease clinical outcome assessment (COA) development and implementation across multiple conditions.
- Examine how qualitative research has informed regulatory decision-making in rare disease drug development and approval.

Session Participants

- **Moderator**
  - *Lindsey Murray, PhD, MPH – Executive Director, Rare Disease Clinical Outcome Assessment Consortium, Critical Path Institute*
- **Presenters**
  - *Bryce Reeve, PhD – Professor, Population Health Science and Pediatrics, Director, Center for Health Measurement, Duke University School of Medicine*
  - *Nicola Williamson, MSc – Patient Centered Outcomes Research Lead, UCB*
- **Panelists**
  - *Terry Jo Bichell, PhD – CEO, COMBINEDBrain*
  - *Michelle Campbell, PhD – Associate Director, Stakeholder Engagement and Clinical Outcomes, Office of Neuroscience, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration*
  - *Sue Vallow, MBA, MA – Senior Director, Patient-Centered Research, Agios*

Expanding the Observer-Reported Communication Ability (ORCA) Measure:

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Assessing the communication ability of individuals with rare neurodevelopmental disorders

Bryce B. Reeve, PhD
Professor of Population Health Sciences
Professor of Pediatrics
Director, Center of Health Measurement
Duke University School of Medicine

Funding received from:

U.S. FDA (UG3FD007304, UH3FD007304)

Disclosures

- The study team members have developed the technology being discussed. If the technology is commercially successful in the future, the developers and Duke University may benefit financially.

Angelman syndrome	Phelan McDemid syndrome
Bosch-Boonstra-Schaaf optic atrophy syndrome	Rett syndrome
GRIN2B-related NDD	Schinzel-Giedion syndrome
Hao-Fountain syndrome	SCN2A-related disorders
HNRNPH2-related disorders	SETBP1 neurodevelopmental disorder
Hunter syndrome	STXB1-related disorders
Malan syndrome	SYNGAP1-related intellectual disability
MECP2 Duplication syndrome	
NeuroDevelopmental Disorders (NDDs)	

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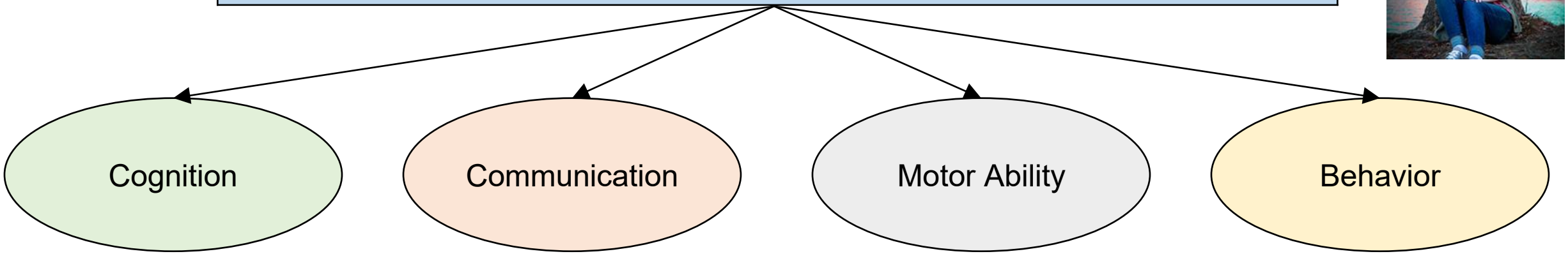
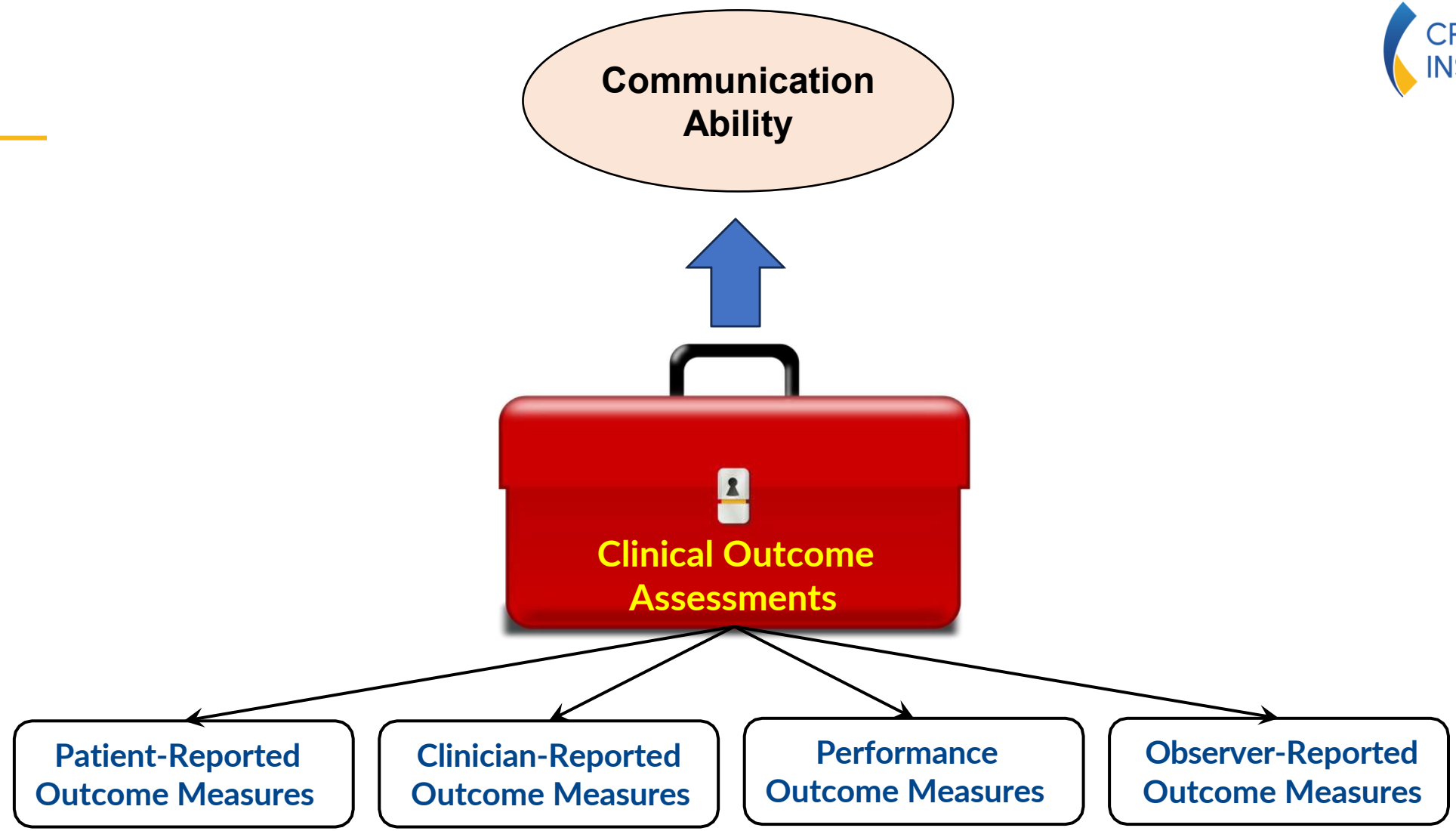
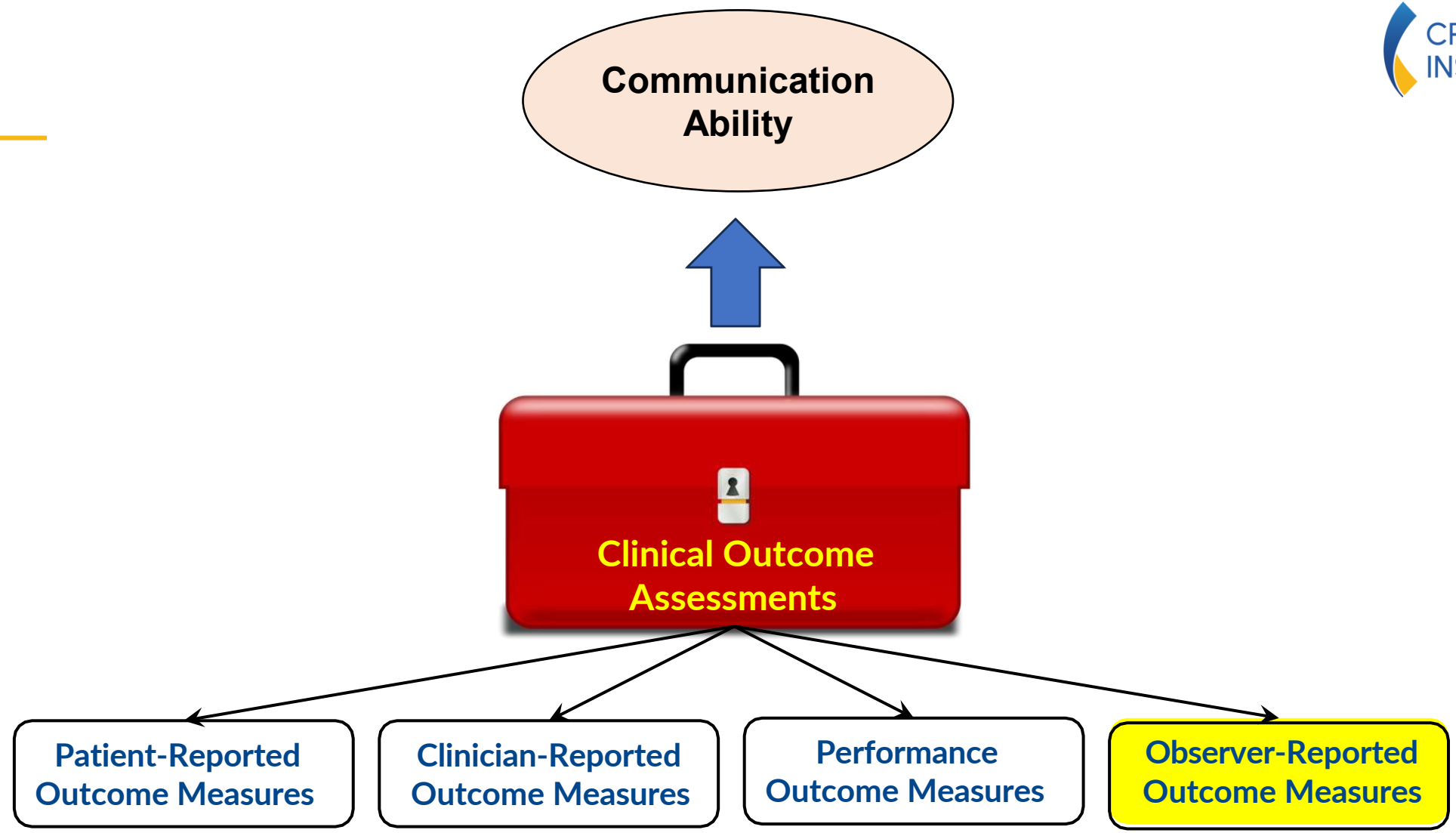



Communication Ability
Clinical Outcome Assessments
Patient-Reported Outcome Measures
Clinician-Reported Outcome Measures
Performance Outcome Measures
Observer-Reported Outcome Measures


Communication Ability
Clinical Outcome Assessments
Patient-Reported Outcome Measures
Clinician-Reported Outcome Measures
Performance Outcome Measures
Observer-Reported Outcome Measures

Observer-Reported Communication Ability (ORCA) measure

a) Caregivers/Parents complete the questionnaire independently.

b) Allows multiple communication modalities.

c) Captures emerging and mastery behaviors.

d) Assesses a broad range of communication concepts.

Concepts Included on the ORCA Measure

Expressive Communication	Receptive Communication	Pragmatic Communication
Seek Attention	Respond to Name	Greeting
Direct Attention	Understand Mood	Comfort Others
Refuse Object	Understand Isolated Words	Play Games
Request Object	Turns in Conversation	Use Names (others & self)
Request Object Out of View	Make Choices	Humor
Request “More”	Respond to Familiar Directions	Feelings and Emotions
Communicate Understanding	Respond to New Directions	Not Feeling Well, Hurt, or Sick
Ask Questions	Answer Questions	
Communicate with Others		
Tell About the Past		

Observer-Reported Communication Ability (ORCA) measure

a) Caregivers/Parents complete the questionnaire independently.

b) Allows multiple communication modalities.

c) Captures emerging and mastery behaviors.

d) Assesses a broad range of communication concepts.

e) Designed with the goal for use in clinical trials.

FDA's Patient-Focused Drug Development (PFDD) Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making

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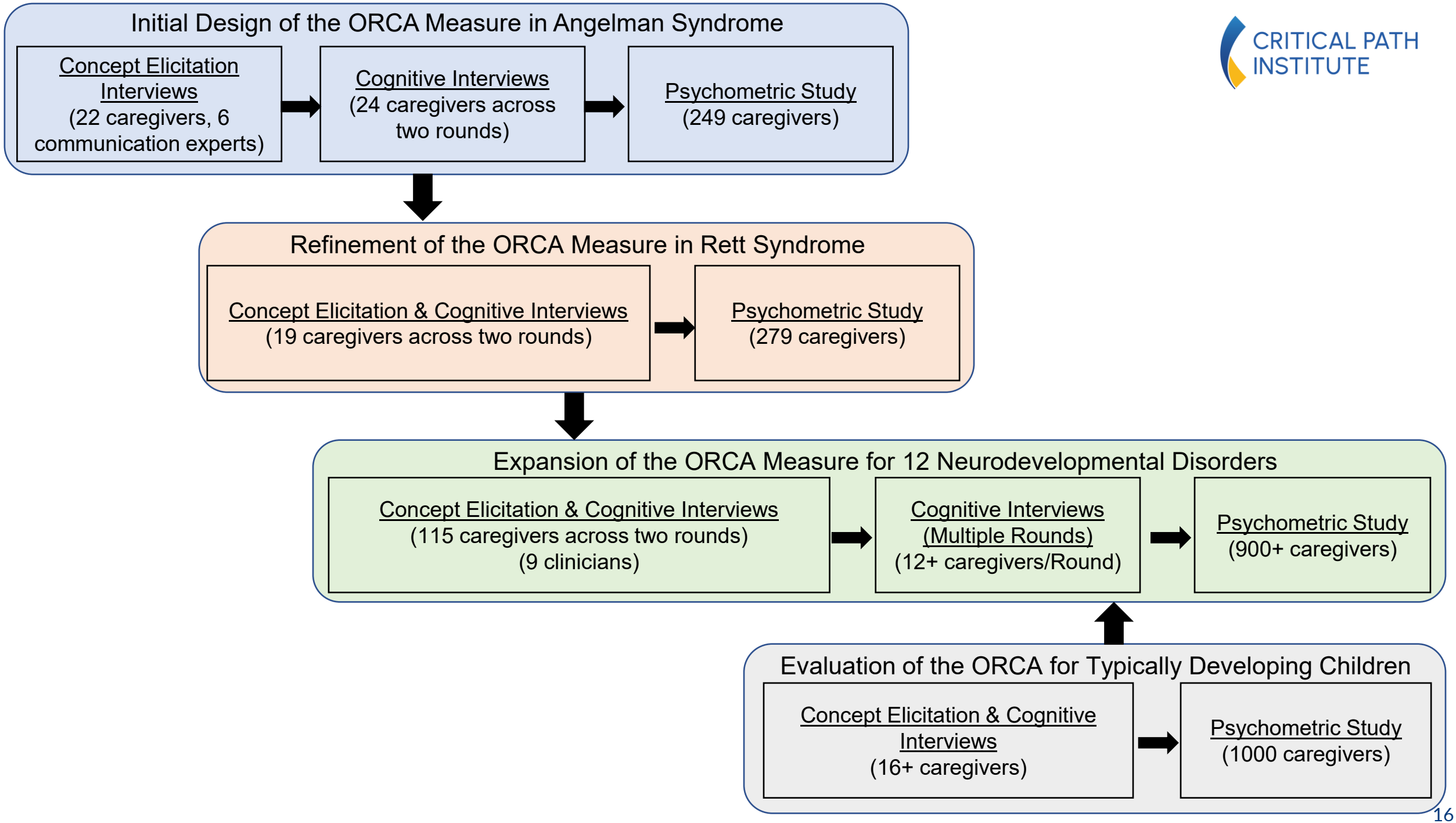
Collecting Comprehensive and Representative Input

Methods to Identify What is Important to Patients

Selecting, Developing, or Modifying Fit-for-Purpose COAs

Incorporating COAs into Endpoints for Regulatory Decision Making

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


Initial Design of the ORCA Measure in Angelman Syndrome
Concept Elicitation Interviews
(22 caregivers, 6 communication experts)
Cognitive Interviews
(24 caregivers across two rounds)
Psychometric Study
(249 caregivers)
Refinement of the ORCA Measure in Rett Syndrome
Concept Elicitation & Cognitive Interviews
(19 caregivers across two rounds)
Psychometric Study
(279 caregivers)
Expansion of the ORCA Measure for 12 Neurodevelopmental Disorders
Concept Elicitation & Cognitive Interviews
(115 caregivers across two rounds)
(9 clinicians)
Cognitive Interviews
(Multiple Rounds)
(12+ caregivers/Round)
Psychometric Study
(900+ caregivers)
Evaluation of the ORCA for Typically Developing Children
Concept Elicitation & Cognitive Interviews
(16+ caregivers)
Psychometric Study
(1000 caregivers)

U.S.
Food and Drug Administration

External Technical Advisory Committee

NDD & Communication Experts
Industry
Psychometrics
Patient Advocacy
FDA

COMBINEDBrain
Patient Advocates
Clinicians

BBSOAS Disorder
GRIN2B
HAFOUS
HNRNPH2
Hunter
Malan
PMS
SGS
SCN2A
SETBP1-HD
STXBP1
SYNGAP1

Core Research Team

COA Methodologists
Speech Language Pathologists
Neuro-Psych

Stakeholder Engagement Group

Patient Advocacy Reps
Clinical Experts

Key Lessons from ORCA Project

1. Despite small sample sizes of rare conditions, we can adhere to the recommendations of the FDA PFDD Guidance.
2. Qualitative work informs our understanding of communication and the clarity and relevance of the ORCA measure.
3. Quantitative work in NDD and TDC provides an interpretable and standardized scaling metric and evidence for the validity of the scores.
4. Inclusive of multiple expertise and patient advocacy groups has made the ORCA project a success.
5. The ORCA's development is performed in a pre-competitive space to maximize its benefit to as many as possible in the rare NDD field.

Current ORCA Team

Nicole Lucas, BS

Alexa Namestnik, MS

Mersedes Brown, MPH

Li Lin, MS

Kevin Weinfurt, PhD

Kelly Gordon, CCC-SLP, MS

Jennifer Kern, CCC-SLP, MS

Abby Radar, MS

Bryce Reeve, PhD

Terry Jo Bichell, PhD, MPH

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The use of qualitative evidence in regulatory decision-making: A review of rare disease approvals from 2022-2025

Nicola Williamson
Patient Centered Outcomes Research Lead
UCB, Slough, United Kingdom

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The findings may not reflect current regulatory expectations, and represent a snapshot based on publicly available regulatory review documents.

Nicola Williamson is an employee and shareholder of UCB.

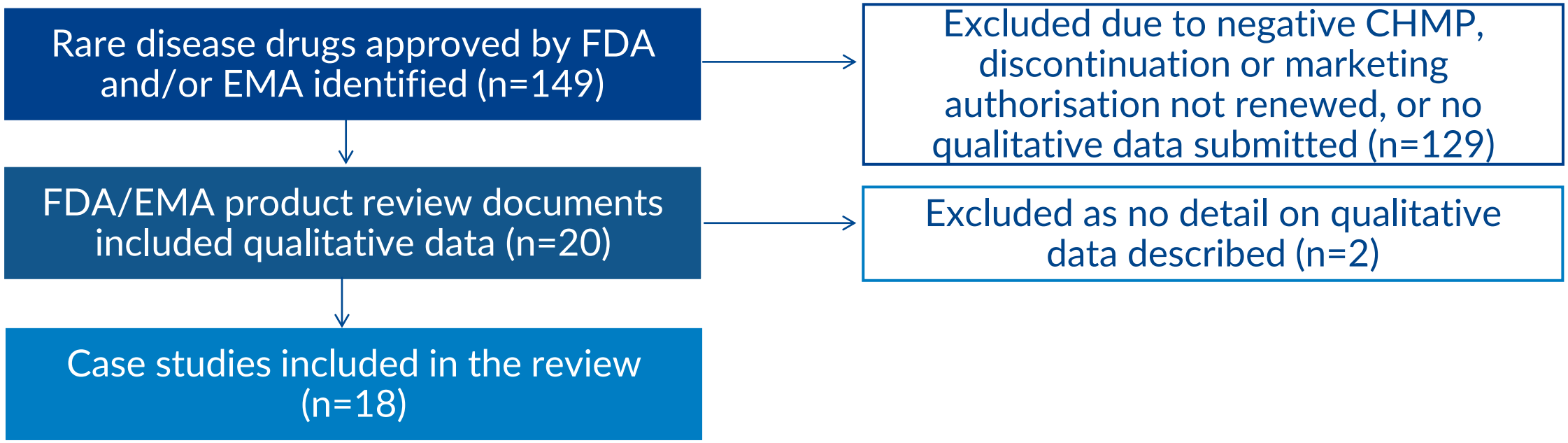
Background and objectives

- Patient experience data (PED) encompasses information collected from patients, caregivers, and other relevant stakeholders to capture lived experiences, perspectives, unmet needs, and treatment priorities.
- Regulatory authorities have increasingly recognised the value of qualitative evidence in informing more meaningful patient-focused regulatory decision-making.
- This is particularly important in rare diseases, where small patient populations, clinical heterogeneity, and limited natural history data often constrain the generation of robust evidence.
- Despite this, the regulatory use and impact of qualitative evidence in decision-making remain incompletely understood.

Objective: To review case studies of rare disease drugs approved by the FDA and EMA between 2022 and 2025 to examine how qualitative data were used as scientific evidence in regulatory decision-making.

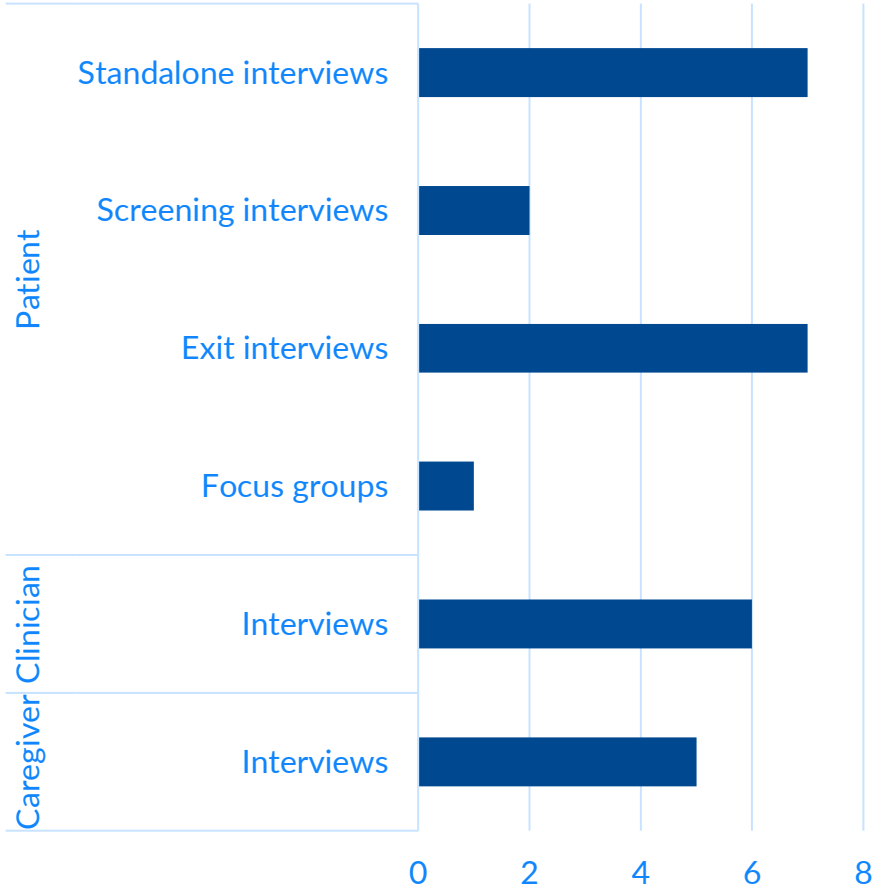
Methodology

- Rare disease drugs, biologics, ASOs and advanced therapies approved by the FDA and EMA from 1st January 2022 to 31st July 2025 were reviewed.



Results: Case studies identified

- Qualitative data were most often generated through **patient input** (n=7)
- Qualitative data primarily supported **secondary COA-based endpoints** (n=16), with fewer for primary (n=3), co-primary (n=2), and exploratory (n=1) endpoints.
- **PROs** were the most frequent COA type, followed by ClinROs (n=4), PerfOs, ObsROs (n=2) and composite (n=1)
- Most therapies were **small molecules** (n=8) or **biologics** (n=7); fewer were advanced therapies (n=2) or ASOs (n=1)
- **Hematology** (n=4) and **oncology** (n=3) were the most common therapeutic areas



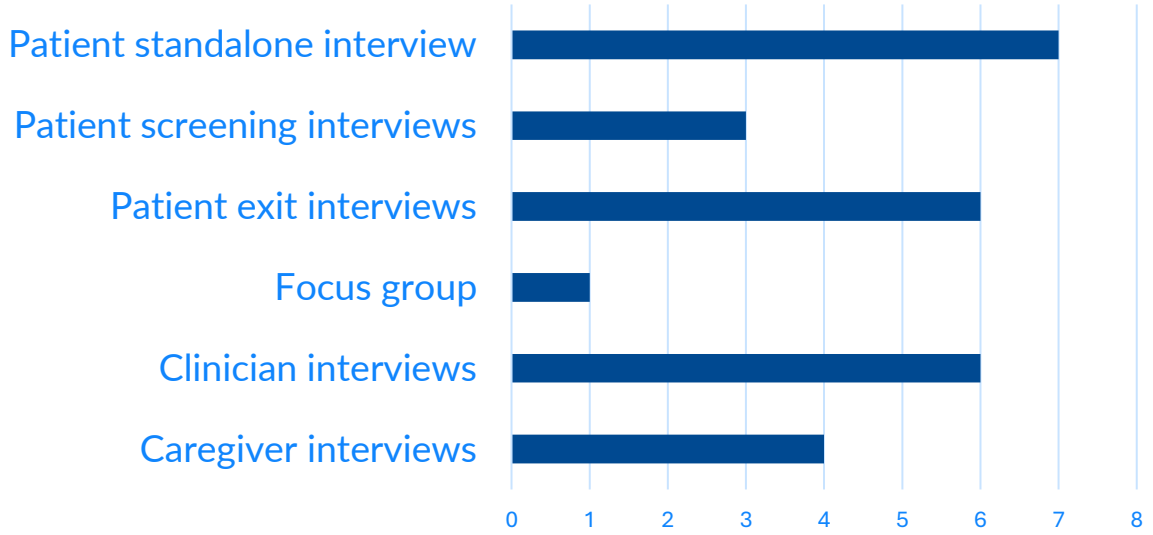
Results: Use in regulatory decision making

- Across 18 case studies, qualitative evidence contributed to regulatory decision-making in the following areas:

Identification of concept of interest (n=13)	Justify COA selection (n=10)	Interpretation of efficacy endpoint (n=9)	Benefit-risk evaluation (n=6)

Qualitative evidence supported identification of the concept of interest in most case studies (n=13/18, 72.2%)

- Qualitative evidence confirmed the **relevance and importance of symptoms** to assess from patient, caregiver, and clinician perspectives (where applicable), supporting **concept selection**, identification of **most bothersome symptoms** and **core symptoms** of the patient experience.



Identification of the core symptoms of HCM

Core symptoms of HCM were identified based on several sources, shown in Table 7 (only includes symptoms reported by the majority from each source). Symptoms assessed by the HCSMSQ-SB and/or the KCCQ-23 CSS are highlighted in blue. Refer to section 5.1.2 Conceptual Framework(s) for more detail.

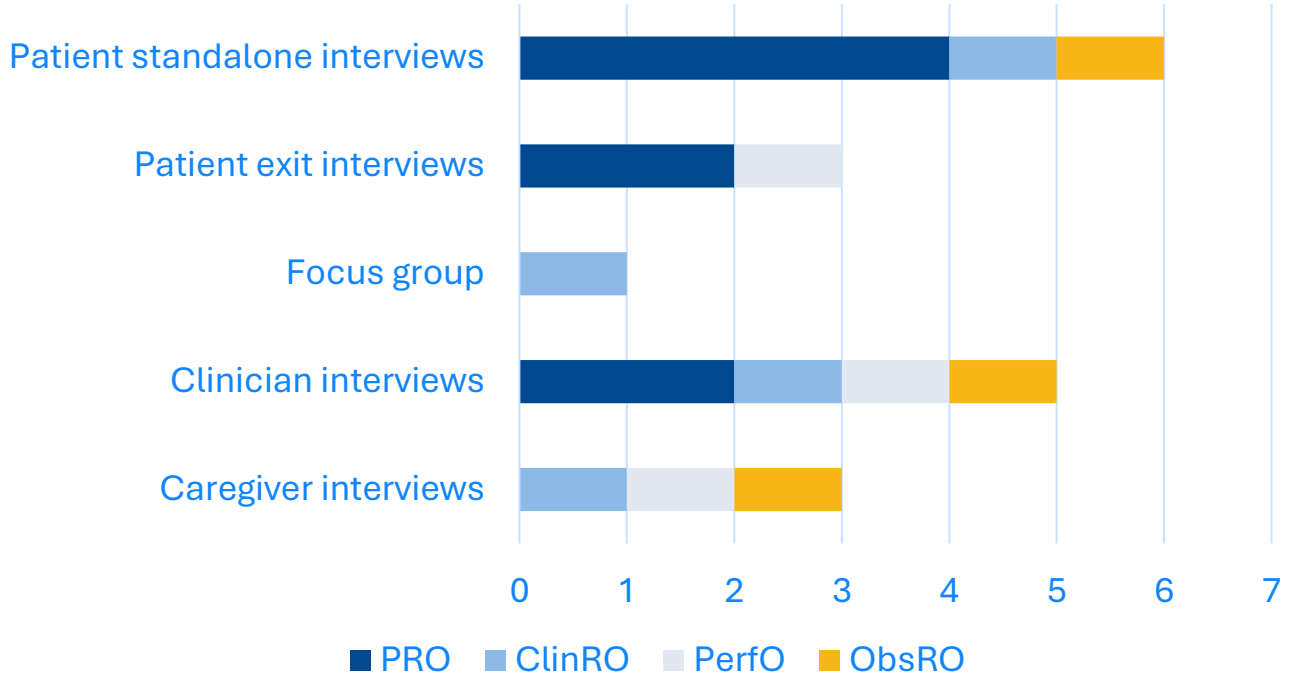
Table 7. Core symptoms and impacts of HCM

	Patient web survey[a] (n=444)	Literature and Guidelines[b]	Clinician interviews[c] (n=3)	CE interviews[d] (n=17)	EL-PFDD Meeting[e]

Reference: FDA COA Consult Review for camzyos

Qualitative evidence supported COA selection in most case studies (n=10/13, 76.9%)

- Qualitative evidence confirmed that the COAs selected measure **clinically relevant**, **important symptoms** (and aspects of symptoms) of the patient experience, supporting the **content validity** of the COAs selected in a specific context of use.



Reviewer's comment(s):
The evidence submitted by the applicant supports the content validity of the HCMSQ-SB and the KCCQ-23 CSS in the proposed context of use.

Reference: FDA COA Consult Review for camzyos

Qualitative evidence supported COA selection (n=10/13), with methodological comments highlighted

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Response options and recall period debriefed on first appearance only

- "Unclear as to whether the **response options** are optimal and/or appropriate for all measurement concepts…as understanding and appropriateness were made only consistently at **time of first appearance of the option type**"
- "Regarding participant comprehension of the response options, the applicant stated that they **did not consistently query about recall period across instructions and items.**"

Reference: FDA COA Review for ogsiveo

Patient standalone interviews, clinician interviews
Small molecule
Desmoid tumors
PRO, Secondary

Lack of input from clinicians to confirm relevance

- "The applicant **did not conduct qualitative interviews with clinicians**. Based on discussion with Clinical, pustules, erythema, and scaling are considered **clinically relevant to the target population**. However, in the absence of cognitive interviews with clinicians, it is **unclear** whether the GPPPGA is **well-understood and interpreted appropriately across clinicians.**"

Reference: FDA COA Review for spevigo

Patient focus groups, survey, patient advisory board
Biologic
Generalized pustular psoriasis flares
ClinRO, Primary

Qualitative evidence provided contextual information to interpret COA-based endpoints (n=3/9)

"The qualitative interviews suggested the majority of patients reported that **pre-treatment expectations for cilta-cel had been met or exceeded** and their **experience** with cilta-cel **was better than with prior MM treatments**. All of these measures **suggest improved HRQoL following treatment** with cilta-cel."

FDA Clinical Review and Evaluation for carvykti, cell therapy, multiple myeloma

"In the long-term adult and pediatric extension studies, COA endpoints didn't reach statistical significance, but a **positive effect was observed** which was **indicative of additional benefits as noted by patient and/or caregivers**."

EPAR, Xenpozyme, biologic, Non–central nervous system manifestations of acid sphingomyelinase deficiency

"All patients appeared to experience a **meaningful improvement in core signs and their most bothersome symptom**…Patients **experienced complete resolution of their core signs and symptoms**, which has a **positive impact in how subjects felt and functioned**…However, given the open-label nature of the study design, knowledge of treatment assignment may lead to overestimation of treatment effect. Therefore, data from the **COAs and qualitative interviews** were evaluated to provide **contextual information for regulatory decision-making**."

FDA BLA Multi-Discipline Review for veopoz, biologic, CHAPLE disease

Qualitative evidence provided contextual information to inform within-person meaningful change thresholds (n=6/9)

"Quantitative anchor-based analyses and qualitative insights from exit interviews **suggested that 'no change'** may be **important and meaningful to patients**…"

Ref: FDA COA Review for altuviio

Patient exit interviews
biologic
Hemophilia A
PRO
Secondary endpoint

"…anchor-based analyses were not conducted due to the lack of an appropriate anchor scale and small sample sizes. As such, **the evaluation of meaningful change relied solely upon qualitative evidence** submitted by the Applicant."

Ref: FDA Integrated Review for miplyffa

Patient, caregiver and clinician interviews
Small molecule
Niemann-Pick Disease, Type C
ClinRO
Co-primary and secondary endpoints

"Qualitative **exit interview findings along with PRO analyses** indicated that **>=1 category change for improvement** on the PGI-S was **considered to be meaningful**…"

Ref: FDA Multi-Discipline Review for yorvipath

Patient standalone and exit interviews, clinician interviews
Biologic
Hypoparathyroidism
PRO
Secondary endpoint

While qualitative evidence informed within-person meaningful change, comments were made on the methodological approach

Smallest level of change queried in qualitative exit interviews without primary anchor

- "The qualitative results are difficult to interpret as **participants were queried on the smallest level of change**. Further, **the primary anchor** (i.e., PGIS-Physical Function) was **not used in the meaningful change** exercises."
- "…DCOA previously commented on the design of the exit interview study…Some of the comments were related to the structure of the meaningful change exercises. For example…
  - Explore participants' thoughts on what they believe **constitutes a meaningful change** (improvement or deterioration) **in terms of PGIS/PGIC category** changes (e.g., 1-category change, 2-category change, etc.).
  - Focus on what constitutes a **meaningful change from the patient perspective**, **rather than the smallest level of change.**"

Reference: COA Review for romvimza

Patient standalone interviews, exit interviews, clinician interviews
Small molecule
Tenosynovial giant cell tumour
PerfO, PRO
Secondary endpoint

Hypothetical discussion of meaningful change in absence of benefit-risk of treatment

- "The patient and caregiver qualitative meaningful change interview results should be interpreted with caution given the hypothetical nature of the interview for respondents in the absence of benefit-harms considerations. Further, the interview was structured to prompt respondents regarding a 1-level change rather than an open-ended question allowing respondents to specify a specific change level, which may have influenced patients and caregivers to provide the 1-level response."
- "Typically, qualitative meaningful within-patient change evidence is derived from clinical trial exit interviews to facilitate the comparison and integration of qualitative patient/caregiver responses with quantitative anchor-based evidence. The qualitative evidence summarized here does not provide direct evidence from patients as it would for a mixed methods approach and was a hypothetical exercise for respondents."

Reference: Integrated Review for miplyffa

Patient, caregiver and clinician interviews
Small molecule
Niemann-Pick Disease, Type C
ClinRO
Co-primary and secondary endpoints

Qualitative evidence would have supported interpretation of meaningful within-patient changes (n=2/18)

- In two additional case studies, small sample sizes limited anchor-based analyses and hindered interpretation of within-person meaningful change on COA-based endpoints.

- The FDA noted that qualitative data would have strengthened the assessment of clinically meaningful within-patient change

> • Anchor-based methods to identify clinically meaningful within-patient change may be challenging to interpret when sample sizes are small. Therefore, we emphasize the importance of alternative methods such as qualitative research with the target patient population to understand meaningful change, which can be done within the clinical trial aligned with completion of the study (i.e., exit interview study) or outside the clinical trial (i.e., standalone qualitative study).

Reference: FDA COA Consult Review for spevigo

Qualitative evidence informed the benefit-risk evaluation (n=6/18)

- Qualitative evidence was mentioned as part of benefit-risk discussions providing supportive testimonies of treated patients feeling better, positive perception and improvement in treatment, and documenting the most bothersome symptoms and impacts on HRQoL

Fatigue is one of the most debilitating symptoms reported by PNH patients (Hill *et al.* 2007). Patient-reported fatigue improved with iptacopan, with a treatment difference in adjusted mean change from baseline in FACIT-F score of 8.29 points (unadjusted two-sided p<0.0001). The latter was greater than the protocol pre-specified 5-point change. Although the patients' awareness of treatment group assignment may have influenced score ratings in favour of iptacopan, the order of magnitude of the score difference in the FACIT-fatigue score suggests a true beneficial effect on fatigue. This is physiologically plausible as this went along with significant Hb increases. Patient interviews concerned the relevance of the concepts measured by the FACIT-fatigue score, advantages and disadvantages of study treatment and changes in PNH disease experience. Patients found that the concepts captured by the FACIT-fatigue score adequately reflected their disease experience. Further, treatment with iptacopan was perceived as advantageous. Thereby, the patient interviews supported a positive patient reported outcome associated with iptacopan.

Reference: EPAR for fabhalta, discussion on clinical efficacy

The Applicant conducted an exit interview substudy to provide further support for the content validity of the FCS-SIS and to facilitate the interpretation of the olezarsen clinical trial results. While the Applicant generated qualitative data to interpret olezarsen clinical trial results, the data are difficult to interpret due to limitations of the substudy (i.e., exit interviews conducted in the OLE phase of Trial CS3).

The data from Trial CS3 demonstrated that for olezarsen (80 mg and 50 mg) there was no change from baseline differences in any of the PRO scores compared with placebo. However, the data from the exit interview substudy indicated that a total of 14 of the 18 patients (78%) reported improvement in at least one of their pre-trial symptoms and impacts and most improvements were considered meaningful.

Reference: FDA Integrated Review for tryngolza, COA evaluation of clinical benefit

Summary

- Qualitative evidence is being reviewed by regulators in their decision-making for rare disease product approvals to identify **concepts of interest**, **justify COA selection**, and inform **interpretation of endpoints** and **benefit-risk evaluations**.

- Qualitative data plays a **critical role in rare diseases** by providing **first-hand insights** into the patient experience.

- The case studies highlight the importance of adopting **scientifically rigorous methods** for generating qualitative research, in line with **key guidance documents** and **best practices.**

- Thoughtful **consideration to designing qualitative studies,** particularly when the goal is to evaluate content validity and meaningful change of COAs.

Panel Discussion and Q&A

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Thank You!

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