

Clinical Outcome Assessment Endpoints for Rare Diseases: Challenges and Methods for Clinical Trials

Dennis A. Revicki, PhD; Evidera, Bethesda, MD, USA

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- Rare diseases affect small populations of patients, often across age ranges and disease progression; however, approximately 75% of rare diseases affect children.
- Developing clinical outcome assessment (COA) measurement strategies are challenging because of genotype/phenotype variations and heterogeneity in severity.
- The United States (US) Food and Drug Administration's (FDA) patient-focused drug development ensures that the patient (and caregiver) perspective is considered in the identification of important measurement concepts and in the design of study methods.
- EURORDIS emphasized the need to assess treatments from the patient's perspective in terms of impact on daily living and functioning.
- Patients often focus on symptoms and their impact on functioning and well-being (i.e., health-related quality of life).

- Heterogeneity in disease presentation, course, and response to treatment in individual diseases
- Unknown or incomplete understanding of disease natural history
- Large number of rare diseases that affect vulnerable populations (i.e., children)
- Rare diseases may be associated with significant—often progressive—disability and cognitive impairment.

- The objective of this presentation is to identify the challenges and potential solutions for selecting, developing, and implementing COAs, including patient-reported outcomes (PRO), in rare disease clinical trials.

- Three attributes are important in determining COAs for clinical trials:
 - Understanding the disease
 - Conceptualizing treatment benefit
 - Selecting/developing the outcome measure

Summary of Challenges

Understanding the Disease or Condition

What is known about the condition?

- Natural history data may be limited
- Heterogeneity in clinical manifestations

How is it treated?

- Disease-specific treatments may not exist
- Treatment variation across regions, age, groups, payers, subgroups

How does condition impact patients and caregivers?

- May differ by disease stage, subtype, age, region
- Little data may exist

Conceptualizing Treatment Benefit

What constitutes meaningful treatment benefit?

- ID of a single COI may be difficult due to heterogeneity of RD subpopulations
- A responder to treatment may be defined differently across subgroups
- Direct measures of treatment benefit (how patients feel and function) may not be possible

How will the clinical study be designed (i.e., the COU)?

- Difficulty with patient recruitment results in less restrictive entry criteria to achieve maximum sample size possible
- Need for creative study design and analysis

Which COA types are needed?

- PRO measure often unfeasible
- ClinRO measure may need to be general in nature
- ObsRO measure must be based on observations--not proxy measures
- PerFO measure development standards are not established

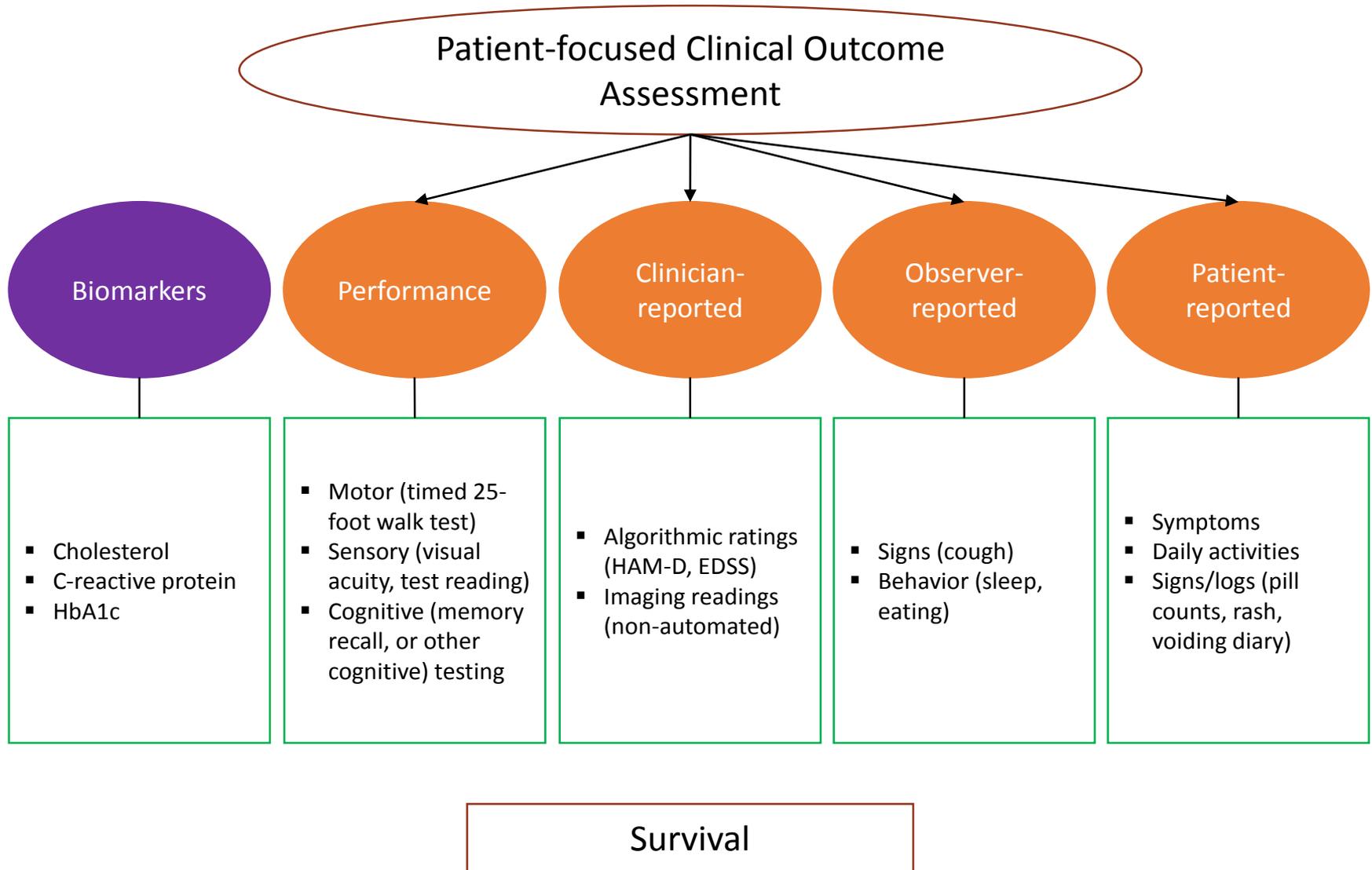
Selecting/Developing Outcome Measure

Are there any extant COAs that are appropriate?

- The answer is usually "no"
- Modification of extant COAs is still time-consuming, but usually quicker than development of a new COA
- Time and resources may not be available for modification or development of a new COA

How to develop or adapt the COA for COU?

- Traditional methods may not be feasible
- No "one-size-fits-all" solution exists
- Difficulty with recruitment for patient engagement and qualitative research
- Need for creativity in COA development methods



- Challenges understanding the rare diseases include incomplete natural history data and heterogeneous disease presentation and patient experience.
- Potential solutions include identifying all available information sources—including expert clinicians, patient advocacy groups, and qualitative research—to develop a better understanding of disease natural history.

- For conceptualizing treatment benefit, understanding the patient's perspective is a challenge, given difficulties in defining context of use because of variations in age and disease severity and progression.
- Strategies include focusing on common symptom subgroups, identifying short-term outcomes, and including several COAs to assess similar concepts.

- For selecting or developing COAs or PROs, challenges include relatively small patient samples and heterogeneity of disease experience.
- Potential solutions include adapting existing measures or item banks (i.e., Patient-Reported Outcomes Measurement Information System [PROMIS], Quality of Life in Neurological Disorders [NeuroQoL]), developing new symptom or function measures, or using generic measures that have demonstrated psychometric properties in similar, but more common diseases.

- There are additional challenges associated with pediatric outcome assessment in terms of stage of development and proxy versus self-reported measures.

- FOP is a rare and progressive genetic condition that involves uncontrolled extraskeletal bone formation (Cohen et al. 1993).
- Currently, there are 800 people diagnosed with FOP worldwide, and it is estimated that there are 3,300–4,000 affected persons based on point prevalence data of approximately 1:2,000,000 (Kaplan et al. 2008).
- FOP is associated with symptoms that typically present around 2–4 years of age, with immobility by a patient's mid-twenties and a shortened life expectancy of approximately 56 years old (Kaplan et al. 2010).
- By 15 years of age, most patients have multiple joints locked-up, including the neck, spine, shoulder, and hip (Cohen et al. 1993).
- Physical functioning declines significantly as FOP progresses.

Sources: Cohen RB, et al. J Bone Joint Surg Am. 1993;75(2):215-9;
Kaplan FS, et al. Best Pract Res Clin Rheumatol 2008;22:191-205;
Kaplan FS, et al. J Bone Joint Surg Am. 2010;92:686-91.

- Objective was to develop a measure of physical function (PF) for adults with FOP.
- PROMIS physical function item banks (Hays et al. 2013) provide a rich source of content for developing disease-targeted outcome measures.

- We reviewed the PROMIS PF item bank for relevant items for FOP, and 44 PF items were identified.
- We then conducted concept elicitation (CE) interviews in 21 patients diagnosed with FOP (with varying levels of disease severity) who attended the 25th International FOP Association meeting in Orlando, FL during the Fall of 2013. Three additional participants only completed the questionnaire.
- Interview data were analyzed to identify concepts of physical functioning that were impacted by FOP.
- Based on the CE findings and PF item data, 26 items were initially selected for the new measure.
- Clinical experts in FOP reviewed the proposed set of items, and five additional items were incorporated into the draft measure.

Are you able to put on a shirt or blouse?

Are you able to cut your food using eating utensils?

Are you able to wash and dry your body?

Are you able to get in and out of bed?

Are you able to go for a walk of at least 15 minutes?

Response scale ranges from “without any difficulty” (5) to “unable to do” (1).

- Comprehension of item content, recall period and response options, and item appropriateness, relevance, and redundancy were assessed in 10 cognitive interviews with FOP patients.
- The cognitive interviews demonstrated that, for the majority of participants, the FOP-PFQ items were relevant and well-understood.
- Instructions, item content, response scales, and recall period were comprehensive, clear, and relevant for most study participants.
- Several modifications were recommended to increase clarity and accuracy of responses.
- The final FOP-PFQ contains 28 items covering mobility, upper extremity function, and transferring between various positions (e.g., lying in bed to standing).

- Qualitative research supports the content validity of the FOP-PFQ and illustrates the application of PROMIS item banks for efficient, new instrument development in a rare and disabling genetic disease.
- Items were identified from the PROMIS PF item bank, which were supplemented by additional item development.
- Instructions, item content, response scales, and recall period were found to be comprehensive, clear, and relevant by most study participants.
- Additional research is needed to evaluate the psychometric properties of the FOP-PFQ.
- The FOP-PFQ is currently included in a clinical trial of a potential treatment for FOP (NCT02190747) and a natural history study of FOP (NCT02322255).

- Clinical trials in rare diseases need to include psychometrically sound and sensitive COAs and PROs:
 - To provide the patient perspective on treatment benefit
 - To translate biomarkers and other clinical endpoints into outcomes that are meaningful to patients and their families.