

Considerations for Clinical Outcome Assessment Development

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- The views expressed in this presentation are those of the speaker and do not necessarily represent the views of the FDA



Overview

- Defining Clinical Outcome Assessments (COAs)
- Perspectives on Selecting or Developing COAs
- FDA Review Considerations for COAs

Defining COAs



- COAs measure or describe **how a patient feels, functions, or survives**
- COAs are different from biomarkers
- Types of COAs include:
 1. Patient-reported outcome (PRO) assessments
 2. Clinician-reported outcome (ClinRO) assessments
 3. Observer-reported outcome (ObsRO) assessments
 4. Performance outcome (PerfO) assessments

Selecting or Developing COAs



- Designing a patient-focused measurement strategy for a clinical trial requires understanding of the disease or condition itself, possible clinical benefits of the intervention, and what is important to patients/caregivers
- The roadmap to patient-focused outcome measurement in clinical trials can be described as:
 1. **Understanding the disease or condition**
 2. **Conceptualizing clinical benefit**
 3. **Selecting or developing the COA(s)**

Understanding the Disease or Condition



- Natural history of the disease or condition
 - e.g. by onset/duration/resolution, diagnosis, pathophysiology, range of manifestations
- Patient subpopulations
 - e.g. by severity, onset, comorbidities
- Healthcare environment
 - e.g. treatment alternatives, clinical care standards, healthcare system perspective
- **Patient/caregiver perspectives**
 - e.g. regarding definition of clinical benefit, benefit-risk tradeoffs, impact of disease

Conceptualizing Clinical Benefit

- Identify **concept(s) of interest (CoI)** for meaningful clinical benefit
 - e.g. survival, feeling, functioning
- Define the **context of use (CoU)** for the clinical trial
 - e.g. disease/condition entry criteria, clinical trial design, statistical analysis plan
- Determine COA type(s)
 - e.g. PRO, ObsRO, ClinRO, PerfO (motor, sensory, cognition)

FDA Review of COAs

- FDA evaluates a COA instrument in the context of its intended use, including study objectives, clinical trial design, patient population, and desired labeling claim(s)
- In other words, there is no such thing as instrument validation for all purposes
- The FDA PRO Guidance (2009)* describes good measurement principles applicable to all COA types

*FDA Guidance for Industry: *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. December 2009. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims>

FDA Review of COAs

- Characteristics of COAs that are reviewed by the FDA include (but are not limited to):
 1. Conceptual framework
 2. Evidence of **content validity**
 3. Evidence of other measurement properties
 - a. Reliability
 - b. Construct validity
 - c. Ability to detect change
- Additionally, interpretation of COA scores (including **clinically meaningful within-patient change**)



Content Validity

- The extent to which the content of a COA instrument represents important aspects of a given concept for the intended use and target population
- Content validity is supported by qualitative and quantitative evidence
- It is important to **document relevant stakeholder input** (e.g., from **interviews with patients, caregivers, etc.**)

Other Measurement Properties

- Aside from content validity, other measurement properties are reviewed, including:
 1. Reliability (*how reproducible is the measure?*)
 2. Construct validity (*e.g., are the quantitative associations with other variables as expected?*)
 3. Ability to detect change
- If possible, these measurement properties should be evaluated in exploratory studies (e.g., prior to phase 3) to ensure that the COA is performing as expected and reveal potential issues with the COA before it is used in phase 3 trials

Interpretation of Meaningful Change

- Statistical significance alone does not indicate whether an **individual patient** has experienced a **meaningful clinical benefit** (and statistical significance is not always feasible, e.g., in small trials)
- FDA recommends **anchor-based methods** to facilitate interpretation of what constitutes a meaningful within-patient change in COA scores
- Selection of appropriate external anchors is very important for interpreting meaningful within-patient change

Closing Thoughts

- Talk to FDA early in, and throughout, the drug development process
- FDA Guidance documents are valuable sources of information regarding FDA's current thinking on topics



Resources

1. [FDA Guidance: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims](#)
2. [FDA Guidance: Patient-Focused Drug Development: Collecting Comprehensive and Representative Input](#)
3. [FDA **DRAFT** Guidance: Patient-Focused Drug Development: Methods to Identify What Is Important to Patients Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders](#)

FDA Guidances are available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>



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