

# Endpoint Selection and Use of Clinical Outcome Assessments (COAs) in Rare Disease and Pediatric Trials

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*Advancing the Development of Pediatric Therapeutics (ADEPT 6): Pediatric Clinical Trial  
Endpoints for Rare Diseases With a Focus on Pediatric Patient Perspectives  
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# Role of Patient Perspective

Dr. Janet Woodcock:

- “It turns out that what is really bothering the patient and what is really bothering the doctor can be radically different things....patients are true experts in their disease.”
- “It's clear you have to start with an understanding of the impact of the disease on the people who have it, and what they value most in terms of alleviation before you set up a measurement and go forward with truly patient-focused drug development.”

(PDUFA V Clinical Outcome Assessment Public Workshop, April 2015)

# Measuring Clinical Benefit

- Clinical benefit is demonstrated through evidence showing that the treatment has a positive impact on:
  - How a patient feels or functions in daily life
  - How long a patient lives (survival)
- Clinical outcome assessments (COAs) as measures of clinical benefit
  - **Clinician**-reported outcomes (ClinROs)
  - **Observer**-reported outcomes (ObsROs)
  - **Patient**-reported outcomes (PROs)
  - **Performance** outcomes (PerfOs)

# Why COAs?

- Measure or reflect a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions
- May be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of clinical benefit

# Rare Disease

- Defined as a disease/condition that affects <200,000 people in the US
- Over 7,000 identified rare diseases
- 85% are genetic
- **50% affect children**

# Some Challenges in Rare Disease Drug Development



- Adequate patient enrollment
- Heterogeneous patient population
- Lack of informative natural history data
- Trial design
  - Defining the patient population
  - Treatment target and measurement concepts
  - Selection of COAs
    - **Pediatric patient perspective: limited use of PROs and high use of ObsROs and PerfOs**
  - Selection of COA endpoint(s)
  - Interpretation of COA endpoint(s) results

# Natural History Data

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## Rare Diseases: Natural History Studies for Drug Development Guidance for Industry

### *DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lucas Kempf at 301-796-1140; (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010; or Office of Orphan Products Development (OOPD) at 301-796-8660.

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Rare Diseases

- “Comprehensive knowledge of a disease can help design and conduct **adequate and well-controlled** clinical trials of **adequate duration** with **clinically meaningful endpoints...**”
- Clinically meaningful and relevant endpoints require **informative natural history studies and patient input**
  - Patient-focused drug development (PFDD) meetings



# Target patient population

- Limited knowledge related to the likelihood, range, and course of clinical manifestations associated with the disease
- Uncertainty regarding clinical characteristics (manifestations and timing)
- Heterogeneity in clinical manifestations and rate of change
- **Pediatric population**
  - Cognitive and linguistic developmental differences
  - Potential differences in disease manifestations by age subgroups

# Treatment Target and Measurement Concepts



- Uncertainty about aspects of the disease that are meaningful to the patient and caregivers and that **might also be affected by the treatment**
- The complexity of the measurement concept and the assessment methods used to measure these concepts

# Selection of COAs

- **Part of the overall trial design challenge**
  - Need to understand natural history of the disease
- COAs need to be fit-for-purpose
- **Pediatric population considerations:**
  - PRO, ObsRO, ClinRO, or Perfo?
  - Willingness and ability to self-report
  - Willingness to perform a particular task
  - Ability and motivation to comply with study assessments
  - If the impact of a disease or condition on how patients feel and function differs across the age span, different COAs may be needed
  - If modifying an existing COA (e.g., for use in a new age group), involve the target population and document the process

# Some Considerations with the Use of COAs



- **Limited use of PROs in pediatric trials**
- ObsRO should focus on directly observable behaviors, signs, and verbalizations
- ClinRO
  - Standardized rater training, rating assessments, and case report form
  - Intra- and Inter-rater reliability
  - Use of central blinded rater(s) or expert panel
  - Adjudication process for disagreements among raters
- PerfO
  - Use of assistive device
  - Learning/practice effects
  - Baseline assessment of cognitive function for subjects

# COA Endpoint Selection in Rare Disease



- Binary endpoint (dichotomized from either ordinal or continuous COA data)
  - Need to pre-specify a single responder threshold that constitutes a clinically meaningful within-patient change
  - Risk of misclassifying patients
- **Continuous or ordinal endpoints**
  - Tend to have more precision in the evaluation of drug effects given small sample size
  - Need to evaluate and justify the clinical relevance of any observed treatment effect

# Multi-Domain Responder Index (MDRI)



- Combining multiple individual endpoints with a pre-specified responder threshold for each endpoint
- Multiple ways to construct an MDRI endpoint
  - One example:

Individual endpoint(s) score	Overall MDRI response (1/0)
+1 = improvement 0 = no change -1 = decline	1 = if any individual endpoint shows improvement

# Important Considerations for MDRI



- Requires clearly defined and clinically relevant endpoints with appropriate pre-specified responder thresholds
- Choice of individual endpoints relies on the requirement that all endpoints are of reasonably similar clinical importance
  - An effect on the MDRI can be primarily or entirely driven by effect on only one individual endpoint
- Degree of improvement and deterioration is often not symmetric
- Amount of missing data for each individual endpoint of the MDRI

# Considerations for Individualized Endpoints

- Example: measuring the most bothersome symptom
- Process to construct an individualized endpoint should be standardized, and criteria for selecting the COAs should be consistent across sites and patients
- Same set of COAs should be assessed for all patients, regardless of their own individualized endpoints
  - Allows for an assessment of new or worsening symptoms and/or functional limitation(s) during the trial duration



# Clinically Meaningful Within-Patient Change



- Why do we care?
  - Statistical significance can be achieved for small differences between comparator groups
    - Does not indicate whether individual patients experienced meaningful clinical benefit
  - Need to assess improvement and deterioration from the **patients' perspective**
  - To ensure that benefit of treatment outweighs the risk
- Multiple mixed method approaches
  - A range of values likely to represent meaningful change in the outcome of interest
  - Quantitative methods, e.g. anchor-based methods
  - Other methods, e.g. **exit interviews**

# Exit Interviews

- Can be used to collect qualitative and quantitative data about patients' experience of disease or treatment burden and changes during the course of the clinical trial
- Requires careful planning and considerations
  - Informed consent
  - Sample size/representativeness of the overall sample
  - Interviewer training
  - Blinding, etc.

# Summary

A well-planned COA strategy in rare disease and pediatric trials is critical to support the selection and interpretation of COA endpoints

