Use of Patient-Reported Outcome Measures in Nontuberculous Mycobacterial Trials

Development of Antibacterial Drugs for Treatment of NTM Disease

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Overview

• Regulatory considerations for clinical outcome assessment (Fit-for-Purpose COAs)
• Roadmap for patient-focused outcome assessment
• FDA review and advice pathways
Measuring Clinical Benefit

• FDA is focused on involving the patient in drug development, and assessing what is relevant and important to patient

• Clinical Benefit--A positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives

• Assessments of how patients feel (symptoms) or function may be essential for approval decisions and provide important information for labeling
Digital health technology tools (e.g., activity monitors, sleep monitors) can also be used to collect clinical outcomes.

**ClinRO**
A measurement based on a report that comes from a trained health care professional after observation of a patient’s health condition.

**PRO**
A measurement based on a report that comes directly from the patient about the status of the patient’s health condition without interpretation of the patient’s response by a clinician or anyone else.

**ObsRO**
A measurement based on a report of observable signs, events or behaviors related to a patient’s health condition by someone other than the patient or a health care professional.

**PerfO**
A measurement based on a standardized task(s) performed by a patient that is administered and evaluated by an appropriately trained individual or is independently completed.

*Digital health technology tools (e.g., activity monitors, sleep monitors) can also be used to collect clinical outcomes.*
• *Patient-reported outcome (PRO)* —

A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient’s health condition without amendment or interpretation of the patient’s response by a clinician or anyone else.

  – Examples: pain, cough, shortness of breath, rescue medication use, performance in daily activities
Fit-for-Purpose*

• For medical product development tools:
  – A conclusion that the level of validation associated with a tool is sufficient to support its context of use

*BEST (Biomarkers, EndpointS, and other Tools) Resource
https://www.ncbi.nlm.nih.gov/books/NBK338448/
What is a “Fit-for-Purpose” COA?

• Appropriate for its intended use e.g.,
  – Study design
  – Patient population

• Validly and reliably measures concepts that are
  – Clinically relevant
  – Important to patients

• Can be communicated in labeling in a way that is accurate, interpretable, and not misleading (i.e., well-defined)*

* If the COA is appropriately applied in medical product development
Good Measurement Principles

- FDA PRO Guidance defines good measurement principles to consider for “well-defined and reliable” (21 CFR 314.126) PRO measures

- All COAs can benefit from the good measurement principles described within the Guidance

- But, judgment and flexibility are needed!
But what about in NTM?
Voice of the Patient Report

- From the 2015 PFDD Meeting, patients described symptoms and impacts on daily life:
  - Coughing
  - Fatigue
  - Shortness of Breath
  - Ability to perform activities
  - Stigma and embarrassment
  - Impact on career and work life
Engage FDA early and throughout medical product development

Understanding the Disease or Condition

A. Natural history of the disease or condition:
   - Onset/Duration/Resolution
   - Diagnosis
   - Pathophysiology
   - Range of manifestations

B. Patient subpopulations:
   - By severity
   - By onset
   - By comorbidities
   - By phenotype

C. Current Clinical Practice(s):
   - Clinical care standards
   - Treatment alternatives
   - Health care system
     (e.g. access to care)

D. Patient/caregiver/expert perspectives:
   - Definition of clinical benefit
   - Benefit-risk tradeoffs
   - Impact of disease

Conceptualizing Clinical Benefit

A. Identify concept(s) of interest for meaningful clinical benefit, i.e.,
   - How a patient:
     - Survives
     - Feels (e.g., symptoms)
     - Functions

B. Define context of use for clinical trials, for example:
   - Disease/Condition entry criteria
   - Clinical trial design
   - Endpoint definition
   - Endpoint positioning

Selecting/Developing/Modifying the Outcome Measure

A. Select clinical outcome assessment (COA) type:
   - Patient-Reported Outcome (PRO)
   - Observer-Reported Outcome (ObsRO)
   - Clinician-Reported Outcome (ClinRO)
   - Performance Outcome (Perfo)

B. Search for a COA measuring the concept of interest in context of use:
   - COA exists and is fit-for-purpose
   - COA exists but needs to be modified
   - COA under development
   - No COA exists (development needed)

C. Develop and Evaluate a COA:
   - Content validity
   - Reliability and construct validity
   - Ability to detect change
   - Interpretation of meaningful within-patient change
Considerations in Developing a PRO in NTM

• Understanding the natural history and disease progression of NTM
  – Are there different subgroups with different disease severity
  – How do physiological changes impact what can be measured

• Symptom based PRO vs Functioning PRO
  – In addition to symptoms what are other important outcomes?

• Talking with patients about their experience with NTM
  – What are the most impactful disease burden and treatment burden?
  – Are all symptoms or impacts alleviated after treatment?
Functioning: What Do We Mean?

• “Functioning” refers to how a patient functions in their daily life
• Different Components of Functioning:
  – Physical
  – Cognitive
  – Psychological
  – Sensory
  – Social
Defining Functioning: What Do Patients Say?

• Ability to actively participate in their family, social, and workplace lives
• Maintaining independence is key
• There are also individual differences in what is valued, both across patients and within patients over time
Key Considerations in COAs to Assess Functioning

• Do the items (or tasks) assess or reflect the important and relevant aspect(s) of the concept of interest (i.e., content validity)?
• Does the tool include instructions and standardization?
• Is it reproducible within and across raters?
• What is the assessment burden/feasibility?
• Is it appropriate for use in all cultures/languages in which clinical study(ies) will be conducted (e.g., multinational trials)?
• Is it sensitive to change and free of ceiling and floor effects?
• Are there significant practice effects (for PerfOs)?
• Are there instructions related to use of adaptive equipment?
• Are there guidelines for interpretation of meaningful within-patient change?
Pathways for FDA Clinical Outcome Assessment Review & Advice

**IND/NDA/BLA Pathway**
- **Within** an individual drug development program
- Investigational New Drug (IND) submissions to FDA
- Potential to result in *labeling* claims

**DDT COA Qualification Pathway**
- **Outside** of an individual drug development program
- Development of novel COAs for use in multiple drug development programs addressing unmet measurement needs
- Potential to result in *qualification* of COA

**Critical Path Innovation Meetings Pathway**
- **Outside** of an individual drug development program
- Potential for *general CDER advice* on specific methodology or technology (e.g., PRO) in its early stages of development
- Meetings are informal, non-binding discussions
Conclusions

• The FDA encourages the development and implementation of patient-focused clinical outcome assessments (COAs) in clinical trials to support drug approvals and labeling claims
  – Early patient input is critical in the road to patient-focused outcome measurement

• Understanding what you are able to measure using a COA will assist in endpoint development
  – Keep the end in mind

• Early communication with the FDA is encouraged
For More Information

• Clinical Outcome Assessment Qualification Program Webpage (includes Roadmap):

• Critical Path Innovation Meetings (CPIM):