U.S. FOOD & DRUG ADMINISTRATION

Use of Patient-Reported Outcome Measures in Nontuberculous Mycobacterial Trials

Development of Antibacterial Drugs for Treatment of NTM Disease

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Overview

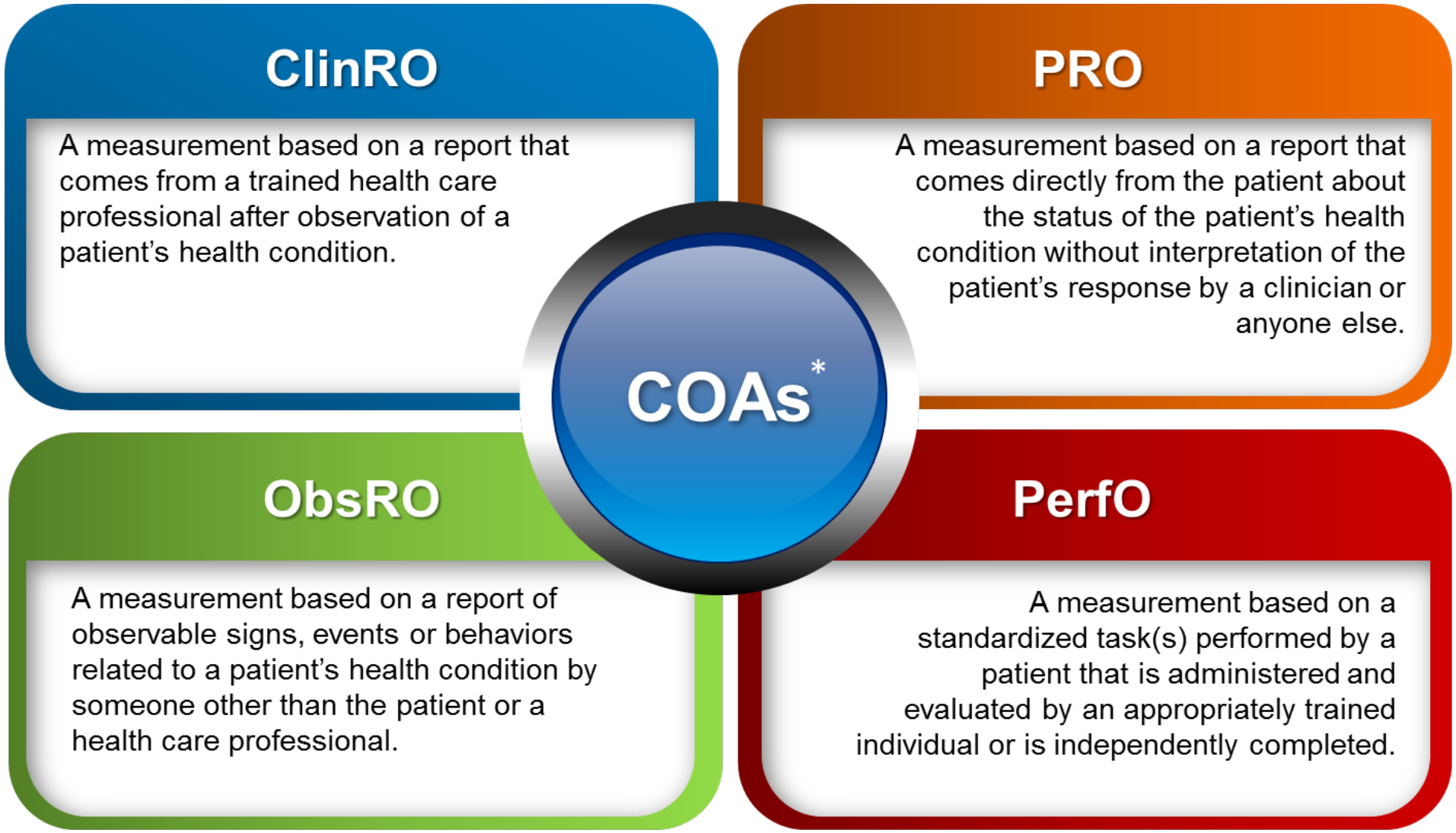
- Regulatory considerations for clinical outcome assessment (Fit-for-Purpose COAs)
- Roadmap for patient-focused outcome assessment
- FDA review and advice pathways

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.

- ***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

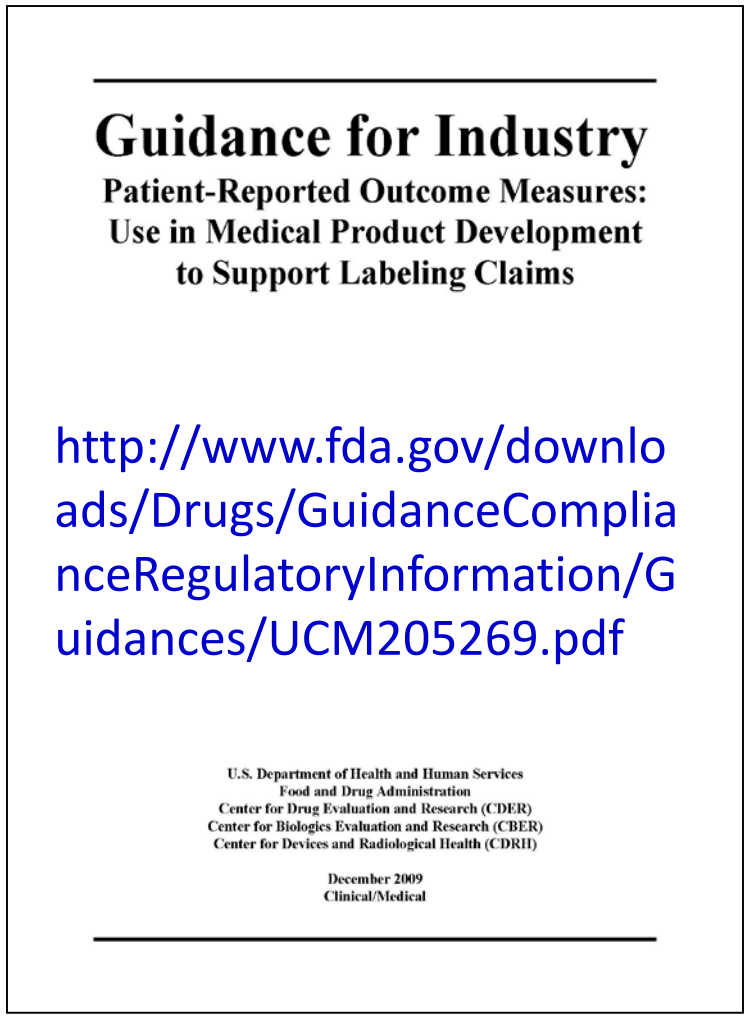
*BEST (Biomarkers, EndpointS, and other Tools) Resource
https://www.ncbi.nlm.nih.gov/books/NBK338448/

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



Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

- 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

1 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

2 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

3 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

Engage FDA early and throughout medical product development

www.fda.gov

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 work place 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):
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm

- Critical Path Innovation Meetings (CPIM):
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm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