Clinical Trial Endpoints from Mobile Technology: Regulatory Considerations

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Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

I have no actual or potential conflict of interest in relation to this activity.
Patient Centered Outcomes

Those outcomes important to patients’ survival, function, or feelings as identified or affirmed by patients themselves, or judged to be in patients’ best interest by providers and caregivers when patients cannot report for themselves.

Donald L. Patrick, Ph.D., MSPH
May 20, 2013
Clinical Benefit: How do we define it?

• A positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives.
  – How long a patient lives
  – How a patient feels or functions in daily life

• Can be demonstrated as either:
  – A comparative advantage in treatment of the disease or condition; OR
  – A comparative reduction in treatment-related toxicity

• Clinical benefit is described in labeling in terms of the outcome of interest measured
Clinical Benefit: How do we measure it?

- Clinical Outcome Assessment (COA)
  - An assessment that describes or reflects how an individual feels, functions or survives
    - Typically measure symptoms, overall mental state, or the effects of a disease or condition on how the patient functions

- A biomarker* is not an assessment of how an individual feels, functions or survives

*Biomarker: A defined characteristic measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention. Examples: molecular, histologic, radiographic, or physiologic characteristics.

Source: http://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-B
Types of Outcome Assessments

• Clinical outcome assessments (COAs)
  – Patient reported outcomes (PROs)
  – Clinician-reported outcomes (ClinROs)
  – Observer reported outcomes (ObsROs)
  – Performance outcomes (PerfOs)

• Biomarker-based outcomes
Performance Outcome (PerfO) Working Definition

A type of clinical outcome assessment. A measurement based on a task(s) performed by a patient according to instructions that is administered by a health care professional. PerfOs require patient cooperation and motivation. PerfO measures include:

- Measures of gait speed (e.g., timed 25 foot walk test)
- Measures of memory (e.g., word recall test)

Note: Measures of activity level/gait as measured by activity monitors can be considered examples of PerfOs.

http://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-P
Does the instrument measure the outcome of interest?

• Well-defined and reliable (21CFR 314.126)
• Appropriate for the target population
• Appropriate for the target indication
• Adequate measurement properties
  – Content validity - for a PerfO may be informed by a number of sources (e.g., literature, clinicians, patients, caregivers)
  – Construct validity
  – Reliability
  – Ability to detect change
Validation of a Mobile-Technology-Based PerfO (Slide 1/2)

- A multi-step process-
  - Analytical validation*: Establishing that the performance characteristics of a tool (i.e., device and algorithm) are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol
  - E.g., For an activity monitor targeting step count: Is the number of steps recorded an accurate representation of the true number?
  - This a complex issue and cannot be assumed in the real world. But, for the purpose of discussion at this workshop, we will assume that analytic validity has already been established.
Validation of the measurement’s usefulness in a clinical trial:

- Is the measurement reflective of a defined clinical benefit that’s relevant and important to a patient’s daily life functioning?

- How do we go from measurement to endpoint?
  - How do we aggregate the measurements into a meaningful endpoint?
  - What does the endpoint represent?
  - How do we interpret the meaningfulness of intra-patient change? Are there normative data to use as a reference point for interpretation?
Good Measurement Principles

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


- 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!
Roadmap to Patient-Focused Outcome Measurement in Clinical Trials

1. Understanding the Disease or Condition
   - A. Natural history of the disease or condition
   - B. Patient subpopulations
   - C. Health care environment
   - D. Patient/caregiver perspectives

2. Conceptualizing Treatment Benefit
   - A. Identify concept(s) of interest (COI) for meaningful treatment benefit
   - B. Define context of use (COU)
   - C. Select clinical outcome assessment (COA) type

3. Selecting/Developing the Outcome Measure
   - A. Search for existing COA measuring COI in COU
   - B. Begin COA development
   - C. Complete COA development
Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

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. Health care environment
     - Treatment alternatives
     - Clinical care standards
     - Health care system perspective
   - D. Patient/caregiver perspectives
     - Definition of treatment benefit
     - Benefit-risk tradeoffs
     - Impact of disease

2. **Conceptualizing Treatment Benefit**
   - A. Identify concept(s) of interest (COI) for meaningful treatment benefit, i.e., How a patient:
     - Survives
     - Feels (e.g., symptoms)
     - Functions
   - B. Define context of use (COU) for clinical trial:
     - Disease/Condition entry criteria
     - Clinical trial design
     - Endpoint positioning
   - C. Select clinical outcome assessment (COA) type:
     - Patient-Reported Outcome (PRO)
     - Observer-Reported Outcome (ObsRO)
     - Clinician-Reported Outcome (ClinRO)
     - Performance Outcome (motor, sensory, cognition)

3. **Selecting/Developing the Outcome Measure**
   - A. Search for existing COA measuring COI in COU:
     - Measure exists
     - Measure exists but needs to be modified
     - No measure exists
     - Measure under development
   - B. Begin COA development
     - Document content validity (qualitative or mixed methods research)
     - Evaluate cross-sectional measurement properties (reliability and construct validity)
     - Create user manual
     - Consider submitting to FDA for COA qualification for use in exploratory studies
   - C. Complete COA development:
     - Document longitudinal measurement properties (construct validity, ability to detect change)
     - Document guidelines for interpretation of treatment benefit and relationship to claim
     - Update user manual
     - Submit to FDA for COA qualification as effectiveness endpoint to support claims
Qualification of CLINICAL OUTCOME ASSESSMENTS (COAs)

- Identify Context of Use (COU) and Concept of Interest (COI)
- Draft Instrument and Evaluate Content Validity
- Cross-sectional Evaluation of Other Measurement Properties
- Longitudinal Evaluation of Measurement Properties/Interpretation Methods
- Modify Instrument

CONCEPT OF INTEREST = CLAIM

SPOKE I
SPOKE II
SPOKE III
SPOKE IV
SPOKE V
Evidentiary Considerations for Performance Outcomes

(For Discussion)

V. Modify Instrument

- Identify a new COU
- Change instrument content (includes procedures for administration/data collection)
- Translate and culturally adapt
- Evaluate modifications using spokes I – IV
- Document all changes

Consider submitting to FDA for qualification of new COA, as appropriate.

IV. Longitudinal Evaluation of Measurement Properties/Interpretation Methods

- Assess ability to detect change and construct validity
- Identify responder definition(s)
- Provide guidelines for interpretation of treatment benefit and relationship to claim
- Document all results
- Update user manual

Submit to FDA for COA qualification as effectiveness endpoint to support claims.

III. Cross-sectional Evaluation of Other Measurement Properties

- Assess score reliability and construct validity
- Confirm administration procedures & training materials
- Prepare user manual
- Document measure development

Consider submitting to FDA for COA qualification for use in exploratory studies prior to longitudinal evaluation.

II. Select or Create Instrument and Evaluate Content Validity

- Define tasks that are intended to reflect aspects of daily functioning consistent with the concept of interest and patient population
- Generate evidence based on patient input/caregiver/expert input (as appropriate) that the tasks are relevant for the population and reflect the concept of interest
- Develop administration procedures & training materials
- Pilot test PerfO to obtain patient and administrator input (including documentation of understanding) prior to larger scale studies
- Refine (as needed) and finalize instrument content
- Other ???

I. Identify Context of Use and Concept of Interest

- Obtain patient and SME input to determine concept of interest (concept measured should be of relevant and important to patients)
- Determine intended population
- Determine intended application/characteristics (type of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework (if the performance outcome is a composite of multiple scores)
- Position COA within a preliminary endpoint model
The Importance of the Context of Use

– Benefit-risk is based on totality of the evidence in the patient population of interest
  • No single outcome assessment is sufficient on its own
  • Different classes of outcome measures used in various combinations to support regulatory decisions
    – Clinical outcome assessments (e.g., patient reported outcomes, clinician reported outcomes, performance measures)
    – Biomarkers
    – Survival
  • The endpoint hierarchy with descriptions of measures and concepts should explain the relationships of endpoints in a clinical trial
Hypothetical Example: Chronic Fatigue Syndrome

• PRO: Fatigue and other symptoms
• PRO: Daily activities
• PerfO (Clinic-based): Exercise capacity
• PerfO (Mobile technology-based): Activity level
• Others
## Pathways for FDA Clinical Outcome Assessment Review & Advice

### 1. IND/NDA/BLA Pathway

**Within an individual drug development program**

- Investigational New Drug (IND) submissions to FDA
- Potential to result in **labeling** claims

### 2. 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

### 3. 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
Summary

• Evidentiary considerations for a mobile-technology based PerfOs are broadly similar to PROs and other types of COAs;
  – Flexibility and judgment important in evaluation

• But, additional evidence is needed to demonstrate
  – The performance characteristics of the mobile device have sufficient sensitivity, specificity, accuracy, and precision
  – The PerfO score and ultimately the endpoint represent important and relevant aspects of patients’ real world functioning

• As with any measure, we need to understand how much within-patient change in score makes a difference in patients’ lives
For more information

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

• Critical Path Innovation Meetings (CPIM):
Thank you!