Development and Validation of Clinical Trial Endpoints

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Goals of Talk

1. Introduce and define concept of endpoints

2. Discuss development & validation of clinical endpoints, for efficacy clinical trials
What is an endpoint?\textsuperscript{1-2}

The measurement that will be statistically compared among treatment groups to assess the effect of treatment and corresponds with the clinical trial’s objectives, design, and data analysis plan.
Why do we need endpoints in efficacy clinical trials? ¹,³⁻⁴, ⁹

...In order to demonstrate a treatment benefit

- improved survival
- improvement in symptoms or functioning
- delayed symptom onset, slower progression
- lower probability of developing disease
- fewer side effects, compared to other available treatments
## Endpoint terms

<table>
<thead>
<tr>
<th>What are we measuring?</th>
<th>Concept of Interest (COI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How are we measuring it?</td>
<td>Clinical Outcome Assessment (COA)</td>
</tr>
<tr>
<td>Why, where, when, &amp; with whom are we measuring it?</td>
<td>Context of Use (COU)</td>
</tr>
</tbody>
</table>
What are we measuring?

What is the clinical problem?
- Biologic, physiologic, symptomatic, functional

What are we doing to address this problem?

What is the intended outcome/concept/claim?
- Improve? Stabilize? Prevent?
Clinical Outcomes Assessment (COA)\textsuperscript{1,3,7,9}

**How are we measuring it?**

*How is this outcome currently defined & measured? (e.g., empirically or clinically)*

- Meaningful to patients?
- Is the measurement...?
  - **Objective**: survival, disease exacerbation, clinical event, etc.
  - **Subjective**: symptom score, “health related quality of life”, etc.
Context of Use

**Why, Where, When, & with Whom are we measuring it?**

**Why** was the endpoint established (intended purpose?)

**Where** will it be used?
- Geographic location? Language / culture?
- Clinical practice variations

**When** will it be used?
- Weekly? Monthly? Once a year?

**With Whom?** Patient sub-population?
Other characteristics of endpoints

- Well-defined and reliable
- Clinically relevant
- Interpretable
- Sensitive and able to detect change
- “Fit for Purpose”
- Ease of use
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
Guidance for Industry
Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

"Claim"
...any statement of treatment benefit

What is a biomarker?\textsuperscript{10}

- A lab measure
- Objectively measured
- Establishes biological activity of...
  - Normal biologic process
  - Disease
  - Response to treatment
Features of Validated, Surrogate Biomarker Endpoints for Efficacy Trials

- **Indirect** endpoints

- Ideally, should exist within the therapeutic pathway between the drug and meaningful benefit

- Expected to reflect changes in a clinically meaningful endpoint
Biomarker Qualification Program

The Biomarker Qualification Program was established to support CDER’s work with external scientists and clinicians in developing biomarkers. As an inter-Office collaborative endeavor within CDER, the Biomarker Qualification Program offers a formal process to guide submitters as they develop biomarkers and rigorously evaluate them for use in the regulatory process.

The goals of the CDER Biomarker Qualification Program are to:

- Provide a framework for scientific development and regulatory acceptance of biomarkers for use in drug development
- Facilitate integration of qualified biomarkers in the regulatory review process
- Encourage the identification of new and emerging biomarkers for evaluation and utilization in regulatory decision-making
- Support outreach to relevant external stakeholders to foster biomarker development

Biomarkers being considered for qualification are conceptually independent of the specific test performing the measurement. A biomarker cannot become qualified without a reliable means to measure it. However, FDA clearance of a testing device for marketing does not imply that the biomarker it measures has been demonstrated to have a qualified use in drug development and evaluation. Additionally, qualification of a biomarker does not automatically imply that a specific test device used in the qualification process for a biomarker has been reviewed by FDA and cleared or approved for use in patient care.

The biomarker may also have potential value outside the boundaries of the qualified context of use. As data from additional studies are obtained over time, submitters of biomarkers will be able to continue working with the Biomarker Qualification Program to submit additional data and expand the qualified context of use.
Guidance Documents (DDT)

- Guidance for Industry: Use of Histology in Biomarker Qualification Studies (PDF - 298KB) (December 2011)
- International Conference on Harmonization: Guidance on E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions (PDF - 111KB) (August 2011)
Conclusions

Clinical Trial Endpoints (Phase III studies)...

...use **validated** Clinical Outcome Assessments, to measure a specific Concept of Interest, for a specific Context of Use.

~and~

*Demonstrate a Treatment Benefit that is Clinically Meaningful*
Source Material

1. “Clinical trial endpoints: Development and validation of measures to support claims in labeling” Presented by Laurie B. Burke PhD, Associate Director for Study Endpoints and Labeling. At Office of New Drugs, CDER, FDA. Accelerating Therapies for Rare Diseases Workshop, October 19, 2010


3. “Exploring Clinical Outcome Assessments in Rare Disease Trials” Presented by Laurie B. Burke PhD, Associate Director for Study Endpoints and Labeling, Office of New Drugs, CDER, FDA, Rare Disease Workshop Series, June 14-15, 2011. Sponsored by: EveryLife Foundation for Rare Diseases

Source Material


8. EveryLife Foundation: Workshop 3, November 2011: Use of surrogate endpoints in rare disease treatment development
9. Sullivan, EJ. *Clinical Trial Endpoints*. FDA, CPI, CTTI


**General Reference:**