# Development and Validation of Clinical Trial Endpoints

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MEDICINE *of* THE HIGHEST ORDER

UNIVERSITY *of* ROCHESTER MEDICAL CENTER

# *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?*[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*

**benefits that matter to the patient**

- 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*

| | | |
|---|---|---|
| **What** are we measuring? | Concept of Interest | COI |
| **How** are we measuring it? | Clinical Outcome Assessment | COA |
| **Why, where, when, & with whom** are we measuring it? | Context of Use | COU |

# *Concept of Interest (COI)*[6]

## *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)*[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*[1, 3,6, 9]

***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*[1, 4-5, 9]

- 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

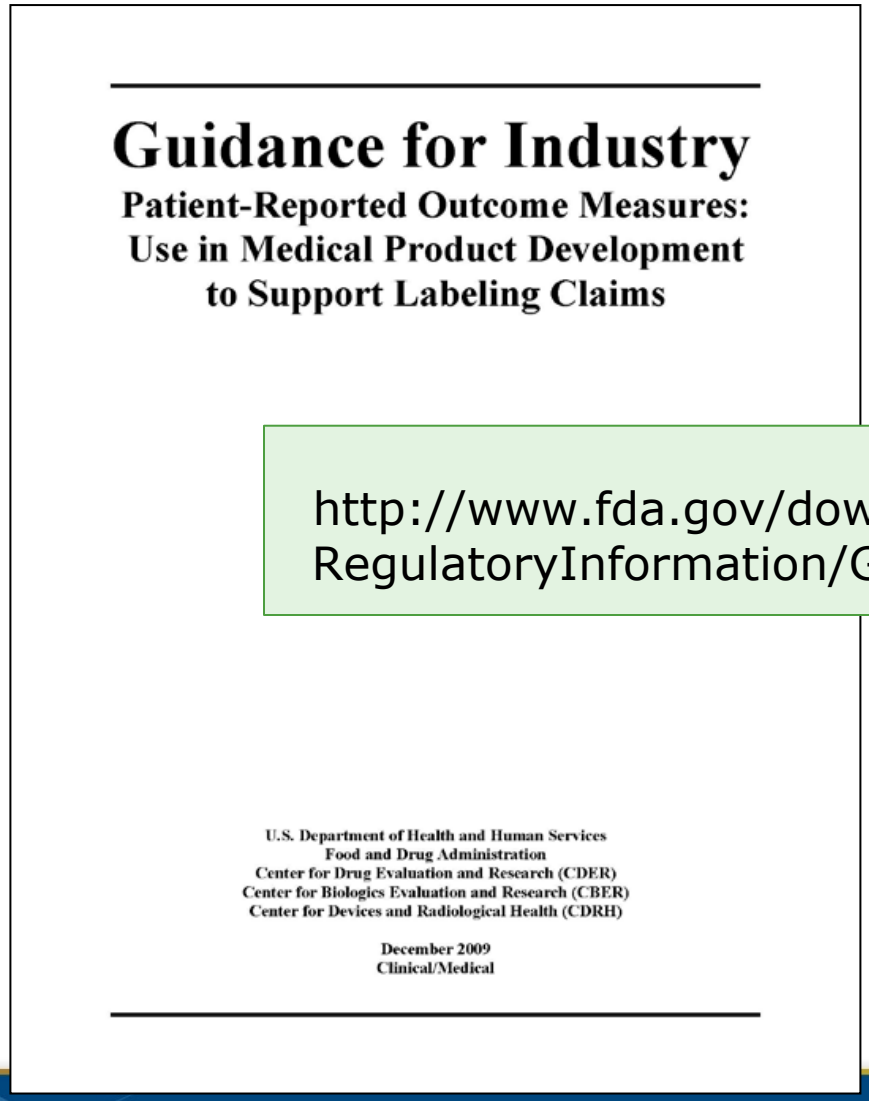
**A. Search for existing COA measuring COI in COU:**
- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

**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

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
http://www.fda.gov/Drugs

# FDA Patient-Reported Outcomes Guidance – Published in December 2009[1]



Guidance for Industry

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

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

"Claim"
...*any statement of treatment benefit*

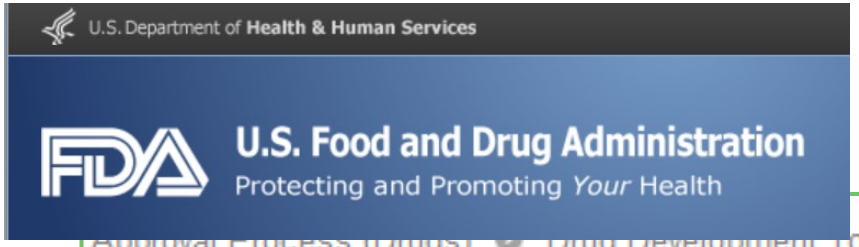
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf

# *What is a biomarker?*[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[11]

- Indirect endpoints
- Ideally, should exist within the therapeutic pathway between the drug and meaningful benefit
- Expected to reflect changes in a clinically meaningful endpoint




Approval Process (Drugs) › Drug Development Tools Qualification Program

## 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.

Internet | Protected M


& Approval Process (Drugs) ● Drug Development Tools Qualification Program

## Guidance Documents (DDT)

- *Guidance for Industry: Use of Histology in Biomarker Qualification Studies* (PDF - 298KB) (December 2011)
- *Guidance for Industry: Qualification Process for Drug Development Tools* (PDF - 189KB) (October 2010)
- 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)
- *Guidance for Industry: Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (PDF - 295KB) (December 2009)
- *Guidance for Industry: Animal Models – Essential Elements to Address Efficacy Under the Animal Rule* (PDF - 135KB) (January 2009)

# 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

2. **Drug Development Tools Qualification Program**: Clinical outcome Assessment (COA) Glossary of Terms. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm370262.htm

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

4. **"Establishing evidence of treatment benefit: focus on outcome assessment".** Presented by Elektra J Papadopoulos, FDA

# Source Material


5. Thomas R Fleming, PhD. "**Introduction to some important issues in evaluating efficacy".** June 14, 2011, Rare Disease Workshop Series – Improving the Clinical Development Process. Everylife Foundation.

6. Nancy Kline Leidy, PhD, VP Scientific Affairs, United BioSource Corporation, Bethesda, MD. **Addressing Content Validity of PRO Measures: The Unique Case of Rare Diseases.** Rare Disease Workshop Series – Improving the Clinical Development Process. Everylife Foundation.

7. Nunnally, J (1978). Psychometric Theory. New York: McGraw-Hill.

8. EveryLife Foundation: Workshop 3, November 2011: **Use of surrogate endpoints in rare disease treatment development**

# Source Material

9. Sullivan, EJ. **Clinical Trial Endpoints.** FDA, CPI, CTTI

10. BIOMARKERS DEFINITIONS WORKING GROUP: BIOMARKERS AND SURROGATE ENDPOINTS: PREFERRED DEFINITIONS AND CONCEPTUAL FRAMEWORK. CLIN PHARMACOL THER 2001;69:89-95.

General Reference:

**Review & Qualification of COA: Public Workshop** 10/19/2011; White Oak. http://www.fda.gov/drugs/newsevents/ucm276110.htm