

A group of several bright orange, round pills is shown in the upper left corner, blurred to create a sense of depth and movement.

# The Role of Patients in Health Outcomes Assessment: A Regulatory Perspective



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Focused Drug Development  
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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.

# Treatment Benefit

- Treatment benefit is demonstrated by evidence that the treatment has a positive impact on how a person with the condition or disease:
  - Survives
  - Feels or Functions in daily life

# Purpose of “Outcome Assessment”

- To determine whether or not a drug has been shown to provide benefit to patients
- A conclusion of treatment benefit is described in labeling in terms of the concept of interest (outcome) measured
- One of the most important aspects of drug development is how that benefit is measured

# Types of Outcome Assessments

- Survival
- Clinical outcome assessments (COAs)
  - Performance outcomes (PerfOs)
  - Clinician-reported outcomes (ClinROs)
  - Observer-reported outcomes (ObsROs)
  - Patient-reported outcomes (PROs)
- Surrogates
  - Often a biomarker\* that is intended as a substitute for how a patient feels, functions, or survives
  - Two types for use in clinical trials to support product approval:
    - Established Surrogates (for regular approval)
    - Reasonably likely to predict clinical benefit (for accelerated approval; require post-marketing studies to confirm clinical benefit)

*\*biomarker: a physiologic, pathologic, or anatomic characteristic that is objectively measured and evaluated as an indicator of some normal or abnormal biologic function, process or response to a therapeutic intervention*

# Evidentiary Standards to Document Treatment Benefit

- Documented by “Substantial evidence” (21 CFR 201.56(a)(3))
- Evidence from “Adequate and well-controlled clinical trials”
- The methods of assessment are “well-defined and reliable” (21 CFR 314.126)

# Good Measurement Principles

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## 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

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- Defines good measurement principles to consider for “well-defined and reliable” (21 CFR 314.126) PRO measures intended to provide evidence of treatment benefit
- All COAs can benefit from the good measurement principles described within the guidance
- Provides optimal approach to PRO development; flexibility and judgment needed to meet practical demands

## Well-defined and Reliable

- The tool adequately measures the concept of interest in the context or clinical setting of interest
- To assess this, we review the tool's measurement properties:
  - Content validity
  - Construct validity
  - Reliability
  - Ability to detect change
  - Information to support interpretation of meaningful change



# What is Content Validity

- Are we asking the right questions in our assessments?
- Do clinical trial participants consistently interpret and understand the questions on the PRO assessment?
- What does the score of the questionnaire represent?



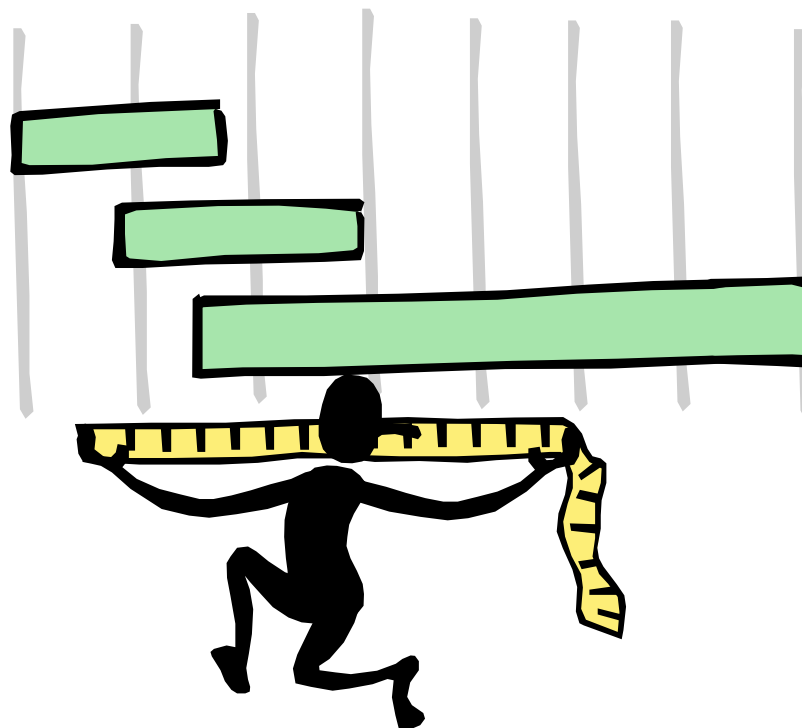
# Challenges with some PRO assessments: Content Validity – Are We Asking the Right Questions?

- Study population = primarily bed-ridden, minimal physical activity very difficult
- Concept of interest (outcome) to evaluate treatment benefit = physical functioning
- Clinical Outcome Assessment = patient-reported questionnaire to assess “physical functioning”
- Question in the assessment = “Do you have trouble running to the bus?”



# Thinking about Meaningful Change

- How much change is meaningful?



# Roadmap to Patient-Focused Outcome Measurement in Clinical Trials

- Intended to illustrate how one might embark upon a sound, orderly, instrument selection or development pathway, beginning with the clinical context in which the instrument is intended to be used.
- The graphic here is meant to help identify the types of things that might be considered in order to improve the ability of an outcome assessment to accurately measure treatment benefit.
  - Most assessment tools are a bit less orderly in their development

## Understanding the Disease or Condition **1**

### 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

## Conceptualizing Treatment Benefit **2**

### 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)

## Selecting/Developing the Outcome Measure **3**

### 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

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# DDT Qualification Guidance

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## Guidance for Industry

### Qualification Process for Drug Development Tools

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

October 2010  
Clinical/Medical

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- Describes a process for obtaining advice and consultation on outcome assessments from CDER outside of individual drug development programs
- Qualification process described for Biomarkers, Animal Models, and Clinical Outcome Assessments (COA)

## Conclusions

- Patient collaboration in outcome assessment decision-making is critical
- Patients are experts and should be engaged to advise on outcome assessments, helping to determine for example:
  - What to assess
  - How to assess
  - When to assess
  - How to interpret and weigh measured treatment benefit

## Conclusions

- Active patient involvement includes:
  - Participating in qualitative research (e.g., focus groups) in the development of assessments
  - Sharing experiences to facilitate understanding of the condition and conceptualizing treatment benefit:
    - During FDA Patient-Focused Drug Development Workshops
    - Providing comments to the docket
    - Working with FDA's Professional Affairs and Stakeholder Engagement staff
    - During AC meetings
  - Leading instrument development efforts (e.g., within the FDA's DDT Qualification Program)
- Patient engagement is optimized when it begins early (e.g., pre-IND) and continues throughout (e.g., IND, NDA) drug development

# Clinical Outcome Assessment Drug Development Tool (DDT) Qualification Website

[http://www.fda.gov/Drugs/DevelopmentApproval  
Process/DrugDevelopmentToolsQualificationProgra  
m/ucm284077.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm)