Approach to Outcome Measure Development or Selection: A Regulatory Perspective

Myotonic Dystrophy Foundation Meeting

September 17, 2015

Nikunj B. Patel, PharmD

Clinical Outcome Assessments Staff (COA Staff)

Office of New Drugs (OND)

Center for Drug Evaluation and Research (CDER)

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 a concept of interest:
  - How long a patient lives
  - How a patient feels or functions in daily life

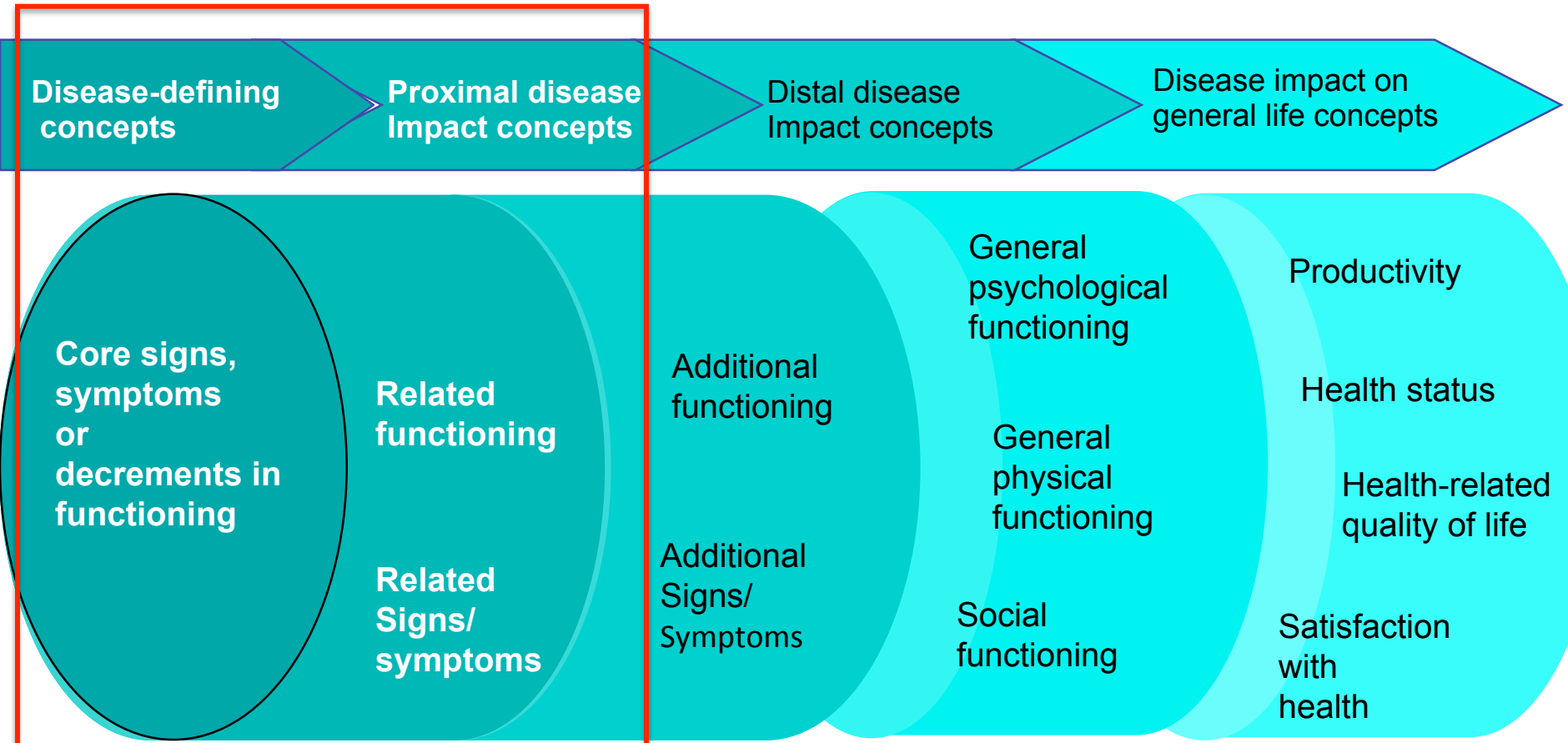
Purpose of Outcome Assessment

- To determine whether or not a drug has been demonstrated to provide benefit to patients
- A conclusion of treatment benefit is described in labeling in terms of the concept of interest, or the *thing* measured by the outcome assessment
- One of the most important aspects of drug development is how that benefit is measured

How to measure how patients feel and function?

- Clinical Outcome Assessments (COAs) can be used to measure how patients feel and function
  - Types of COA
    - Patient-reported outcome (PRO)
    - Clinician-reported outcome (ClinRO)
    - Observer-reported outcome (ObsRO)
    - Performance outcome (PerfO) assessments

Evidence of Treatment Benefit (Proximal to Distal)



Evidentiary Standards to Document Treatment Benefit

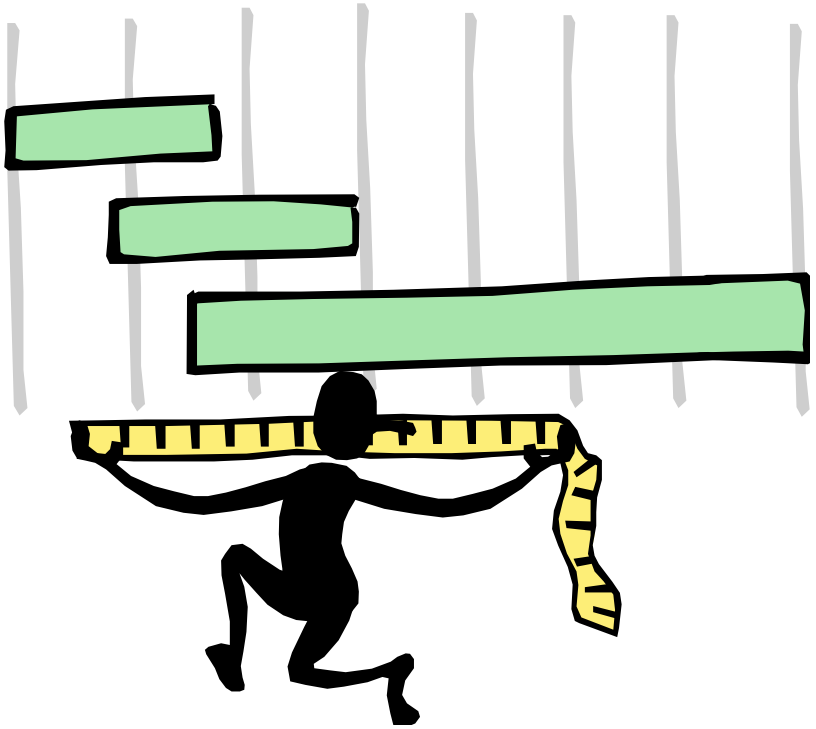
- Documented by "Substantial evidence" (21 CFR 201.56(a)(3))
- Evidence from "Adequate and well-controlled clinical trials"
- The methods of assessment are "well-defined and reliable" (21 CFR 314.126)

When is a Clinical Outcome Assessment Adequate for use?

- Regulatory standard: measures are *well-defined and reliable*
  - Empiric evidence demonstrates that the score quantifies the concept of interest in the targeted context of use
- What does this mean?
  - This means measuring the right thing (concept of interest), in the right way in a defined population (targeted context of use), and the score that quantifies that 'thing' does so accurately and reliably, so that the effects seen in the outcome assessment can be interpreted as a clear treatment benefit.

Thinking about Meaningful Change

- How much change is meaningful?



How FDA Can Help: Providing Advice on Clinical Outcome Assessments

- Provide advice and recommendations on clinical outcome assessments, including PROs:
  - For individual drug development programs (within an IND)
  - Through the Drug Development Tool (DDT) Clinical Outcome Assessment Qualification Program

Helpful Links

- FDA's Patient-Reported Outcome (PRO) Guidance for Industry:
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071975.pdf
- DDT Clinical Outcome Assessment Qualification Program webpage:
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm
    - Includes Roadmap and Wheel and Spokes diagrams
- FDA's DDT Qualification Program Guidance for Industry:
  - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf

BACK-UP SLIDES

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

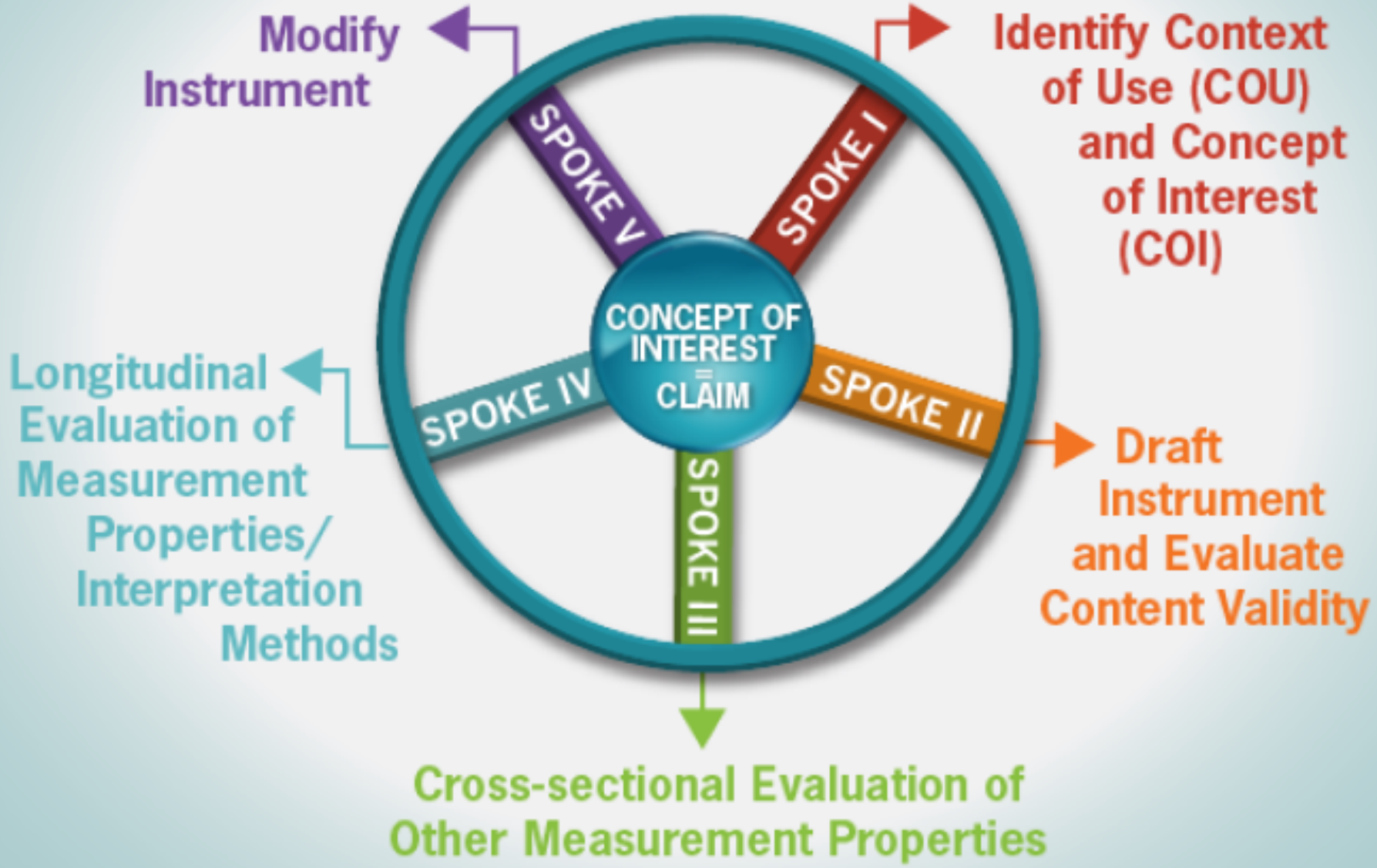
A. Search for existing COA measuring COI in COU:
- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

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

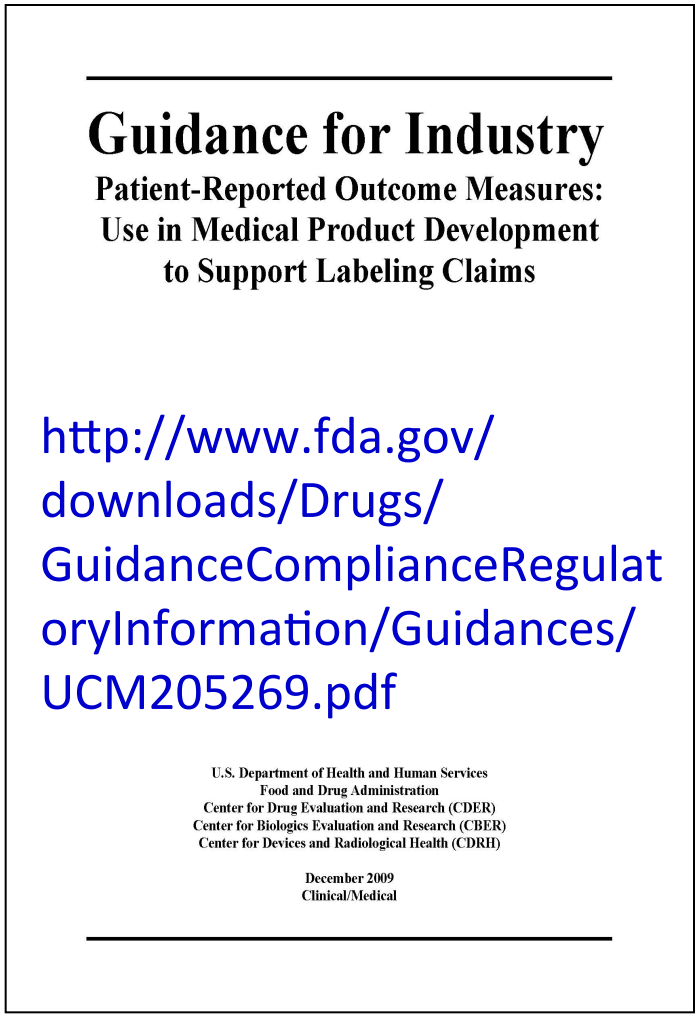
C. Complete COA development:
- Document longitudinal measurement properties (construct validity, ability to detect change)
- Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- Submit to FDA for COA qualification as effectiveness endpoint to support claims

Qualification of

CLINICAL OUTCOME ASSESSMENTS (COAs)



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

- 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

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?

Defining Context of Use

Each of the following variables can impact the adequacy of a COA to support a claim:

- **Disease definition including, if appropriate**
  - Disease subtype
  - Disease severity
  - History of previous treatment
- **Patient subpopulations**
  - Patient demographics
  - Reporting ability
  - Culture and language
- **Clinical trial design and objectives**
  - Endpoint positioning
  - Endpoint definitions
  - Analysis plan
  - Methods for interpretation of study results
  - Targeted labeling claim
- **Clinical practice and study setting**
  - Inpatient vs. outpatient
  - Geographic location
  - Clinical practice variation

Endpoint Definition and Positioning

- Create study objectives based on the *concept of interest* in the *context of use*
- Position the outcomes as trial endpoints that will be interpretable in comparison with a control group
- Define endpoints using COA scores
- Plan analysis
  - Measurement of change over time in individual patients that are combined for a means of assessing a group score
    - Analysis of means
    - Analysis of proportions
  - Hierarchy for testing multiple assessments