An Approach to Outcome Measure Development: A Regulatory Perspective

EMA Workshop on Alzheimer's disease
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Disclosure

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

Treatment Benefit

- Demonstrated by evidence that the treatment has a positive impact on a concept (outcome) of interest:
  - How long a patient lives
  - How a patient feels or functions in daily life

- Can be demonstrated as either:
  - A comparative advantage in how patients survive, feel or function
  - A comparative reduction in treatment-related toxicity

Purpose of Outcome Assessment

- To determine whether or not a drug has been demonstrated to provide treatment benefit
- A conclusion of treatment benefit is described in labeling in terms of the outcome targeted for measurement i.e., the concept of interest

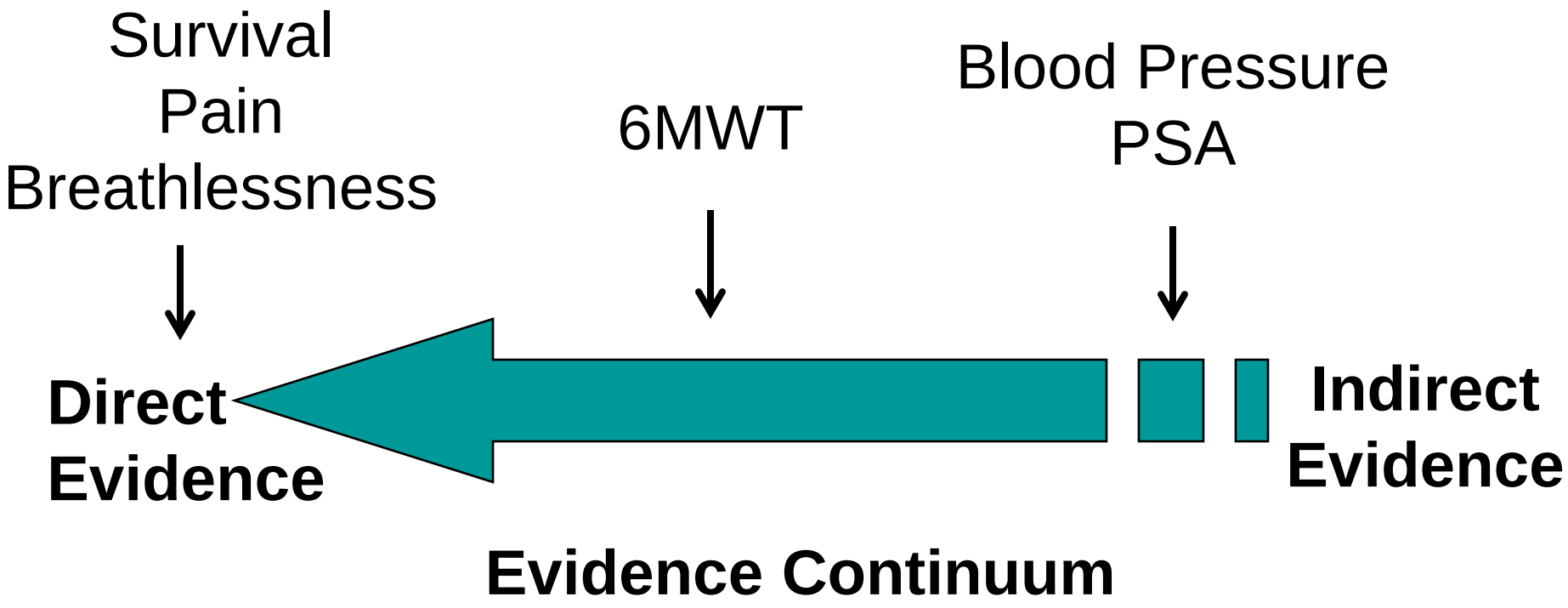
Types of Outcome Assessments

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

Evidence of Treatment Benefit

- **Direct** evidence of treatment benefit:
  - Derived from endpoints that **actually measure** survival or aspects of how patients feel and function in daily life
- **Indirect** evidence of treatment benefit:
  - Derived from endpoints that measure outcomes (concepts) that are **related to (but do not actually measure)** the meaningful aspects of how patients survive, feel or function

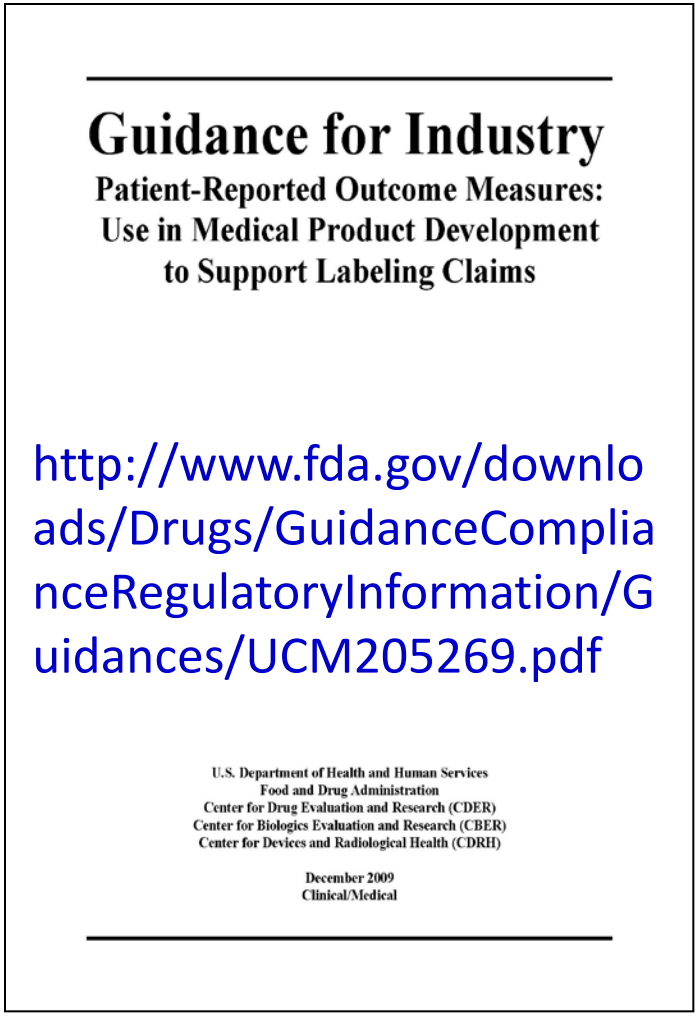
Direct Verses Indirect Evidence of Treatment Benefit



When is a COA adequate for use?

- Drug application review (IND/NDA/BLA)
  - Substantial evidence of treatment benefit includes requirement for *well-defined and reliable* assessments (21CFR 314.126)
  - Empiric evidence that demonstrates that the score quantifies the concept of interest (i.e., the outcome) in the targeted context of use so that the data can be interpreted and appropriately conveyed in labeling

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

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 (particularly test-retest)
  - Ability to detect change

Review of ClinRO, ObsRO, PRO, and PerfO Measures: Any Differences?

SAME:

I. Instrument
II. Targeted Claims
III. Endpoint Model
IV. Conceptual Framework
V. Content Validity
VI. Other Measurement Properties
VII. Interpretation of Scores
VIII. Language Translation and Cultural Adaptation
IX. Data Collection Method
X. Modifications
XI. Clinical Trial Design and Data Analysis Issues
XII. Key References

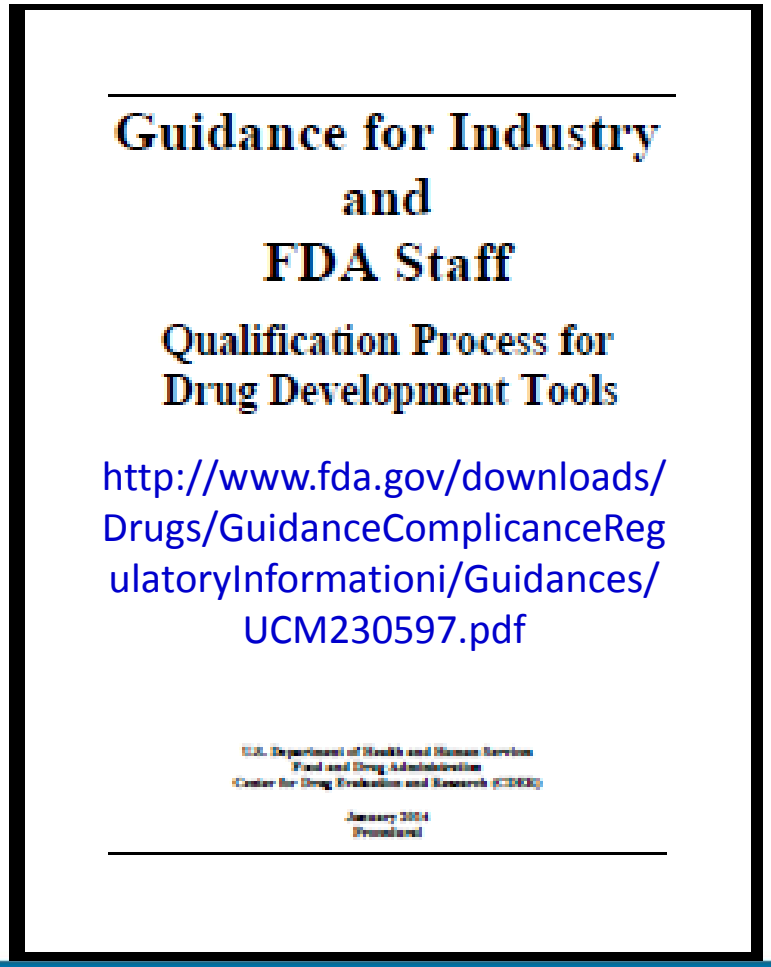
DIFFERENT:

Nothing?

Seeking Advice from FDA

- Discuss plans early!
- 2 pathways:
  - In the context of an Investigational New Drug (IND) program
  - Drug Development Tool (DDT) Qualification

Drug Development Tool Qualification Guidance (Final January 2014)



Guidance for Industry
and
FDA Staff

Qualification Process for
Drug Development Tools

http://www.fda.gov/downloads/Drugs/GuidanceComplicanceRegulatoryInformationi/Guidances/UCM230597.pdf

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

January 2014
Procedural

- Describe a process NOT evidentiary standards
- Qualification process described for Biomarkers, Animal Models, and Clinical Outcome Assessments (COA)

Qualification of COAs

- COA qualification is a conclusion that within the stated context of use, the results of measurement can be relied upon to represent a specific concept (i.e., outcome) with a specific interpretation when used in drug development and regulatory decision-making
  - Plain language: Within a specific clinical context, we're measuring the right thing, in the right way, and we can rely upon the results of the qualified assessment across clinical trials within that clinical context

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 that is in alignment with the objectives of the drug development program and the clinical trial context of use

Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

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

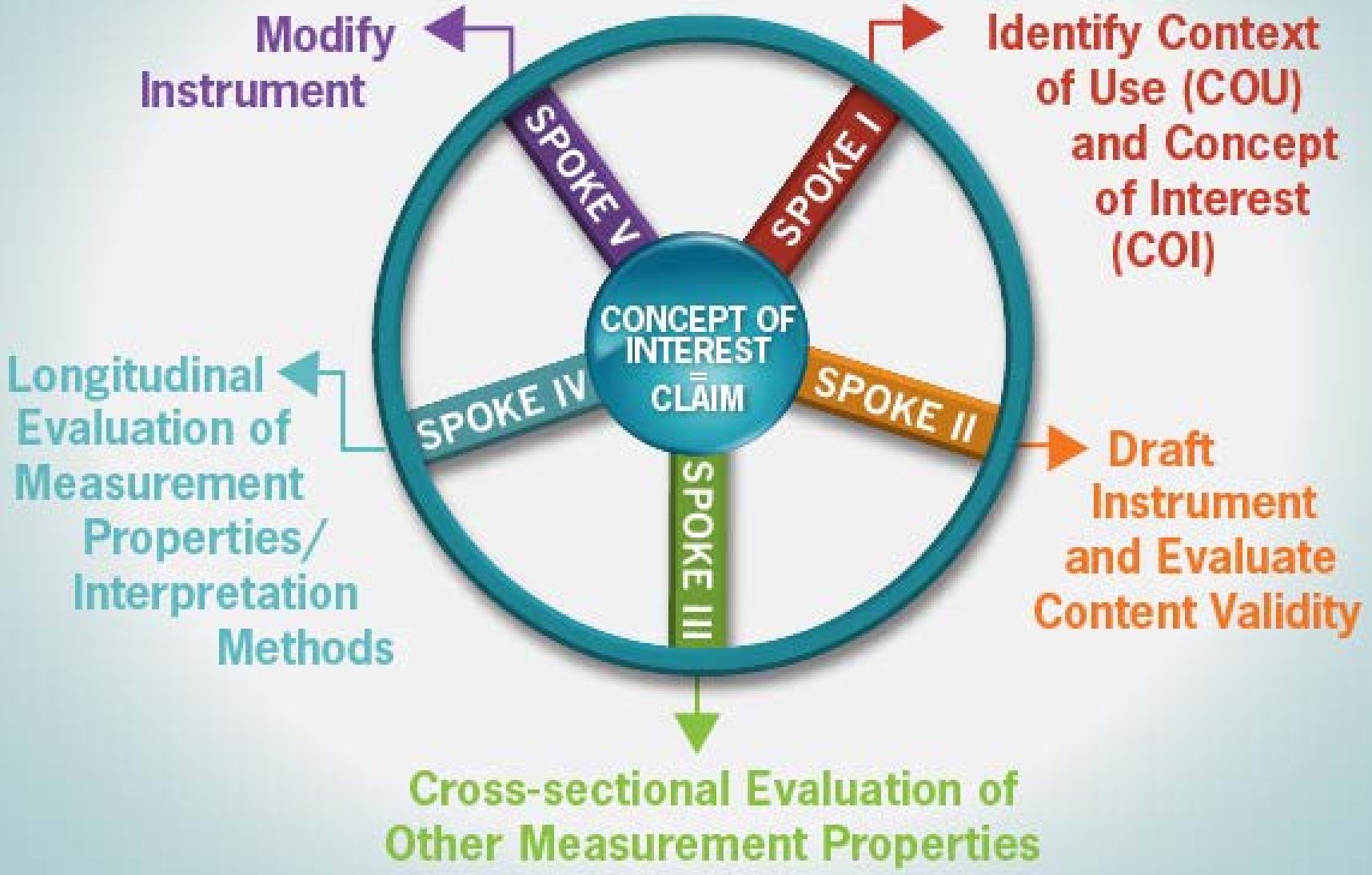
A. Search for existing COA measuring COI in COU:
- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

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

Qualification of

CLINICAL OUTCOME ASSESSMENTS (COAs)



Conclusions

- The roadmap to well-defined and reliable outcome assessment begins with an understanding of the disease or condition
- Outcome assessment development relies upon a well-defined context of use and targeted concept (outcome)
- The qualification process allows for the development of publicly available COAs for use in multiple drug development programs over time

Where to find more information

- Clinical Outcome Assessment Qualification Program Webpage: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm