Measuring How Patients Feel and Function

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Roadmap to Engaging CDER Public Workshop

Silver Spring, MD
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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

A New Era of Patient Empowerment

Dr. Janet Woodcock:

- "It turns out that what is really bothering the patient and what is really bothering the doctor can be radically different things….patients are true experts in their disease".
- "It's clear you have to start with an understanding of the impact of the disease on the people who have it, and what they value most in terms of alleviation before you set up a measurement and go forward with truly patient-focused drug development."

PDUFA V Clinical Outcome Assessments Public Workshop, April 1, 2015

Today: increasing roles of…

- Patient groups
- Communications e.g., social media
- Multi-stakeholder collaborations

It takes a village

- While patients are experts in their disease, they are not necessarily experts in clinical trials or in endpoint measure development

It takes a village: patient focused drug development cannot be done by any one group in isolation!

FDA's Patient-Focused Drug Development Initiative

- Patients are uniquely positioned to inform understanding of the therapeutic context for drug development and evaluation
  - There is a need for more systematic ways of gathering patient perspective on their condition and treatment options
  - Current mechanisms for FDA to obtain patient input often limited to discussions related to specific applications under review

- Patient-Focused Drug Development (PFDD) is part of FDA commitments under PDUFA V*
  - FDA is convening 24 meetings on specific disease areas in FY 2013-17
  - Meetings can help advance a systematic approach to gathering input

*The fifth authorization of the Prescription Drug User Fee Act, enacted in 2012

PFDD meetings for Fiscal Years 2013-2017

Fiscal Year 2013	Fiscal Year 2014	Fiscal Year 2015	Fiscal Years 2016-2017
• Chronic fatigue syndrome/ myalgic encephalomyelitis • HIV • Lung cancer • Narcolepsy	• Sickle cell disease • Fibromyalgia • Pulmonary arterial hypertension • Inborn errors of metabolism • Hemophilia A, B, and other heritable bleeding disorders • Idiopathic pulmonary fibrosis	• Female sexual dysfunction • Breast cancer • Chagas disease • Functional gastrointestinal disorders • Parkinson's disease and Huntington's disease • Alpha-1 antitrypsin deficiency	• Non-tuberculous mycobacterial lung infections • Psoriasis • Neuropathic pain associated with peripheral neuropathy • Patients who have received an organ transplant • Sarcopenia • Autism *Details to be announced* • Alopecia areata Fall 2017 • Hereditary angioedema

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm347317.htm

Outcomes of PFDD Meetings

- Each PFDD meeting results in a report that faithfully captures patient input
- Aims:
  - Support FDA staff in conducting the risk benefit-risk assessment for drugs under review
- May also:
  - Assist in advising drug sponsors on their drug development programs
  - Support drug development more broadly through:
    - Identifying specific areas of unmet need for patient populations
    - Identifying outcome measures that can be developed for clinical trials

Externally-Led PFDD Meetings

- There is external interest in expanded efforts to gather patient input in support of drug development and evaluation
- Meetings conducted by external stakeholders provide an opportunity to expand the benefits of PFDD
  - Meetings should target disease areas where there is an identified need for patient input on topics related to drug development
  - FDA's PFDD meetings can serve as a model
- Possible mechanisms the patient group could explore:
  - Public meeting (conducted within Metro D.C. area)
  - Web-only meeting
  - Small internal meeting at FDA, with patients
- For more information, please visit:
  http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm

Bridging from patient input to patient-focused clinical trial endpoints

Clinical Benefit: How do we define it?

- A positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives.
  - How long a patient lives
  - How a patient feels or functions in daily life
- Can be demonstrated as either:
  - A comparative advantage in treatment of the disease or condition; OR
  - A comparative reduction in treatment-related toxicity
- Clinical benefit is described in labeling in terms of the outcome of interest measured

Types of Outcome Assessments

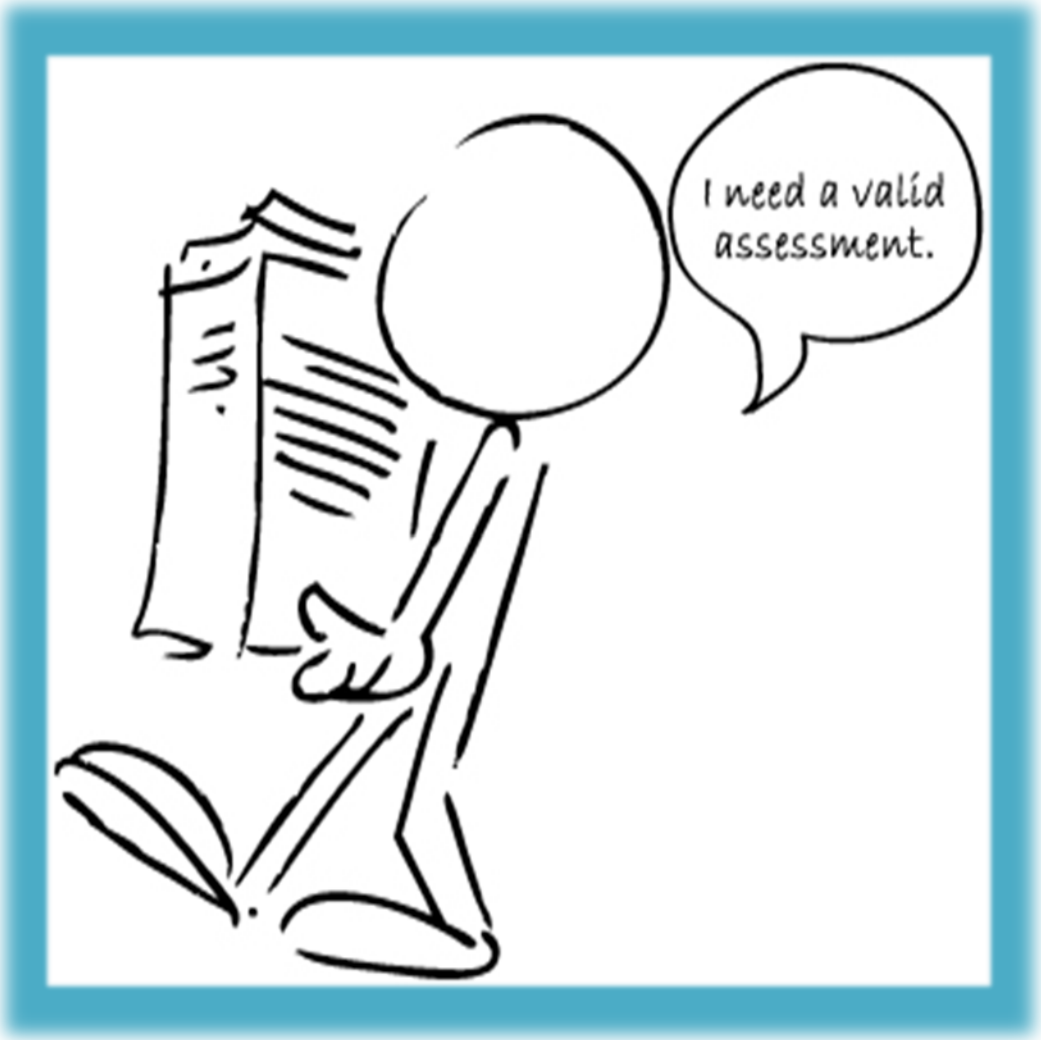
- Clinical outcome assessments (COAs)
  - Patient reported outcomes (PROs)
  - Clinician-reported outcomes (ClinROs)
  - Observer reported outcomes (ObsROs)
  - Performance outcomes (PerfOs)

- Biomarkers

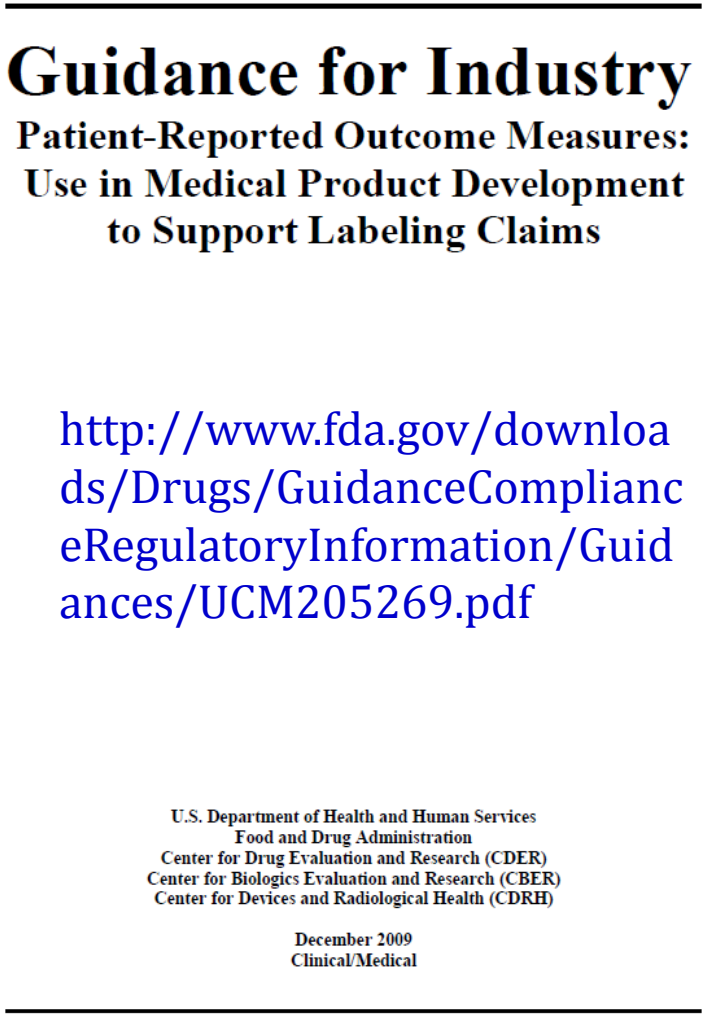
- ***Patient-reported outcome (PRO)*** —

A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.

  - Examples: pain intensity, seizure episodes, asthma symptoms, rescue medication use, health-related quality of life


I need a valid assessment.

Good Measurement Principles



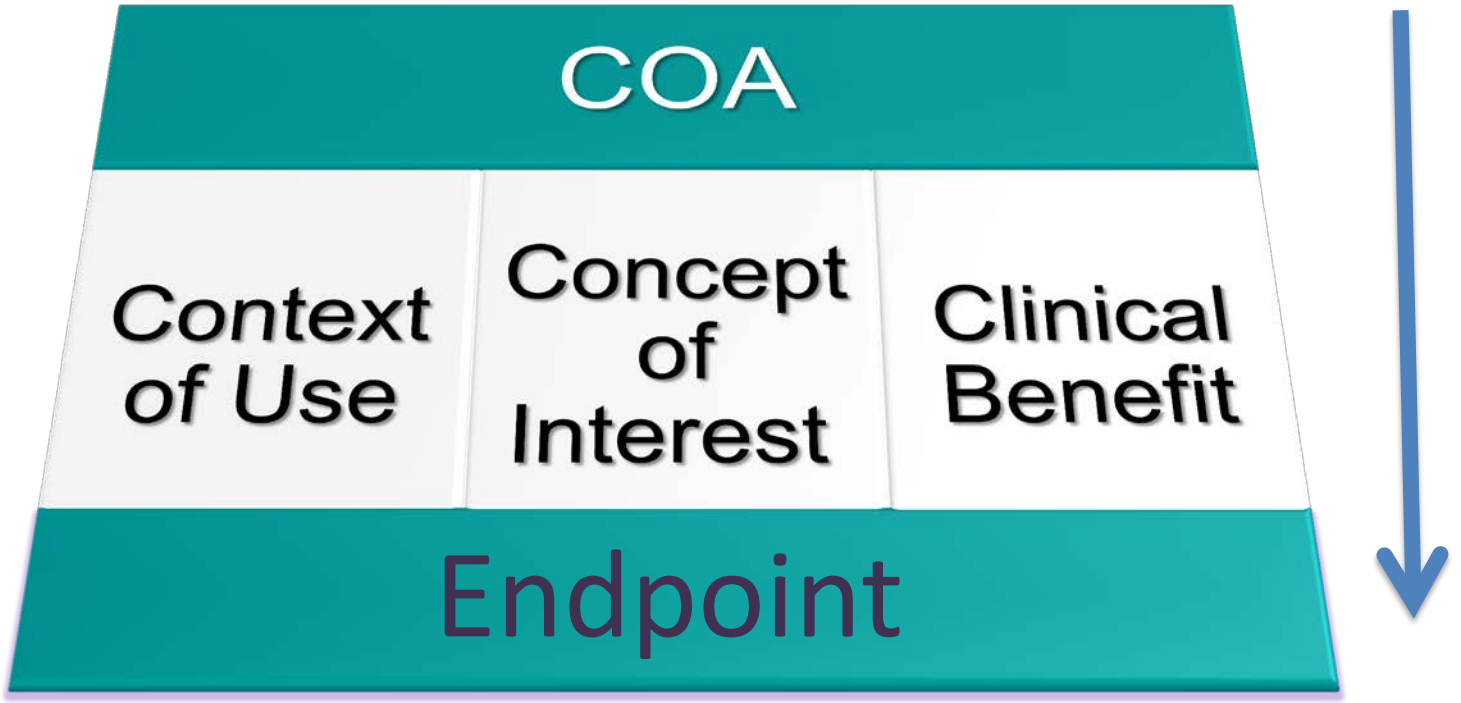
- Defines how the Agency interprets "well-defined and reliable" (21 CFR 314.126) for PRO measures intended to provide evidence of treatment benefit

- All COAs can benefit from the good measurement principles described in the PRO Guidance (i.e., valid, reliable, sensitive to change)

- Provides optimal approach to PRO development

- **But, flexibility and judgment are needed to meet practical demands!**

From COA Development to Study Endpoint



The Challenge:

- Well-developed and fit-for-purpose PRO instruments do not exist for many diseases/conditions

- Development of fit-for-purpose PROs and other COAs can be time- and resource-intensive to ensure that they are fit-for-purpose (i.e., well-defined and reliable)

HOW TO ADDRESS THIS CHALLENGE

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

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http://www.fda.gov/Drugs

Idiopathic Pulmonary Fibrosis

Natural history **-Rare,** chronic, progressive -Variable progression -Median survival 3 to 5 years	**Treatment benefit goals for which endpoints needed** -Symptoms & signs -Targeted impacts of IPF on patients' lives	**Search for existing PRO measures** -ATAQ-IPF (A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis)
Patient subpopulations -Males > females -5th and 7th decade -Caucasians-predominant -Oxygen use	**Context of use** -Study design and objectives -Subpopulations and stage of disease -Other	**Begin COA development** -ATAQ-IPF modification underway for clinical trial use -Qualitative research and quantitative research in the target patient population with IPF
Health care environment -Unmet therapeutic needs **Patient/caregiver input** -Survival -Disease progression -Symptoms and impact on life	**Select Clinical Outcome Assessment Type** -PRO -ClinRO -ObsRO -Perfo	**Complete COA Development** -Longitudinal evaluation of ability to detect change -Guidelines for interpretation of clinically meaningful change (e.g., responder definition)

Patients' Input Ultimately Helps Us

Determine:

- WHAT is measured to provide evidence of clinical benefit
- HOW best to measure concepts in a clinical study
- WHAT a meaningful improvement is in clinical benefit

Ways FDA can work with stakeholders in selecting or developing COAs

Pathways for FDA Clinical Outcome Assessment Review & Advice

1

IND/NDA/BLA Pathway

Within an individual drug development program

Investigational New Drug (IND) submissions to FDA

Potential to result in *labeling* claims

2

DDT COA Qualification Pathway

Outside of an individual drug development program

Development of novel COAs for use in multiple drug development programs addressing unmet measurement needs

Potential to result in *qualification* of COA

3

Critical Path Innovation Meetings Pathway

Outside of an individual drug development program

Potential for *general CDER advice* on specific methodology or technology (e.g., PRO) in its early stages of development

Meetings are informal, non-binding discussions

Closing Thoughts

- The FDA encourages the development and implementation of patient-focused clinical outcome assessments (COAs) in clinical trials to support drug approvals and labeling claims
  - Early patient input is critical in the road to patient-focused outcome measurement
- The identification of tools is just one aspect of patient focused drug development
  - The values of patients need to drive the selection of outcome measures as patients are the ultimate end users of this information
- We are continuing to learn best ways to engage patients in drug development
- Early communication with the FDA is encouraged

Thank You!

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 diagram
    - Table of current qualification projects (with permission by submitter)
- FDA's DDT Qualification Program Guidance for Industry:
  - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf


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Back Up Slides

FDA Review of Clinical Outcome Assessments

Does the instrument measure the outcome of interest?

- Well-defined and reliable (21CFR 314.126)
- Appropriate for the target population
- Appropriate for the target indication
- Adequate measurement properties
  - E.g., content validity: PRO development relies on patient input to support content validity

Goal of Clinical Outcome Assessment

- In clinical trials, clinical outcome assessments are measurements that are used to assess a particular patient outcome, such as:
  - How long a patient lives
  - How a patient feels or functions in their daily lives

Clinical Benefit: How do we measure it?

- Clinical Outcome Assessment (COA)
  - An assessment that describes or reflects how an individual feels, functions or survives
    - Typically measure symptoms, overall mental state, or the effects of a disease or condition on how the patient functions

- A biomarker* is not an assessment of how an individual feels, functions or survives

*Biomarker: A defined characteristic measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention. Examples: molecular, histologic, radiographic, or physiologic characteristics.

Source: http://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-B

Roadmap to

PATIENT-FOCUSED OUTCOME MEASUREMENT

in Clinical Trials

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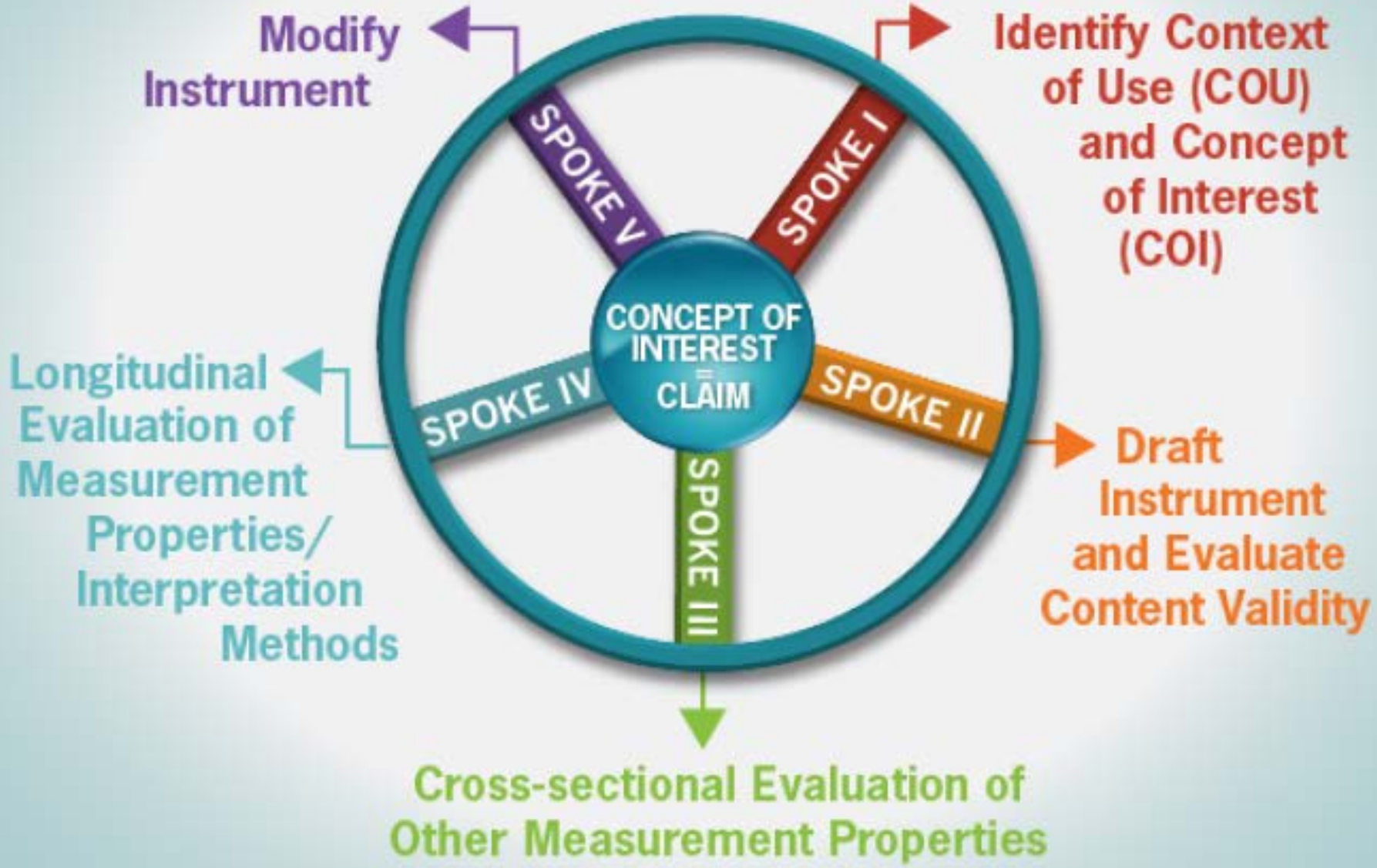
Qualification of

CLINICAL OUTCOME ASSESSMENTS (COAs)



Two Regulatory Review Pathways: Clinical Outcome Assessments

- **The traditional way**
  - Within an individual drug development program
    - IND applications to FDA; clinical trials
    - **Consult with Agency early and often!**

- **A newer process: Drug Development Tool Qualification**
  - Outside of an individual drug development program

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

CDER Qualification of Clinical Outcome Assessments

- What is Qualification? COA qualification is a conclusion that within the stated context of use (COU), the results of measurement can be relied upon to represent a specific concept (COI) with a specific interpretation when used in drug development and regulatory decision-making

- CDER qualification is currently reserved for those COAs that are ultimately intended to support primary or secondary endpoints in clinical trials

- Qualified instruments shall be made available publically available

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COA DDT Qualification

- The program prioritizes instrument development to fill a critical measurement gaps for patient-centered outcomes
  - Through development of a new tool or modification of an existing tool
- 2 qualified: Exacerbations of Chronic Pulmonary Disease Tool (EXACT) and EXACT-Respiratory Symptoms

CRITICAL PATH INNOVATION MEETINGS

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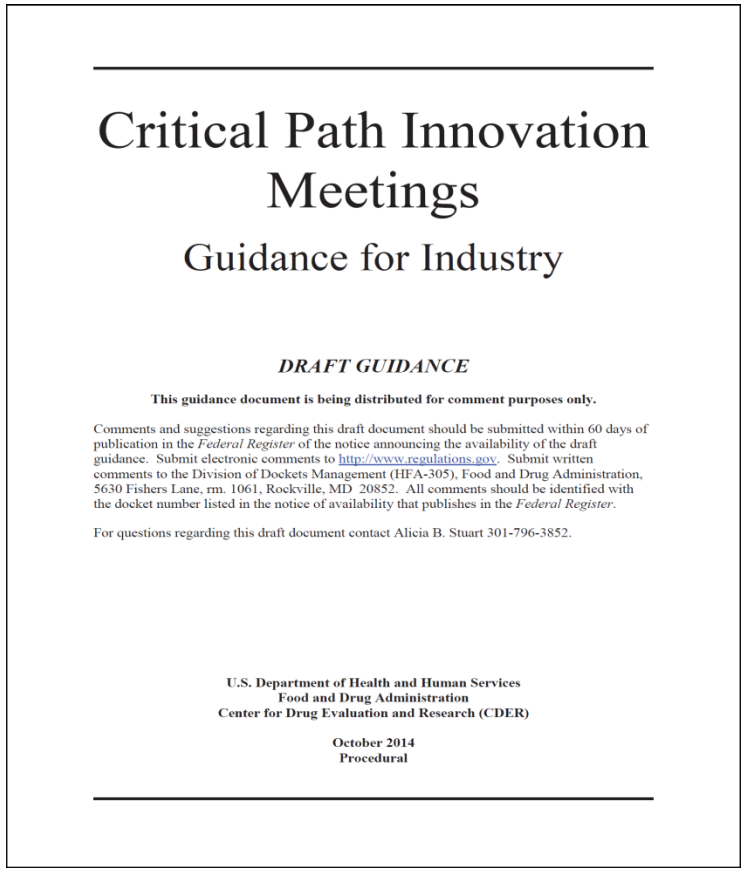
Critical Path Innovation Meetings*



Critical Path Innovation Meetings

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Alicia B. Stuart 301-796-3852.

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

October 2014
Procedural

- Provides an example of how FDA has responded to the request for earlier COA communications
- Voluntary process that can be used as a venue for a discussion of the potential approaches to developing COAs to provide evidence of treatment benefit
- <u>What it's not:</u>
  - Not a venue for regulatory advice on a specific product development program

*CPIM topics can include: biomarkers, COAs, natural history studies, innovative approaches to clinical trial design and analysis and others.