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for Industry (REdI)
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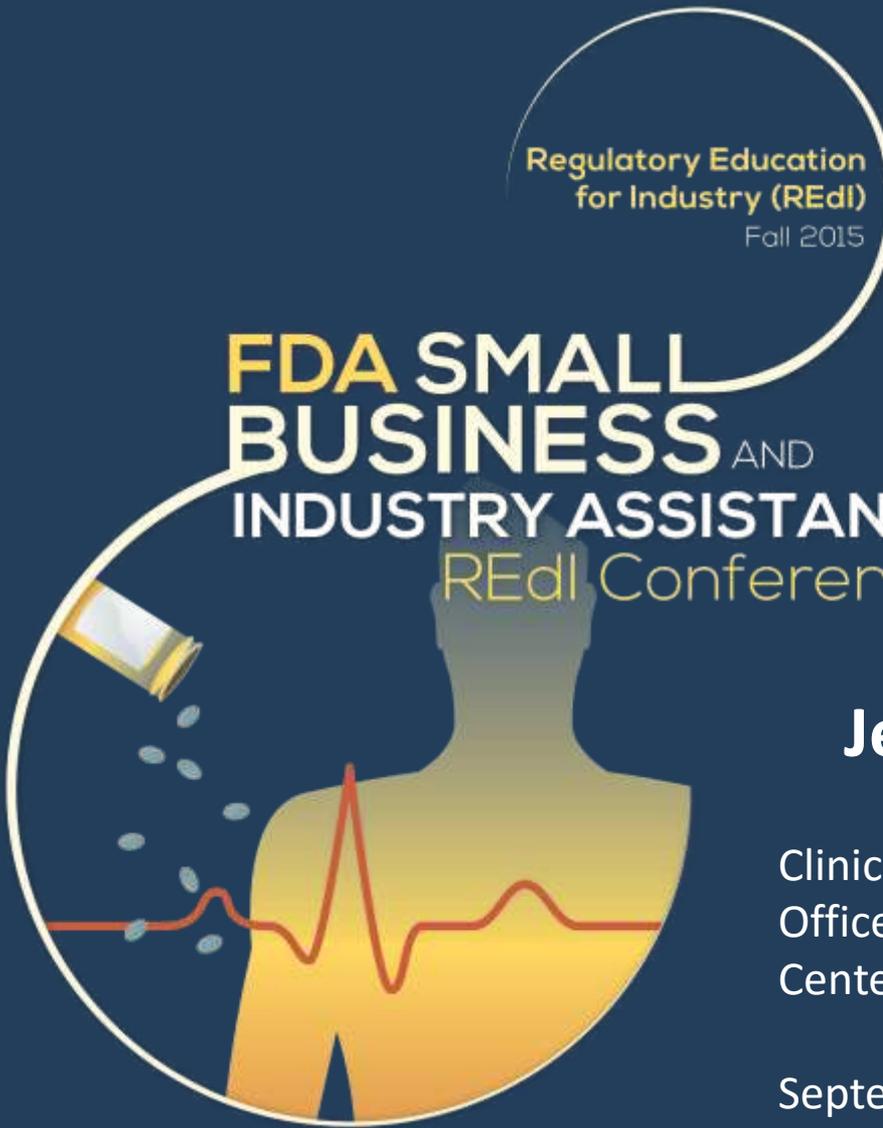
**FDA SMALL
BUSINESS** AND
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REdI Conference

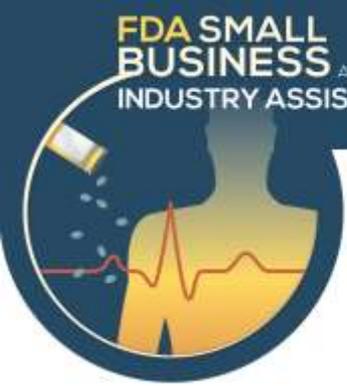
Clinical Outcome Assessment Implementation in Clinical Trials

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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.



Topics

- Treatment benefit
- Clinical Outcome Assessments (COAs)
- Ways to work with FDA to develop clinical outcome assessments
- Practical considerations and resources



Patient-Focused Drug Development

Dr. Janet Woodcock:

- “....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.”



Treatment Benefit

- Treatment benefit is demonstrated by evidence that the treatment has a positive impact on:
 - How long a patient *lives*
 - How a patient *feels* or *functions* in daily life



Purpose of Outcome Assessments

- To assess 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 concept of interest (i.e., what is being measured by the assessment)



Types of Outcome Assessments

- **Clinical Outcome Assessments (COAs)**
 - e.g., survival, symptoms, etc.
- **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



Clinical Outcome Assessments

- Measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions
- May be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit



Types of Clinical Outcome Assessments

- Patient-reported outcomes (PRO)
- Clinician-reported outcomes (ClinRO)
- Observer-reported outcomes (ObsRO)
- Performance outcomes (PerfO)



Clinical Outcome Assessment Types

Determine the most appropriate reporter for the concept of interest in the context of use

- If the concept:
 - Can only be observed or felt by the patient and the patient is able to report it (e.g., symptom severity)
 - **Patient-reported outcome (PRO)**
 - Can be observed and requires clinical judgment
 - **Clinician-reported outcome (ClinRO)**



Clinical Outcome Assessment Types

- If the concept:
 - Can only be captured by observation in daily life (outside of a healthcare setting), and the patient is unable to report for him or herself
 - **Observer-reported outcome (ObsRO)**
 - Requires observation of a patient's function by performing a set of defined tasks in the clinical setting
 - **Performance outcome (PerfO)**



Well-Defined and Reliable

FDA's Regulatory Standard (21 CFR)

Part 314 – Applications for FDA Approval to Market a New Drug

- Sec. 314.126 - Adequate and well-controlled studies
 - (b) An adequate and well-controlled study has the following characteristics:
 - (6) *The methods of assessment of subjects' response are **well-defined and reliable**. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.*



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/Guidances/UCM193282.pdf>

- Defines how the Agency interprets “well-defined and reliable” (21 CFR 314.126) for PRO measures intended to provide evidence of treatment benefit
- Describes good measurement principles, which can be applied to other COAs
- Provides optimal approach to PRO development; flexibility and judgment needed to meet practical demands

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



A Well-Defined and Reliable Assessment

- **Measurement properties** support that an assessment adequately measures the **concept of interest** in the **context of use**
- **Measurement Properties:**
 - **Content validity**
 - Construct validity
 - Reliability (particularly test-retest)
 - Ability to detect change



What Is Content Validity?

Content validity is the extent to which the instrument measures the concept of interest

- **Qualitative** studies should support that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use (i.e., context of use)
- **Quantitative** data can contribute to content validity evidence, but are not sufficient alone



Qualitative Evidence to Support Content Validity

- **Identify concepts using qualitative research**
 - Literature review
 - Expert input
 - Input from the appropriate population who will be completing the instrument (e.g., patients, observers, clinicians)
- **Generate items using concept elicitation**
 - Focus groups and/or individual patient interviews
- **Refine or confirm the questions using cognitive interviews**
 - Are respondents understanding and answering the questions as intended or expected?
 - Comprehensive?

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 for meaningful treatment benefit, i.e., How a patient:

- Survives
- Feels (e.g., symptoms)
- Functions

B. Define context of use 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 concept of interest in the context of use:

- 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





Understanding the Disease or Condition

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Defining the Healthcare Environment

- Identify:
 - Currently available treatment alternatives
 - How will this influence clinical trial entry criteria and design?
 - Clinical practice variations and standards of care that may impact treatment, study design, and outcome measurement
 - Ex: All patients with a COPD exacerbation are hospitalized in Spain but not in the US



1. Understanding the Disease or Condition

D. Patient/caregiver perspectives

- Definition of treatment benefit
- Benefit-risk tradeoffs
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Patient and Caregiver Perspectives

Some considerations:

- Symptom burden
- Relationship of symptoms and signs to daily functioning
- Impact of disease on daily life
- Accommodations made by patients to deal with disease



Conceptualizing Treatment Benefit

2



2. Conceptualizing Treatment Benefit

A. Identify concept(s) of interest for meaningful treatment benefit, i.e., How a patient:

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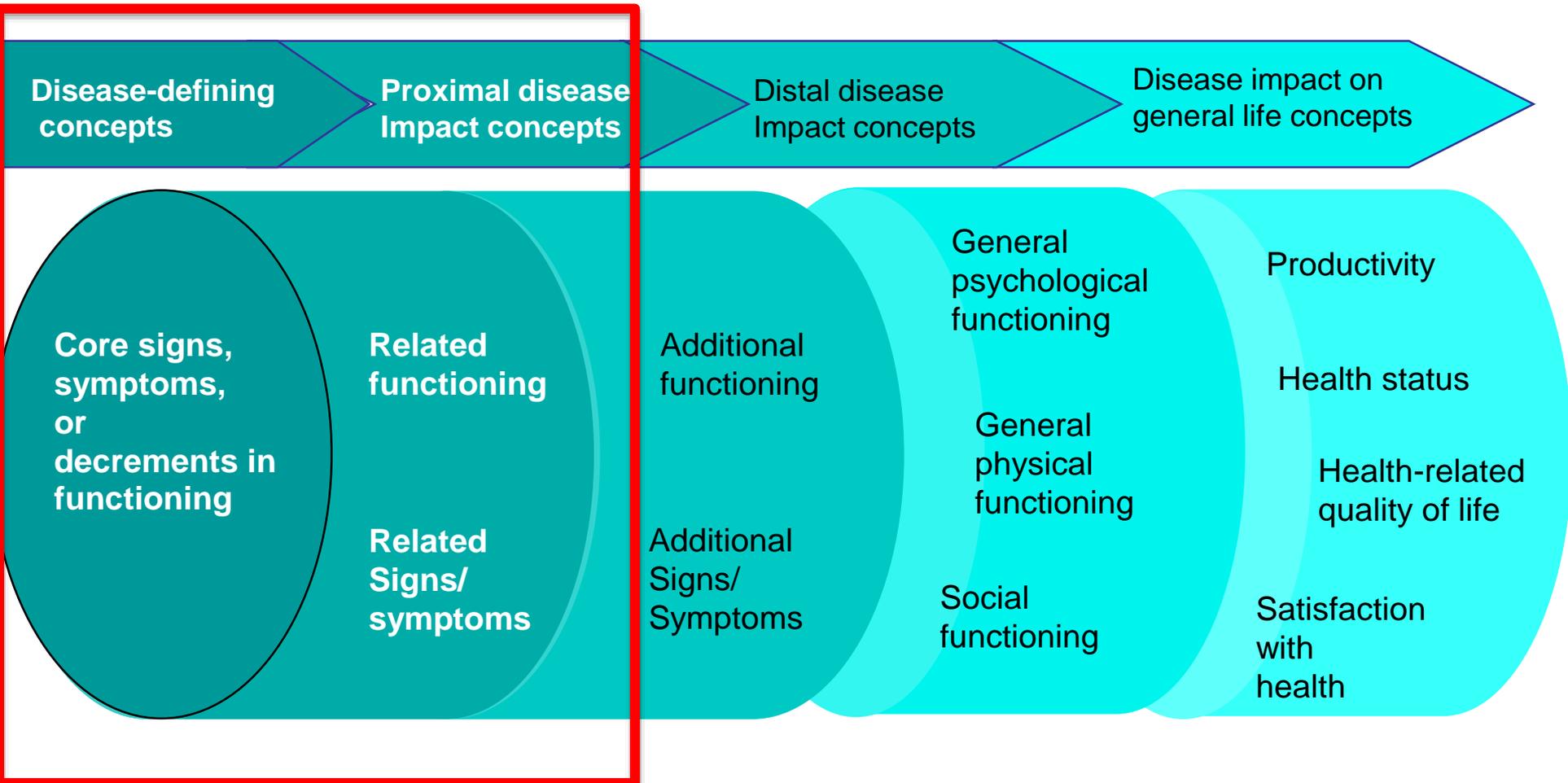


Identifying the Concept(s) of Interest for Meaningful Treatment Benefit

- If a survival study is not appropriate, identify outcome concepts that represent core
 - Signs
 - Symptoms
 - Aspects of functioning that define the disease in the targeted population
- Identify other concepts that are clinically important



Evidence of Treatment Benefit (Proximal to Distal)





2. Conceptualizing Treatment Benefit

B. Define context of use for clinical trial:

- Disease/Condition entry criteria
- Clinical trial design
- Endpoint positioning



Clinical Trial Context of Use

- Identify the targeted patient enrollment criteria for future clinical trials based on:
 - Phenotype
 - Demographics
 - Possible drug MOA
 - Regulatory requirements (e.g., pediatrics)
 - Marketing goals (e.g., improvement over existing therapies)
- Identify other aspects of the targeted clinical trial context of use that may have an impact on the adequacy of an outcome assessment



Defining Context of Use

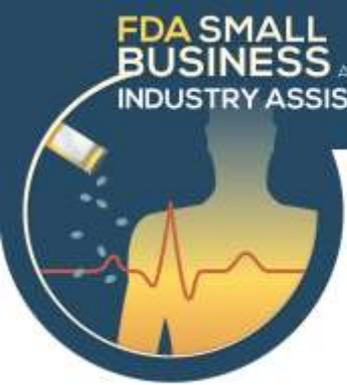
Each of the following variables can impact the adequacy of a COA to support a claim:

- **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 appropriate clinical outcome assessment scores
- Plan analysis
 - Measurement of change over time
 - Analysis of means
 - Analysis of proportions
 - Hierarchy for testing multiple assessments



2. Conceptualizing Treatment Benefit

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Considerations When Selecting a Clinical Outcome Assessment

Not all clinical outcome assessments are appropriate for use in clinical trials to support approval and labeling

– May be useful for other purposes:

- Diagnostic
- Prognostic
- Trial eligibility and trial enrichment
- Epidemiologic or population studies
- Clinical practice decision-making

– Measures used successfully for these other purposes will not necessarily be appropriate outcomes assessments (i.e., they may not be able to reliably detect treatment benefit in clinical trials or support labeling claims in a non-misleading way)

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Clinical Trial Design Considerations

- If the concept of interest is intended to support labeling claims, then it should be stated as a specific clinical trial objective or hypothesis
- Endpoint model and hierarchy for testing multiple assessments
- Blinding and randomization
- Frequency and timing of assessments
- Clinical trial quality control
- Minimize missing data



Unmet Measurement Gaps

- Well-developed and fit-for-purpose COAs do not exist for many conditions
- COAs can provide meaningful data on their own, or assist in interpretation of other outcome measures
- Development of such COAs can be time and resource-intensive to ensure that they are well-defined and reliable



Working with FDA to Develop Clinical Outcome Assessments

- The traditional way
 - Within individual drug development programs
 - Investigational New Drug Applications (INDs)
- A newer process
 - Within the DDT Qualification Program;
independent of an individual drug development program



CDER Drug Development Tool Qualification Program

- A process for working with FDA/CDER to develop drug development tools (DDTs), including COAs, intended for use across different drug development programs
- **Qualification** is a conclusion within the stated context of use, results of the assessment can be relied upon to measure a specific concept and have a specific interpretation and application in drug development and regulatory decision-making (i.e., “fit-for-purpose”)



DDT Qualification Guidance

Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools

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

- Describes a process, NOT evidentiary standards
- Biomarkers, Animal Models, and COAs
- COA Qualification Webpage:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm>

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

January 2014
Procedural



Practical Considerations

- **Seek out resources and expertise in this area**
 - Publications and references
 - Utilize experts in COA development
 - FDA
- **Engage in early discussions with FDA**
 - For pre-INDs or INDs, reach out to respective review divisions
 - Drug Development Tool Qualification Program
 - Critical Path Innovation Meetings Guidance for Industry
- **Plan ahead**
 - Finding or developing a clinical outcome assessment takes time and effort – consider this when planning your timelines and milestones



Finding a Path Forward

Regulatory standards and science

AND

Incorporating patient voice, efficiency,
innovation, and flexibility in drug
development



Useful Links

- Clinical Outcome Assessments Staff:
 - <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm349031.htm>
- FDA's Patient-Reported Outcome (PRO) Guidance for Industry:
 - <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>
- CDER Drug Development Tool Clinical Outcome Assessment Qualification Program:
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm>
 - Glossary, COA Roadmap
- ISPOR Task Force Publications
 - <https://www.ispor.org/taskForces/TFindex.asp>



Thank You!

Questions?

Please complete the session survey:

[surveymonkey.com/r/DRG-D1S5](https://www.surveymonkey.com/r/DRG-D1S5)



BACK-UP SLIDES



Quality of Life

- A general concept that implies an evaluation of the effect of all aspects of life on general well-being
- Not well-defined or reliable for purpose of medical product claims because:
 - it implies evaluation of *non-health related aspects* of life
 - “quality of life” does not have the same meaning for every patient



Health-related Quality of Life (HRQL)

- A multi-domain concept that represents the patient's general perception of the effect of illness and treatment on **physical, psychological, and social** aspects of life
- Claiming a statistical and meaningful improvement in HRQL implies that:
 - all HRQL domains that are important to interpreting change in how the clinical trial's population feels or functions as a result of the targeted disease and its treatment were measured;
 - a general improvement was demonstrated;
 - AND
 - no decrement was demonstrated in any domain