

Clinical Trial Outcome Assessments

Identifying Intrinsic Characteristics

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Marc K Walton MD, PhD
Associate Director for Translational Medicine
Office of Translational Sciences
CDER-FDA

*The views expressed are those of the author, and do not
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Why Discuss Outcome Assessments?

- Increasing activity in outcome assessments
 - Developing new OA
 - Refining existing OA
 - Applying existing OA in new settings
- FDA Critical Path Initiative
 - Recognized OAs can be an important tool to advancing therapeutics and the process of drug development and approval
- Investigators, Industry, and FDA need to determine if they are acceptable
 - What are key issues
 - How to begin

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Drug Development Tool Qualification

- Program developed by CDER to aid developing and applying new tools in drug clinical trials
- Clinical trial outcome assessment is one of the qualification programs
- Qualified tools become publicly known and widely available
- Encourages collaborative approach to OA development
 - Consortia
 - FDA advisory role
- May avoid delays in drug development programs

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Purpose of Outcome Assessments

- To provide evidence of a specific treatment benefit
- Treatment benefit is a favorable effect on a meaningful aspect of how a patient feels, functions, or survives
 - Usually an effectiveness benefit
 - ❖ May be a comparative safety benefit
 - Survival has well established methods for evaluation, easy to interpret
 - Feels and Functions are more complex
- Treatment benefit regulatory uses:
 - Marketing approval
 - Labeling claims

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Feels and Functions as Effectiveness

- Feels
 - A patient's physical sensation or perceived mental state related to health within typical 'daily' life
 - Pain
 - Severely low mood (depression)
- Functions
 - A patient's ability to perform an activity that is a meaningful part of typical 'daily' life
 - Not isolated physiologic processes (eg liver metabolism)
 - Not ability to perform actions not part of usual life

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Evidence Supporting Effectiveness

- Evidence from Adequate & Well controlled clinical trials
- The methods of assessment of subject's response are well-defined and reliable (21CFR314.126)
- Effects on the OA can be reliably interpreted as a treatment benefit
 - Understanding what the assessment means in terms of how the patient feels or functions

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Discussion Focus

- Workshop discussion chiefly intended for
 - OAs in adequate & well-controlled trials
 - New OAs and OAs in new settings
- Issues in determining if the OA is:
 - Well-defined
 - Reliable
 - Interpretable
- What should be evaluated & how?
- Determining if the OA is 'fit for purpose'
 - OAs cannot be judged in isolation
 - Important to identify the purpose

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Intrinsic Characteristics of an Assessment

- Patient assessments have certain intrinsic characteristics
- Not related to how the assessment is used in a clinical trial
- The characteristics do not describe a judgment of whether it is suitable to be used in any particular manner
- Recognizing these characteristics will aid the process of evaluating whether it is well-defined and reliable

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Characteristics of a Patient Assessment

- Dimensions
 - Characteristics that are largely orthogonal
 - Categories within a dimension are mutually exclusive
 - ❖ Not gradations of a characteristic
 - Raise distinct issues for evaluation
- Is it Psyche Influenced?
- Who is performing the rating?
- What is the relationship to true treatment benefit?
- What is the setting of the measurement?

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Dimensions of an Assessment (1)

- Psyche Influenced?
 - Is the assessment influenced by human choices
 - Conscious or unconscious
 - Rater or patient
 - Judgment, cooperation, motivation
 - Influenced: Psychomodulated
 - ❖ As OA most often intended to learn about patient's current state of feels or functions
 - Not influenced: Biomarker
 - ❖ As OA often intended to predict a future state of feels or functions
- Framework particularly aids communication regarding psychomodulated assessments

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Dimensions of an Assessment (2)

- Who is performing the rating?
 - Patient, Clinician, Observer, (Instrument)
- What is the relationship to true treatment benefit
 - Direct vs Indirect
 - Indirect means the concept being measured is not the exact directly meaningful concept
 - ❖ “indirectness” is graded within the category
 - ❖ When used as an OA establishing the relationship between changes in measured concept and the intended meaningful concept is important
 - Usually not important dimension for non-OA use
- What is the setting for measuring
 - Naturalistic vs Artificial Procedure

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Dimensions of an Assessment (3)

- Categories within a dimension are not judging fitness, preferability, suitability; just categorizing an aspect
- Other dimensions exist
 - Not included in these basic dimensions
 - Some will also influence suitability for a given situation
 - Sensitivity - graded, not distinct categories
 - ❖ OA sensitivity to change in the measured concept
 - ❖ Change in the meaningful aspect of feels or functions when to change in the measured concept

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Identification of OAs

- Name of actual assessment
- Concept that the OA actually measures
- Indirect measures:
 - Not evaluating feels or functions directly
 - Also need to name the meaningful aspect of feels or functions intended to be inferred
- Direct measures:
 - Measured concept is meaningful
- Examples
 - Numeric rating scale *for* Pain Intensity
 - ETDRS Eye chart *for* visual acuity *for* vision-dependent activities

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Identification of OAs

- Essential to identify the meaningful concept that is intended
- Essential to identify the intermediate concept for Indirect measures
- Caution regarding name of tool
 - Name of tool does not make it 'something'; its characteristics do
 - Some indirect tools are given a name not reflecting what is measured; can create confusion and miscommunication

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Acceptance Criteria for OAs

- Well-defined
- Reliable
- Interpretable
 - Self-evident for Direct measures
- Indirect measures
 - Well-defined is related to the concept actually measured
 - Also essential to establish a relationship between changes in the measured concept and the intended ultimate meaningful concept

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Other OA Terms

- Multi-component measures
 - Need to be dissected; more difficult to evaluate if a mixture of direct and indirect sub-measures
 - Not-well-defined measures (eg, amorphous 'global' measures) may be impossible to evaluate and accept
- Clinical measure / endpoint
- Surrogate endpoint
- Mortality
 - Unique
- Proxy-reported assessment
 - Not a valid method

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2-D Representation of the Framework

- Multiple possible hierarchy orders to squash four dimensions onto a 2-D drawing
- All are equivalent
- Dimensions can be applied in any order and wind up in the same place
- Display may be selected to highlight characteristics of particular focus

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Assessment Characteristics Chart

Dimension								
Psyche Influence		Psychomodulated Measures						Biomarker
Who Measures		Patient		Clinician		Observer		Instrument
Relationship to Treatment Benefit		Direct	Indirect	Direct	Indirect	Direct	Indirect	Indirect
How Obtained	Naturalistic	10cm VAS	Rescue Medication Use	PANSS	Joint flexion spasticity	Observed seizures	Observed infant behavior	HbA1c
	Artificial Procedure	NONE	Alcohol Presentation Challenge	NONE	9-Hole Peg test, 6-min Walk, FEV1	NONE	?	Endocrine stimulation tests

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Other Issues

- Any single endpoint is not expected to evaluate the entire disease
 - May require multiple OAs to evaluate all the major features of a disorder
 - Treatment benefit claims are the disease features specifically shown to benefit by the OA
- Risk-Benefit
 - Not usually from any single OA
 - Most OAs measure only one benefit
 - Usually need several OAs to get an evaluation of treatment effect on all major features of disease
 - Risks usually measured separately from benefits