Clinical Outcome Assessment: A Regulatory Perspective

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Disclaimer

- Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position.

Agenda

- Role of COAs in assessing clinical benefit
- FDA review of COAs
- Pathways for engagement

Regulatory considerations for COA selection or development

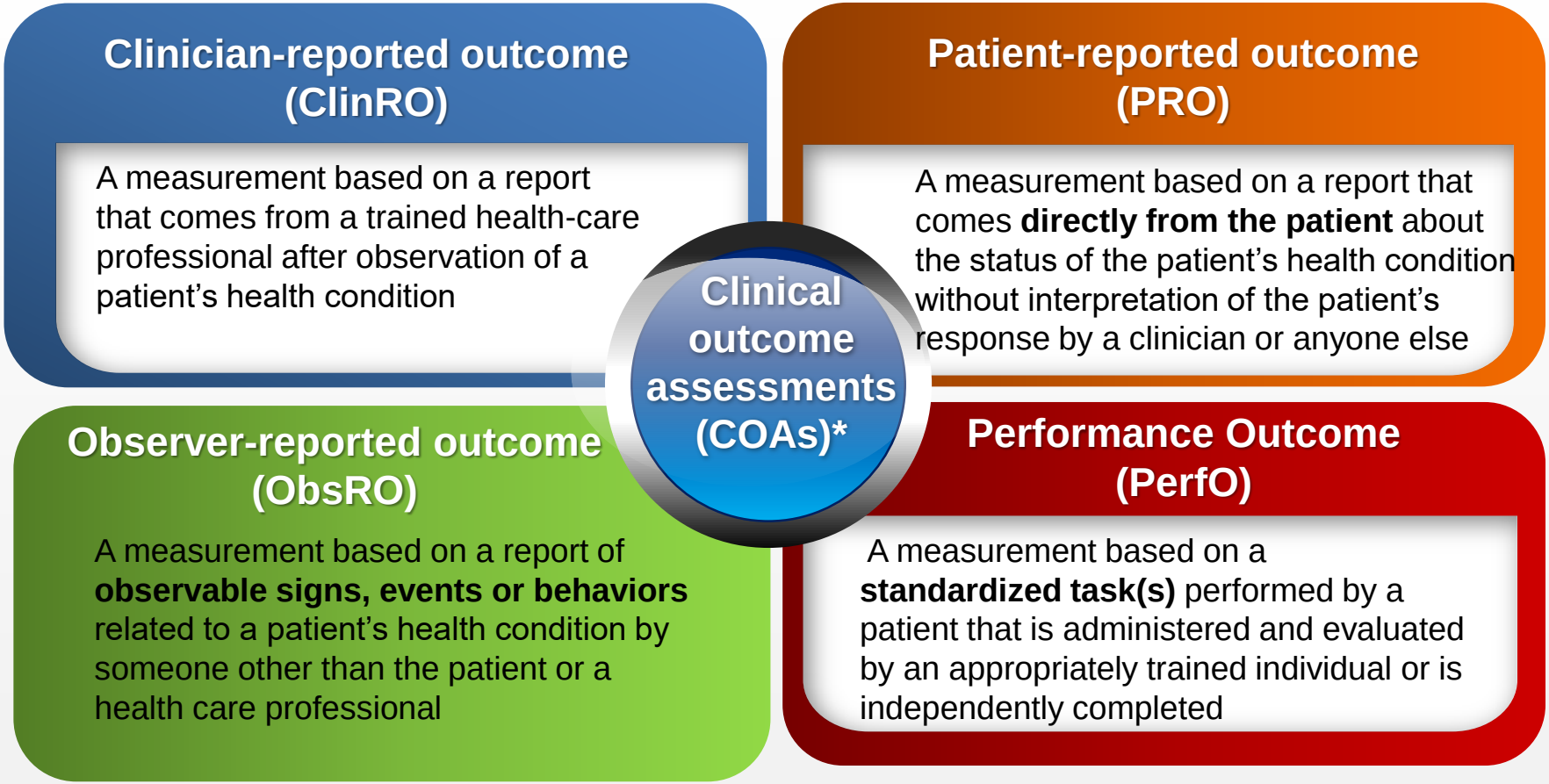
Purpose of Efficacy Outcome Assessment

- **Clinical Benefit:**
  - A positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual **feels**, **functions**, or **survives**.

Source: FDA-NIH Resource: Biomarkers EndpointS and other Tools (BEST glossary)

Clinical Outcome Assessments (COAs)

- COA- *An assessment that describes or reflects how an individual feels, functions or survives*
- COAs include
  - Patient-reported outcome measures
  - Clinician-reported outcome measures
  - Observer-reported outcome measure
  - Performance outcome measures

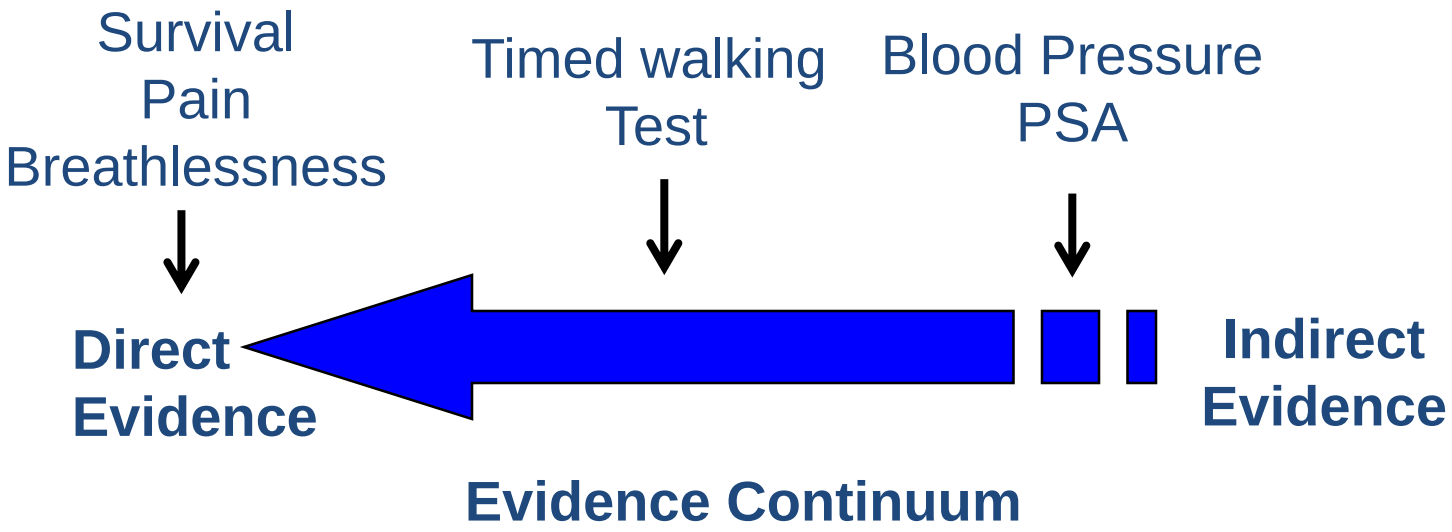


*Digital health technology (e.g., activity monitors, sleep monitors) can also be used to collect clinical outcomes.

Evidence of Clinical Benefit

- Direct evidence of clinical benefit is derived from studies with endpoints that measure survival, or how patients feel and function in daily life
- Indirect evidence of clinical benefit is derived from studies with endpoints that measure other things that are related to how patients survive, feel or function

Direct Verses Indirect Evidence of Treatment Benefit



FDA Review of COAs

Why does FDA evaluate outcome assessments?

1. Form the basis of labeling claims:

   Claims cannot be false or misleading

2. Should minimize unwanted variability (noise) and be sensitive to true change in a patient's status

How does FDA review COAs?

- FDA evaluates an instrument in the context of its intended use, including clinical trial design, patient population, desired labeling claim
- In other words, there is no such thing as instrument validation for all purposes
- FDA PRO Guidance (2009)* describes good measurement principles applicable to all COA types

*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf

Measurement properties (1/2)

- **Content Validity (Important for labeling claims)**
  - Extent to which the content of an instrument represents important aspects of a given concept for the intended use and target population
  - Supported by qualitative and quantitative evidence

Measurement properties (2/2)

- **Other measurement properties** (quantitative)
  - Reliability (How reproducible is the measure?)
  - Construct validity (e.g., Are the quantitative associations with other variables as expected?)
  - Ability to detect change

Some common COA review issues (1/2)

- Was the instrument developed with input from the relevant stakeholder(s)?

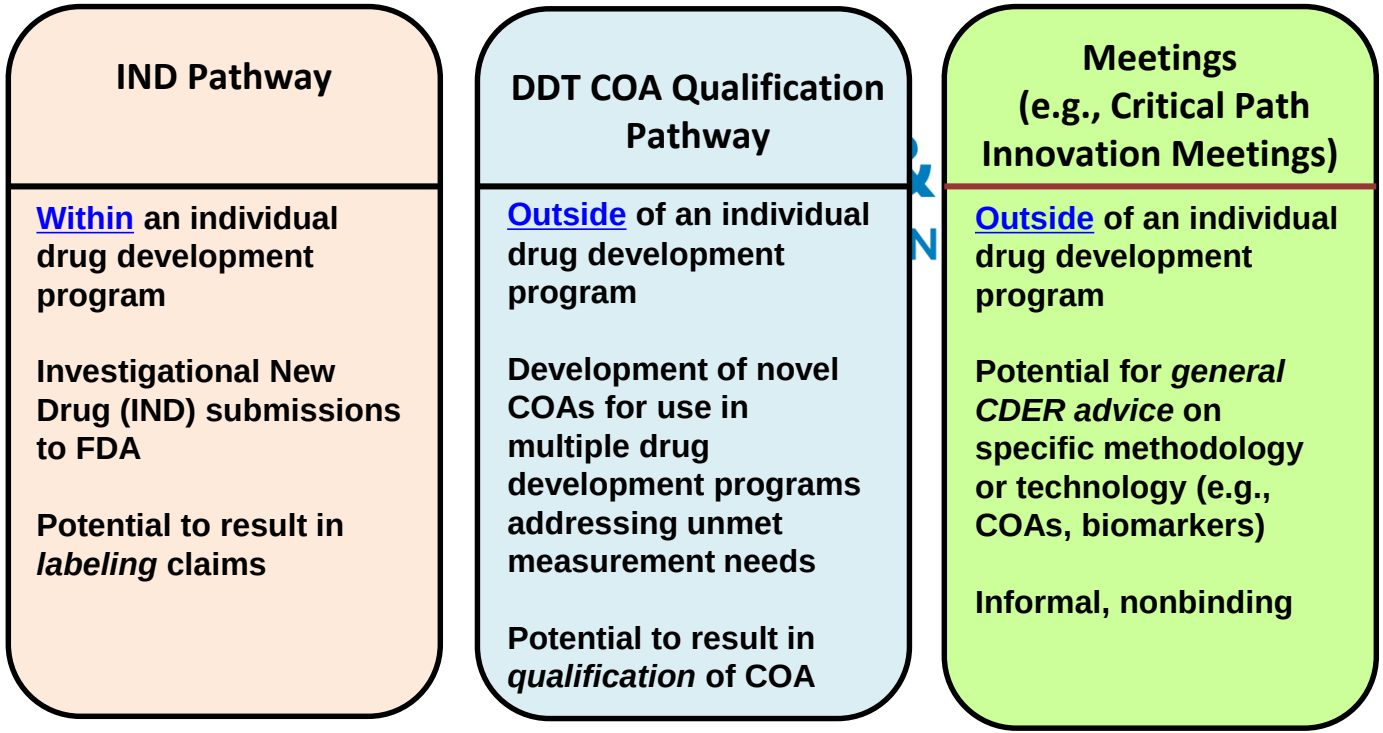
  If not,

  - It may omit what is most important and relevant
  - May include irrelevant content
  - The instructions, questions and response options may not be well-understood

Some common COA review issues (2/2)

- Is the instrument appropriate for the study design/patient population/ or research question? **If not,**
  - It may be poorly matched to the severity of the patient (e.g., patient may be at the low or high end of the scale)
  - It may not be reliable, valid or responsive to change (e.g., use of a dexterity test developed for the general population in a population with visual impairment)
  - It may capture something important to patients, but not what the drug is targeting
- Is the instrument's concept clear and well-defined? Is its content reflective of the concept of interest?
  - If not, it may be difficult or impossible to accurately describe in labeling

Pathways for Engagement



DDT = Drug Development Tool; COA = Clinical Outcome Assessment; PRO = Patient-Reported Outcome
NDA = New Drug Application; BLA = Biologics Licensing Application

DDT Qualification Process

- An FDA review pathway for DDTs intended for potential use in multiple drug development programs
  - **Qualification:** Regulatory conclusion that within the stated context of use, the results of the DDT measurement can be relied upon to have a stated interpretation and utility – “fit for purpose”
  - Process is ***voluntary***: A DDT does not need to undergo this process to have regulatory acceptance
  - Qualification allows an instrument to be reviewed once (for a particular context of use) and once qualified, further review will not be necessary when used in the qualified context of use
  - Three CDER qualification programs: Biomarkers, COAs and animal models under the Animal Rule

Resources

- **FDA Division of Clinical Outcome Assessment Website:** http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm349031.htm#Endpoints
- **DDT Qualification Program Website**
- https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs
- **Final 2009 PRO Guidance:** http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
- **BEST Glossary (Biomarkers EndpointS and other Tools:** https://www.ncbi.nlm.nih.gov/books/NBK326791/
- **Critical Path Innovation Meeting Website & Guidance:** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm
- **Patient-focused drug development guidance series Website:** https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm610279.htm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