Clinical trial endpoints for use in medical product development

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Disclaimer

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

Overview

- Background and key terms
- Clinical outcome assessments
- Surrogate endpoints
- Use of multiple endpoints

Purpose of Efficacy Outcome Assessment

- **Clinical Benefit:**
  - A positive clinically meaningful effect of an intervention on how an individual **feels, functions,** or **survives**
- We use efficacy endpoints to assess the clinical benefit of medical products
- Ultimately, how we describe this clinical benefit to patients, providers and other stakeholders is determined by the **concept** (or outcome) that was measured

What is an endpoint?

- Endpoint: A precisely defined variable intended to reflect an outcome of interest that is prespecified (i.e., chosen before the data are analyzed) and statistically analyzed to address a particular research question

FDA-NIH Biomarker Working Group. (2016). BEST (Biomarkers, EndpointS, and other Tools) Resource. https://www.ncbi.nlm.nih.gov/books/NBK326791/pdf/Bookshelf_NBK326791.pdf

Drug regulations for outcome assessments

- *"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 the criteria used to assess response**."*
- 21 CFR 314.126(b)(6)

Why does FDA evaluate endpoints to ensure they're well-defined and reliable?

1. Endpoints form the basis of labeling claims:

   Claims cannot be false or misleading

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

Clinical vs. Surrogate Endpoints*

- Clinical endpoints
  - Endpoints that describe or reflect how an individual *feels, functions or survives*
  - *Assessed using* ***clinical outcome assessments (COAs)***

- Surrogate endpoints
  - Endpoints used as a substitute for a direct measure of how a patient feels, functions or survives and thought to predict such effects
    - Usually based on a biomarker (i.e., A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions)

*Source: BEST (Biomarkers, EndpointS, and other Tools) Resource

Building blocks of an endpoint

- How is it assessed? Using what instrument/tool*?
- When is it assessed? What are the timepoints? Duration of observation?
- What is the endpoint formulation? E.g.,
  - Mean change from baseline
  - Responder definition
  - Time-to-event (e.g., death, tumor progression)
  - Number of events in a time period (e.g., migraine episodes in 12 weeks)
  - Area under the curve (e.g., blood glucose level)

*An assessment system comprising three essential components: 1) materials for measurement; 2) an assay for obtaining the measurement; and 3) method and/or criteria for interpreting those measurements.

But, how do we arrive at these endpoint components?

What do we need to consider when developing or reviewing an endpoint?

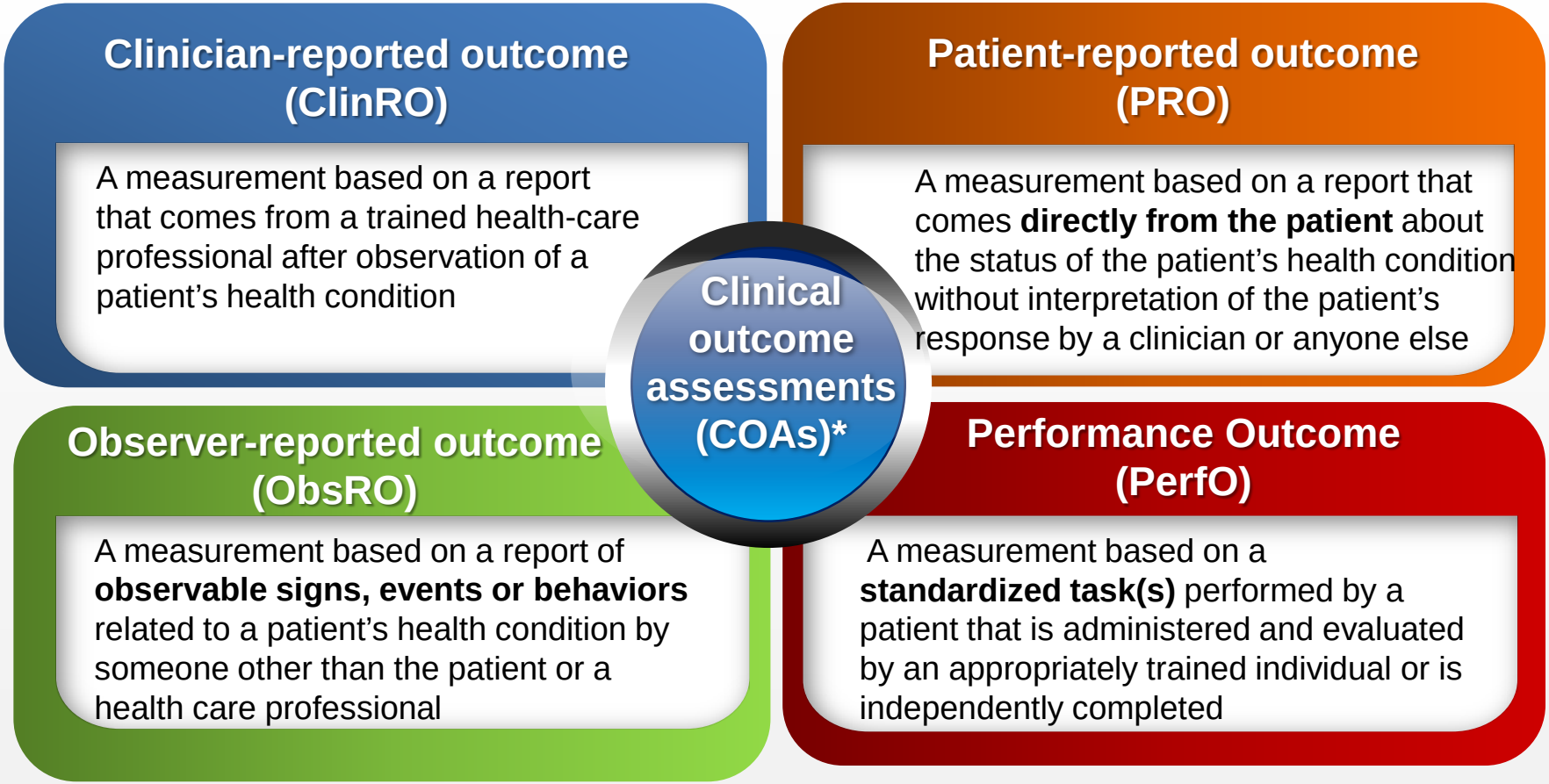
Important considerations (1/2)

- Does the endpoint align with the study objectives?
- What are the most important concepts to (the majority of) patients that are also modifiable with the intervention?
- Is there an existing tool to assess the concept in the target population? What is the level of validation of the tool or instrument? Does it reliably measure what it claims in the context it will be used?
- Are there clear instructions and training for patients, investigators, caregivers to provide standardization of assessment and minimize noise? Is there a user manual/training materials for the tool?
- Are the assessments overly burdensome to patients, study staff? Expense? Specialized equipment?

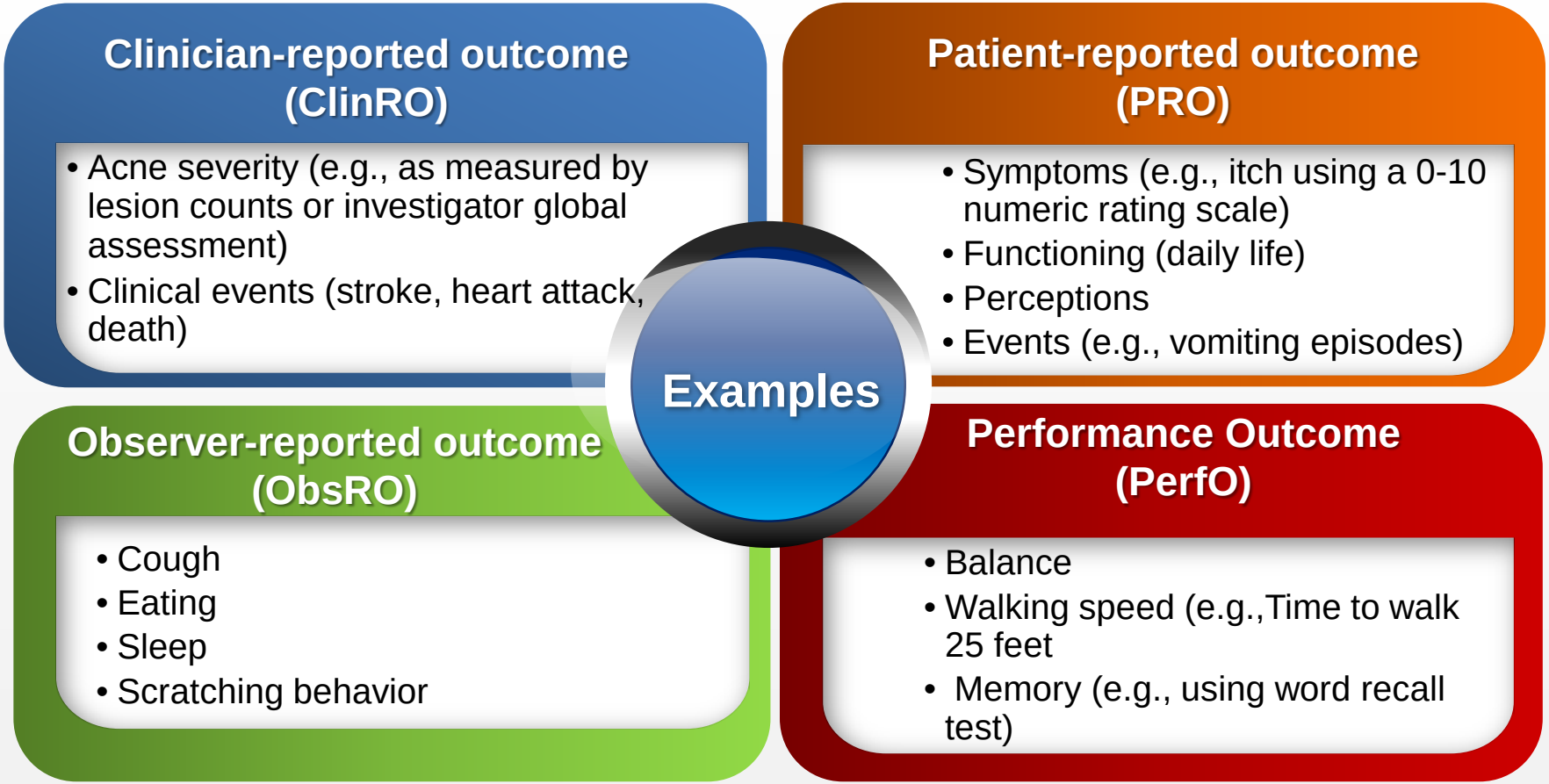
Important considerations (2/2)

- For a surrogate endpoint, does it validly predict a specified clinical benefit in the intended patient population?
- When (and how often) will the endpoint be assessed? Is the period of observation sufficient to observe the change in patient status?
- Are patients assessed at early discontinuation (or early cross over) to avoid missing observations?
- How will the endpoint be analyzed? Is the analysis appropriate for the endpoint?
- What is clinically meaningful within-patient change? How will the endpoint be interpreted and communicated?
- How are a clinical trial's endpoints related to each other?
- Others…

Clinical outcome assessments



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



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

How does FDA review COAs?

- FDA evaluates an instrument in the context of its intended use (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

Key characteristics to be evaluated

- **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
- 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

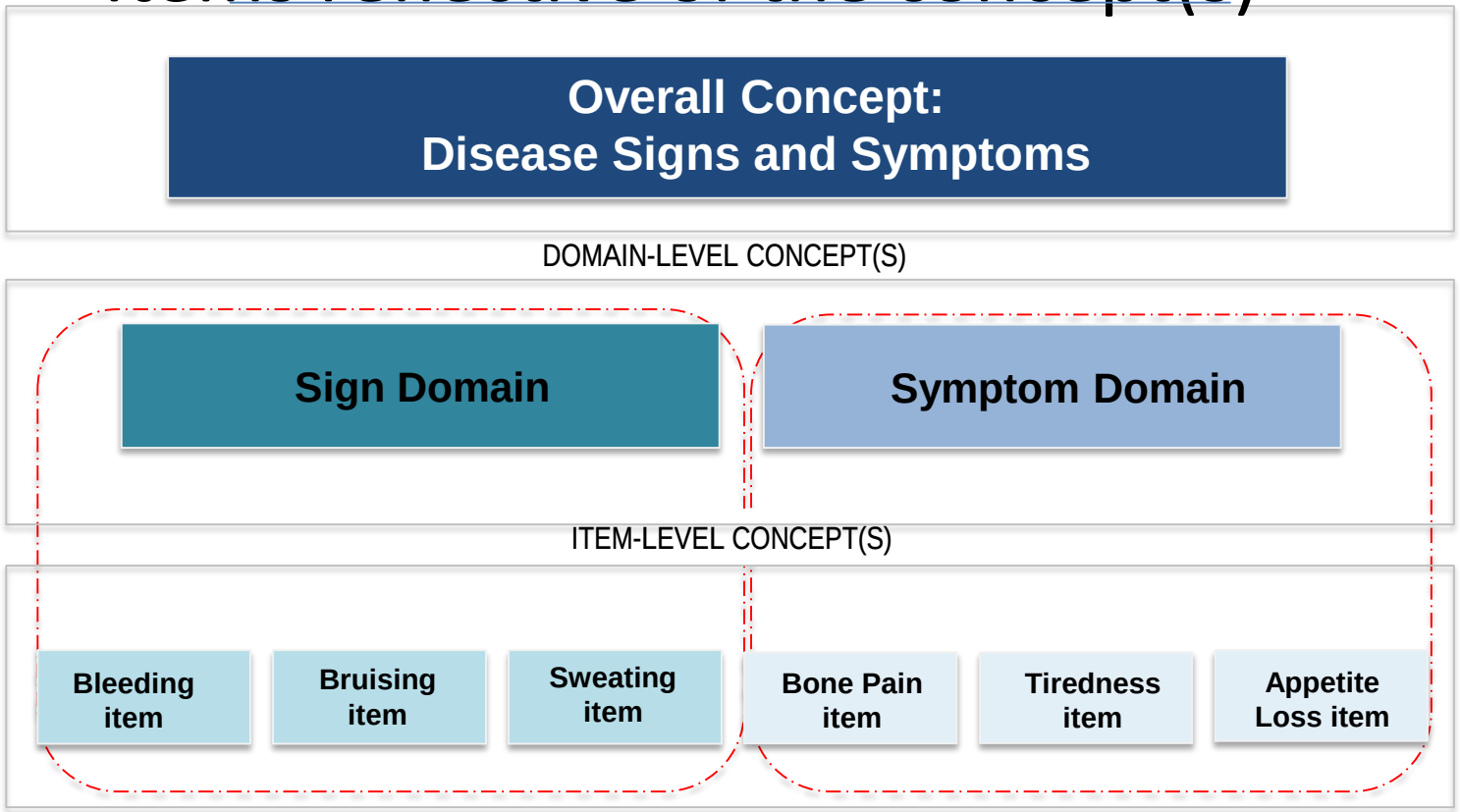
Some common COA review issues

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

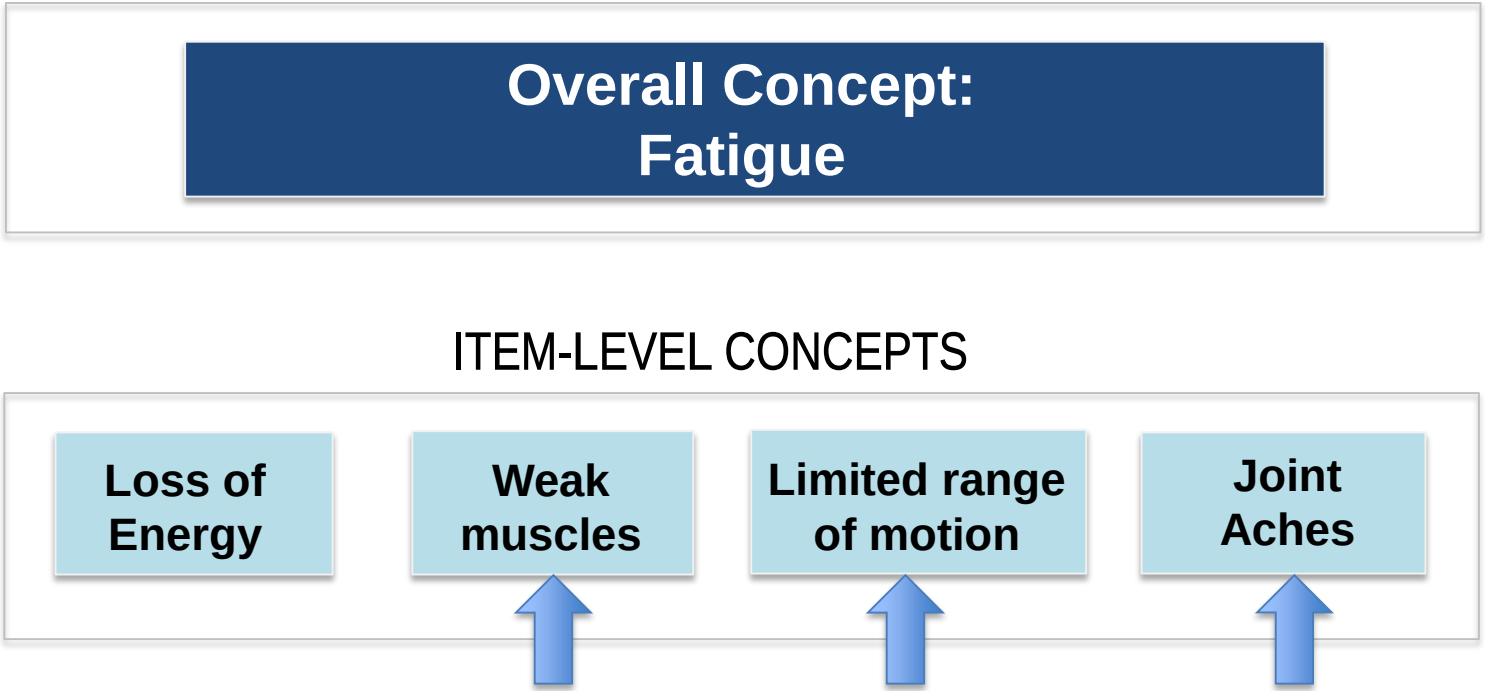
  If not,
  - It may omit what is most important and relevant
  - May include irrelevant questions
  - The instructions, questions and response options may not be well-understood
- Is the instrument appropriate for the study design/patient population/ or research question? **If not,**
  - It may be poorly 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

Examples

Hypothetical Example: Items reflective of the concept(s)



Hypothetical example: Item content **not** reflective of the target concept (lacks content validity)



We would question content validity if…

- Context of use:
  - Study population = progressive neurodegenerative disorder, non-ambulatory
  - Drug is intended to slow rate of progression
- Instrument: questionnaire to assess physical functioning
- One question: “Do you have trouble running to the bus?”

Content validity in creating a PRO Instrument

- Patient input into the items and response options provide assurance that the measure captures the concept of interest

1-Mild

2-Discomforting

3-Distressing

4-Horrible

5-Excruciating

Questionable ability of response options to reliably distinguish patients by pain severity

How do we evaluate clinical meaningfulness?

1. Does the endpoint **assess or reflect** something that matters to the patient? [Note: Clinical exam findings may not always be reflective of what matters to patients.]

2. How much of a difference on the measure (within-person change) makes a difference in patients' lives?

   Statistical significance ≠ Clinical significance

3. What are the risks in relation to the benefits? (Benefit: Risk relationship)

4. In addition to mean changes, it's important to look at the distribution of patients' responses (some have larger effects and others have smaller effects)

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Surrogate endpoints

Endpoints used as a substitute for a direct measure of how a patient feels, functions or survives and thought to predict such effects

Why use a surrogate endpoint?

- Useful when demonstrating meaningful effect on a clinical endpoint is:
  - Not feasible within a reasonable timeframe or sample size
    - Very low event rates
    - Very long latency of the clinical outcome (e.g., slow rate of decline)
  - Not ethical
- Potential benefits: Faster drug development and smaller studies
  - e.g., Faster to establish an effect on blood pressure vs. a benefit on stroke

Categories of surrogate endpoints*

- **Validated** (Support: Traditional approval)
  - **Clear mechanistic rationale** and **clinical data** providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical outcome
- **Reasonably likely** (Support: Accelerated approval)
  - **Strong mechanistic and/or epidemiologic rationale** such that an effect on the surrogate endpoint is expected to be associated with an endpoint intended to assess clinical benefit in clinical trials, but **without sufficient clinical data** to show that it is a validated surrogate endpoint

* **BEST Glossary (Biomarkers EndpointS and other Tools)**

Examples:
Validated Surrogate Endpoints

Validated surrogate endpoint measure* (Support traditional approval)	Predicted clinical outcome
Systolic blood pressure	Occurrence of stroke
HIV viral load	Development of AIDS diagnosis
Hemoglobin A1c (HbA1c)	Complications of diabetes (kidney, retina)

*When used in the appropriate context

Examples:
Reasonably Likely Surrogate Endpoints

Reasonably likely surrogate endpoint measure* (Support accelerated approval)	Predicted clinical outcome
Radiographic evidence of tumor shrinkage (response rate) in certain cancer types	Overall survival
Clearance of bacteria from the blood stream (laboratory measure)	Clinical resolution of infection

*When used in the appropriate context

A few words on surrogate endpoint development & evaluation

- Can't begin to evaluate a surrogate endpoint unless you define the clinical outcome that you're predicting
- **Prognostic information is insufficient** to demonstrate surrogate is valid—need clinical trial data to show a predictive relationship
  - 'A correlate does not a surrogate make.'—Fleming and DeMets
  - Examples of failures of apparently reasonable proposed surrogate endpoints have led to caution e.g., Cardiac Arrhythmia Suppression Trial (CAST)
- Status of a biomarker as a surrogate endpoint is **context specific** and a biomarker cannot assumed to be a general surrogate endpoint

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Use of multiple endpoints

Totality of evidence: Use of multiple measures

- Benefit-risk is based on totality of the evidence in the patient population of interest
  - Different outcome measures are often used in various combinations to support regulatory decisions
  - The endpoint hierarchy with descriptions of measures and concepts should explain the relationships of endpoints in a clinical trial

Multiple Endpoints in Clinical Trials

Draft Guidance for Industry (January, 2017)

- Three endpoint families:
  - Primary: to establish effectiveness and/or safety features of the drug
  - Secondary: to support primary or show additional effects (after "win" on primary)
  - Exploratory: all other endpoints
- Categories of "Multiple primary endpoints" include:
  - Multiple primary endpoints: Need to "win" on **at least one** of two or more
  - Coprimary endpoints: Need to "win" on **ALL** of two or more
  - Composite endpoints: More than one clinical outcome important (all expected to be affected by the drug) and **any one** would be considered an "endpoint event," but event rates are low
    - E.g., "MACE": cardiovascular death, non-fatal MI, and non-fatal stroke

In closing…

- Endpoint development and implementation is a multistakeholder, multidisciplinary endeavor
- Clinical investigators are well-positioned to provide input into many important questions including:
  - Are the study objectives and endpoints designed to answer important questions for medical decision making?
  - Is it clear how the assessments should be administered (including clear instructions, training and user manuals)?
  - Do the COAs reflect concepts/outcomes that are (a) important to patients and (b) expected to change in the trial?
- As a clinical investigator, you play a key role in the success of outcome measurement!

Resources

- **FDA COA Staff Website:** http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm349031.htm#Endpoints
- **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/
- **Multiple Endpoints in Clinical Trials Guidance:** https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536750.pdf
- **DDT COA Qualification Website:** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm
- **COA Compendium:** www.fda.gov/COACompendium
- **Surrogate Endpoint Table:** https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm613636.htm
- **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

To learn more about the science of clinical outcome assessment…

- The *Science of Clinical Outcome Assessment (COA) in Medical Product Development – An Intensive Online Educational Series* has launched and is live on the portal.

- CE Classroom: https://ce.pharmacy.umaryland.edu/ProductDetails.aspx?ProductID=311

- Non-CE Classroom: https://ce.pharmacy.umaryland.edu/ProductDetails.aspx?ProductID=313

Thank you!


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