



## Clinical Trial Outcome Assessments

### *Concept Definition and Context of Use*

Clinical Trial Outcome Assessment Workshop  
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*The views expressed are those of the author, and do not  
necessarily represent an official FDA position*

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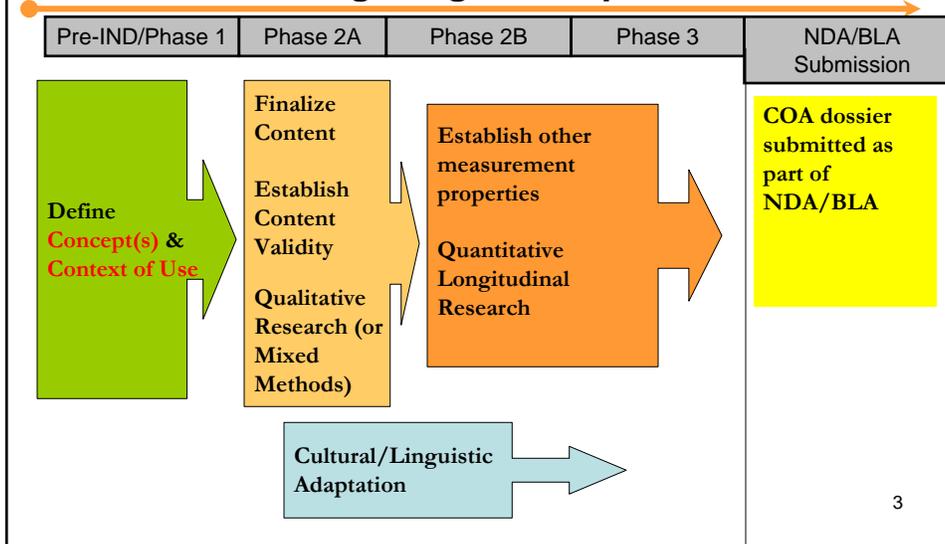


## Clinical Trial Outcome Assessments (COAs)

- FDA reviews clinical trial outcome assessments when:
  - Used to provide substantiation for treatment benefit claims
  - Primary or key secondary endpoints
  - Consistent with effectiveness or comparative safety benefit objectives
- Two processes for FDA submission and review
  - As part of a drug application (IND/NDA/BLA) review
  - Under the DDT qualification process
- The same FDA review principles apply to both processes
- Initial consideration for good measurement principles set forth in the FDA PRO guidance
  - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>
- The goal of this workshop is to explore issues not yet addressed by FDA guidance

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## Timeline for COA Development During Drug Development



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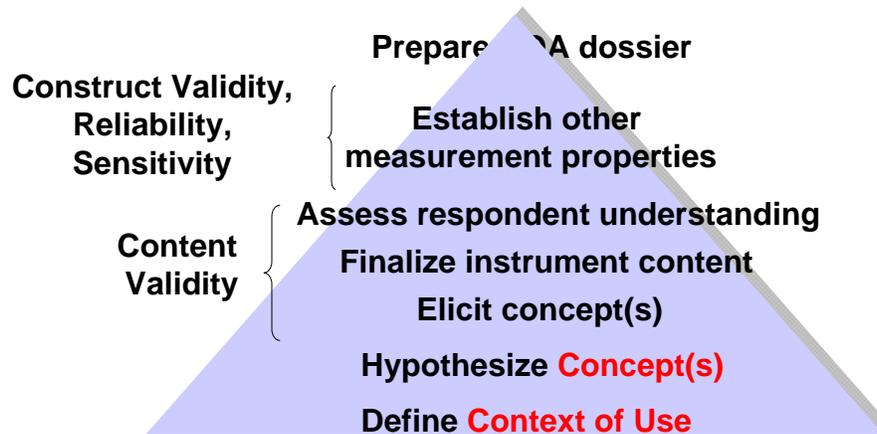
## Qualification: COA Development Independent of Drug Development

- A new regulatory process to provide **publicly available** drug development tools independent of the application process  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>
- Two stages of the qualification process
  - Consultation and advice
  - Qualification review
- For COAs, FDA qualification represents a conclusion that within the stated **context of use**, the results of assessment can be relied upon to measure a specific **concept** and have a specific interpretation and application in drug development and regulatory decision-making and labeling

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## Clinical Trial Outcome Assessment Development and Review

Goal: Well defined and reliable COA

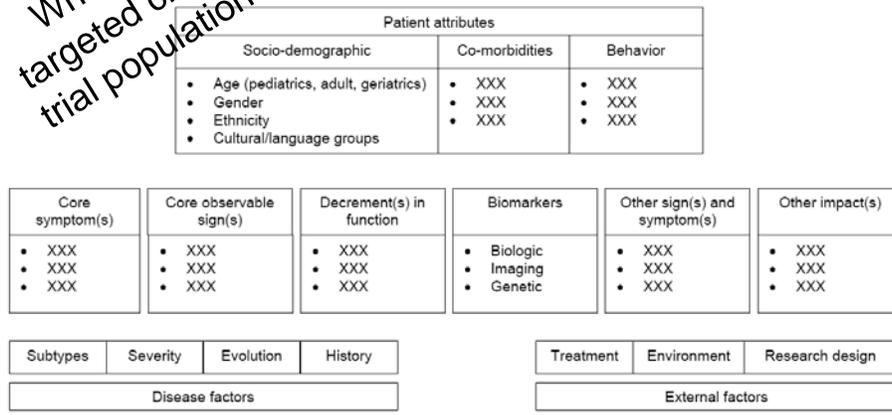


## **Context of Use** for COA Development & Review

- Disease definition
- Target subpopulation (age, disease severity)
- Clinical trial design and objectives
- Endpoint model
- Geographic location of the study sites
  - Language and culture
  - Clinical practice variations
- Targeted claim
- Other (e.g., electronic format)

## Context of Use for COA Development & Review: Disease Definition

Who is the targeted clinical trial population?

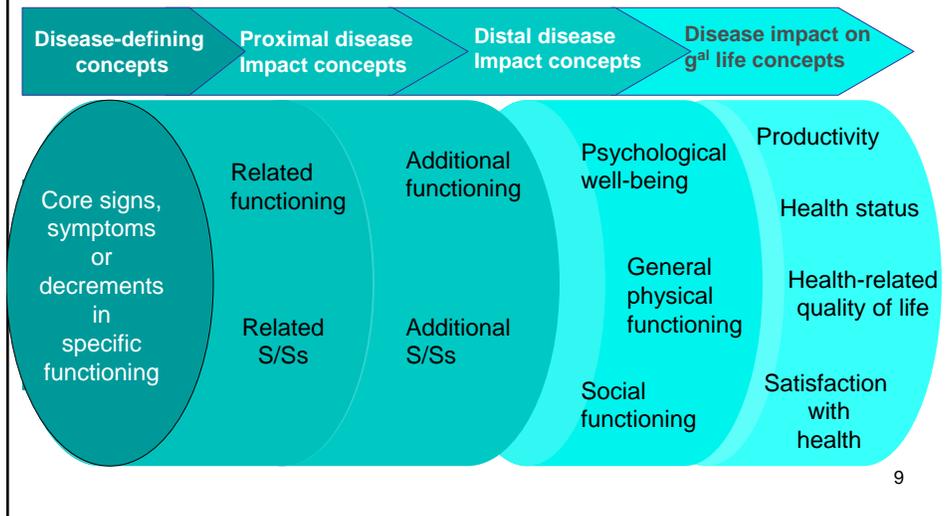


## Context of Use for COA Development & Review: Endpoint Model

The role and hierarchy of relevant outcome concepts in clinical trials (i.e., all primary and secondary endpoints)

<u>Endpoints</u>	<u>Concepts</u>	<u>COA/Biomarker/Survival</u>
<b>Primary</b>	→ Concept A	OA 1
<b>Secondary with Hierarchy</b>	→ Concept B	OA 2
	→ Concept C	OA 3
	→ Concept D	OA 4
	→ Concept E	OA 5
<b>Exploratory</b>	→ Other concept	Other OA

## Concept Definition for COA Development and Review



## “Well Defined and Reliable”

- Patient variability identified and addressed
  - True variability/heterogeneity in the population and within the patient over time
  - COA developed to adequately assess all important population subsets to be enrolled in future trials
- Random variation minimized (error)
  - Test-retest or inter-rater reliability optimized
- Systematic, non-random variation minimized (validity)
  - COA is appropriate and comprehensive in **context of use**
- Experiment design and conduct error eliminated
  - With explicit training and instructions for use
- Result: Assay sensitivity and interpretability of clinical trial results improved

## On the topic of “Is it VALIDATED?”

- It is wrong to speak of a "reliable and valid" test. Reliability and validity are **not immutable, inherent properties of a scale** but rather a result of interaction between the COA and the **context of use**.  
— paraphrased from Streiner and Norman
- “...validity usually is a matter of degree rather than an all-or-none property, and validation is an unending process....Strictly speaking, one validates the use to which a measuring instrument is put rather than the instrument itself. Tests are often valid for one purpose but not another.”  
— Nunnally JC & Bernstein IH

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## Conclusion

- Goals for COA development process
  - Efficient
  - Available in a timely manner
  - Appropriate for the intended **concept(s)** and **context of use**
- Identify **context of use** and measurement **concepts** early in product development to allow plenty of time for:
  - Evaluating existing measures
  - Modifying or developing a measure
- Allow time to interact with FDA early
- Consider a consortium approach

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