

Regulatory Considerations When Conducting Clinical Trials for the Treatment of Autism Spectrum Disorder

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Evaluating Clinical Outcomes

- Typical development programs use established endpoints to evaluate clinical outcomes
 - PANSS, BPRS
 - HAM-D, MADRS
 - HAM-A
 - ABC-I
- Open to new clinical endpoints
 - BUT, the onus is on the sponsor to make the case for that endpoint

Clinical Outcome Assessments

- Four types of COAs
 - Patient-reported outcome (PRO) measures
 - Clinician-reported outcome (ClinRO) measures
 - Observer-reported outcome (ObsRO) measures
 - Performance outcome (PerfO) measures.
- Two pathways for evaluating a new endpoint
 - Qualification
 - In the context of a drug development program

Qualification

- Based on a review of the evidence to support the conclusion that the COA is a *well-defined and reliable assessment* of a specified concept of interest for use in adequate and well-controlled studies in a specified context of use.
- Represents a conclusion that, within the stated context of use, 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.
- For COAs that do not provide evidence of how patients feel or function in daily life, qualification also includes a review of the evidence that the concept assessed is an adequate replacement for how patients feel or function in daily life.

Qualification of **CLINICAL OUTCOME ASSESSMENTS (COAs)**

V. Modify Instrument

- Identify a new COU
- Change wording of items, response options, recall period, or mode/method of administration/data collection
- Translate and culturally adapt
- Evaluate modifications using spokes I - IV
- Document all changes

Consider submitting to FDA for qualification of new COA, as appropriate.

IV. Longitudinal Evaluation of Measurement Properties/ Interpretation Methods

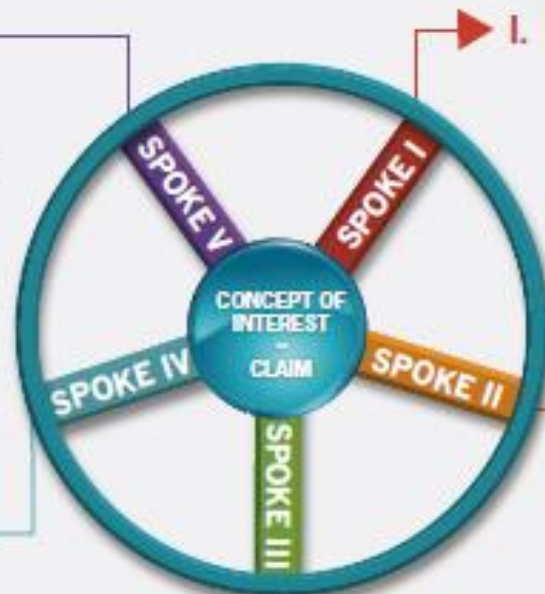
- Assess ability to detect change and construct validity
- Identify responder definition(s)
- Provide guidelines for interpretation of treatment benefit and relationship to claim
- Document all results
- Update user manual

Submit to FDA for COA qualification as effectiveness endpoint to support claims.

III. Cross-sectional Evaluation of Other Measurement Properties

- Assess score reliability (test-retest or inter-rater) and construct validity
- Establish administration procedures & training materials
- Document measure development
- Prepare user manual

Consider submitting to FDA for COA qualification for use in exploratory studies prior to longitudinal evaluation.



I. Identify Context of Use (COU) and Concept of Interest (COI)

- Outline hypothesized concepts and potential claims
- Determine intended population
- Determine intended application/characteristics (type of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework
- Position COA within a preliminary endpoint model
- Document COU and COI

II. Draft Instrument and Evaluate Content Validity

- Obtain patient or other reporter input
- Generate new items
- Select recall period, response options and format
- Select mode/method of administration/data collection
- Conduct cognitive interviewing
- Pilot test draft instrument
- Finalize instrument content, format and scoring rule
- Document content validity



Qualification

- Bar is high
- Only one patient-reported outcome (PRO) has been qualified
 - Exacerbations of Chronic Pulmonary Disease Tool (EXACT)
 - Qualified January, 2014

Review Outside the Qualification Process

- If you plan to include a novel endpoint in your drug development program, ask for feedback early
- The Division will consult with the Clinical Outcomes Assessment Staff (formerly SEALD)
- Be sure to:
 - Identify the construct of interest and context of use
 - Describe how the instrument was developed and validated
 - Provide data supporting the instrument's reliability, validity, and ability to detect a treatment response

Thinking Outside the (Diagnostic) Box

- Indications don't have to be based on diagnostic categories
 - Irritability associated with autism
 - Reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorders
 - Impulsive aggression
 - Cognitive impairment associated with schizophrenia

Clinical Meaningfulness

- Clinically meaningful endpoints that directly measure how a patient **feels, functions, or survives**
- For rating scales, helpful to conduct cognitive interviewing
 - Define meaningful change from patients' perspectives
 - Identify responder definition(s)
 - Provide guidelines for interpretation of treatment benefit and relationship to claim
- Patient-Focused Drug Development meetings
 - Autism is on schedule for FY 2016/17
 - Results in “Voice of the Patient” report

The Search for Biomarkers

- Information on biomarker qualification process also available on FDA website
- Multiple efforts underway to identify potential biomarkers
 - EU-AIMS
 - ABC-CT
 - FNIH
 - RDoCs
- Contrast in EMA vs FDA approach
- Biomarkers cannot establish a clinically meaningful benefit