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

Tiffany R. Farchione, MD
Deputy Director
Division of Psychiatry Products
Center for Drug Evaluation and Research

ISCTM 12th Annual Scientific Meeting
February 18, 2016
(No Financial Disclosures)

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.

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

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.

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

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.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
http://www.fda.gov/Drugs

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