Addressing Methodological Challenges in International CNS Clinical Trials

ISCTM AUTUMN CONFERENCE WORKSHOP
Boston Park Plaza
October 6, 2014
Working Group Chairs: Richard Keefe, PhD; Amir Kalali, MD
A REVIEW: PURPOSE AND USE

THE FDA PRO GUIDANCE

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I have relevant financial relationships with the concepts described, reviewed, evaluated, or compared in this presentation.

Financial - financial compensation from Santium, with 100% ownership interest and income generated from government, healthcare and pharmaceutical industries; providing services centered on psychological assessment instrumentation, including management of psychometric and linguistic validations, and health outcomes research.

Non-financial - No relevant non-financial relationships to disclose.
FDA PRO GUIDANCE
A POSITION DOCUMENT

FDA’s current thinking and attitude to dominant research trends in the pharma industry.

FDA’s expectations for:
   Â  alignment in information exchange
   Â  optimal turn-around timeline

Think of it as a **communication guide** for the type of information FDA expects to see in your submissions.

Do **NOT** think of it as a methodology manual.

**REMEMBER:**
The Guidance could never be a set of concrete requirements that pharma must follow line-by-line to ensure approval from FDA. That is why the guidance is not overly specific. If it were, even if only interpreted as such, it would limit progress in CNS drug development, your scientific and medical objectivity and judgment, and also disregard a monumental volume of psychometric research.

Draft: February 2006; Final: December 2009
PRO GUIDANCE

INTENDED PURPOSE

To accelerate evaluation of claims for medical product labeling.

When...

PROs are used as clinical trial endpoints, and patients' voice is important in approval process.

Claim — statement or implication of treatment benefit

Labeling — packaging insert; description and summary of use, safety, and effectiveness of the medical product (i.e. drug, device, biologic etc.)

- Aimed at confirmatory trials
- Emphasizes need for supporting documentation:
  - PRO development
  - nature of modification
  - psychometric properties and scoring
  - statistical analysis and interpretation
- Supports industry’s view that PROs are important for insights into unobservable symptoms, and relevant patient experiences without clinical interpretation by observing physicians.
- Explains FDA’s SEALD division’s logic and process when evaluating PRO label claims
- Passively implies application to ClinROs and ObsROs
WHY A GUIDANCE FOR PROs?

HISTORICAL CONTEXT: DENIALS OF CLAIMS


Rejection rates for PRO claims remain high across therapeutic areas.
PRO GUIDANCE

CONTENT

1. EVALUATION OF A PRO INSTRUMENT

2. CLINICAL TRIAL DESIGN

3. DATA ANALYSIS & INTERPRETATION

4. GLOSSARY

5. APPENDIX: DOSSIER TEMPLATE

ENDPOINT MODEL
(PRO role in trial)

SELECTION

REAL WORLD
TPP, CDP development, or even later

WHEN?
During TPP development

MODIFICATION / DEVELOPMENT

Does this make sense for pharma to undertake?
Why pharma?

INSTRUMENT
PRO
ClinRO
ObsRO

VALIDITY
RELIABILITY
SENSITIVITY

CONCEPTUAL FRAMEWORK

- Examples of hierarchical relationship chart of concept, domains & items
- Should align with trial objectives

WHEN
12-18 mos. before trial

REAL WORLD
?

COST EFFICIENCY:
Pharma*: $725K - $2.1MM vs. Commercial Test Dev: $300K - $1MM

* Reference for breakdown of pharma cost:
INSTRUMENT MODIFICATION & DEVELOPMENT: The Agile Way

Qualification of CLINICAL OUTCOME ASSESSMENTS (COAs)

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

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 as exploratory endpoint prior to longitudinal evaluation

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

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


LINGUISTIC VALIDATION
SPOKE I - V
PRO GUIDANCE

SOURCES OF CONFUSION RE: LINGUISTIC VALIDATION

Â Inconsistency in detail across guidances
Â Lack of specificity in method
Â Scientifically compromising

DHHS / FDA GUIDELINE (1988)
Guideline for the Format and Content of the Clinical and Statistical Sections of an Application

vs.

FDA PRO GUIDELINE (2009)

USE THE SPOKE WHEEL!

DHHS / FDA GUIDELINE (1988)
Modifications of existing or new instruments

1. For language translations and cultural adaptation processes, include:
   a. Description of the expertise of the translators
   b. Description of procedures used (forward, back, reconciliation, harmonization, assessment of measurement properties)
   c. Description of patient testing
   d. Results of translation / adaptation including clear description of all translation issues and how they were resolved

2. For content, wording, format, or mode of administration changes, describe results from studies conducted to evaluate modification, or rationale for not conducting studies.

3. For use in a new indication or new population, document instrument development and assessment of measurement properties as described above.

FDA PRO GUIDELINE

VIII. Language Translation and Cultural Adaptation

A. Process used to translate and culturally adapt the instrument for populations that will use them in the trial.
B. Description of patient testing, language- or culture-specific concerns, and rationale for decisions made to create new versions.
C. Copies of translated or adapted versions.
D. Evidence that content validity and other measurement properties are comparable between the original and new instruments.

SOURCES OF CONFUSION RE: LINGUISTIC VALIDATION

• Inconsistency in detail across guidances
• Lack of specificity in method
• Scientifically compromising


PRO GUIDANCE

LINGUISTIC VALIDATION

Where is it??

It’s not in the PRO Guidance; or in the DDT Guidance, or in the 1988 Content/Format Guidance....

THE ñWILD PAPERñ from ISPOR

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PRO GUIDANCE

IMPACT

Has it made a difference?

- Admireable intent with recommendations based on sound scientific principles.

- Inconsistent implementation of guidance within SEALD and across other FDA reviewing divisions.

- Some FDA reviewing divisions appear to prefer claims based on specific PROs (usually primary endpoints).

YES, SOME, BUT…

Evidence suggests that since the release of the Draft PRO Guidance, many PRO claims continue to be approved by FDA reviewing divisions; however, the reviewing divisions are not always adhering to the current standards when assessing PRO data for a claim.
