Perspectives on Mixed Methods to Assess Content Validity of a PRO Measure

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Use of Mixed Methods to Assess and Assure Content Validity: The PRO Consortium Perspective

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PRO Consortium: Members

PRO Consortium: Goals

- Enable pre-competitive collaboration that includes FDA input/expertise
- Develop qualified, publicly available PRO instruments
- Avoid development of multiple PRO instruments for the same purpose
- Share costs of developing new PRO instruments
- Facilitate FDA's review of medical products by standardizing PRO endpoints

PRO Consortium

Criteria for selection of specific PRO instruments for development

- Disease/condition with unmet measurement need and a priority area for the member firms
- Disease/condition with regulatory 'demand' for pre-competitive PRO instruments based on feedback from FDA
- Disease/condition currently reliant on more 'objective' measurement where subjective impact of disease via PRO assessment should be assessed

PRO Consortium Working Groups

- Asthma
- Cognition (mild cognitive impairment due to AD)
- Depression
- Functional Dyspepsia
- Irritable Bowel Syndrome
- Lung Cancer (NSCLC)
- Rheumatoid Arthritis

Goal of Each Working Group

To produce and/or compile the necessary evidence to enable new or existing PRO instruments to be “qualified” by the FDA for use in clinical trials where PRO endpoints can be used to support product labeling claims.

FDA Qualification

- Qualification is based on an FDA review of evidence that supports the conclusion that a PRO instrument provides a **well-defined and reliable assessment of a targeted concept in a specified context of use**.

- FDA's *Guidance for Industry: Qualification Process for Drug Development Tools* (draft - October 2010)

PRO Instrument Qualification

…has the potential to:

- More effectively incorporate the patient's voice into the evaluation of treatment effects
- Increase number of accepted PRO measures used to support claims in product labeling
- Enhance comparability/consistency of endpoints across clinical trial
- Improve efficiency for sponsors in endpoint selection
- Improve product labeling

Initial Working Group Stages

Scoping Stage

FDA to review Scoping Stage Summary Document

Vendor Selection Stage (prepare/release RFP, proposal review, & vendor selection)

Qualitative Research Stage

FDA reviews Qualitative Research Summary Document

Quantitative Research Stage

FDA reviews Quantitative Research Summary Document in draft "Qualification Dossier"

Qualification Stage

FDA to review "Qualification Dossier" and make "fit-for-purpose" determination

Milestone Documents

Scoping Stage Summary Document:

- PRO concept identification
- Proposed: target population, conceptual framework, claim, and endpoint model

Qualitative Research Summary Document:

- Evidence for content validity of draft PRO measure including confirmation or revision of conceptual framework

Milestone Documents

Quantitative Research Summary Document:

- Evidence supporting measurement model and other measurement properties (i.e., reliability, construct validity, responsiveness) of final PRO instrument

Qualification Dossier:

- Upon successful completion of the previous steps, the summary documents are combined into a "qualification dossier" that is submitted to the FDA

Reasons for Reconsidering Stages

The *Qualitative Research Stage* provided evidence that the right content was identified and that items were selected/developed to capture that content; however, no quantitative item analysis was performed to provide evidence that the content was being adequately measured.

Reasons for Reconsidering Stages

The *Qualitative Research Stage* did not provide evidence that:

- proposed multi-item scales are unidimensional
- all items are providing unique information
- the full range of item response options are used by respondents
- there are no floor or ceiling effects
- the proposed scoring scheme functions properly

Evolving Working Group Stages

Scoping Stage

FDA to review Scoping Stage Summary Document

Vendor Selection Stage (prepare/release RFP, proposal review, & vendor selection)

Content Validity Stage

FDA reviews Content Validity Summary Document

Psychometric Analysis Stage

FDA reviews Psychometric Analysis Summary Document

Qualification Stage

FDA to review "Qualification Dossier" and make "fit-for-purpose" determination

Continued Evolution

- The FDA's SEALD team is preparing a white paper delineating the questions they believe need to be answered to document content validity

- The PRO Consortium has convened a consultant panel to respond to the white paper and describe methodological and statistical approaches that can be used to answer the FDA's questions

Conclusions

- This issue is far from settled within the PRO Consortium and beyond
- The right mix of qualitative and quantitative research during the Content Validity Stage remains an open question
- Whatever the outcome, decisions need to be driven by science and informed by pragmatism