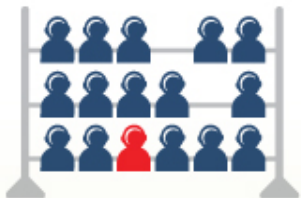




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RARE DISEASE WORKSHOP SERIES

Improving the Clinical Development Process

Addressing Content Validity of PRO Measures: The Unique Case of Rare Diseases

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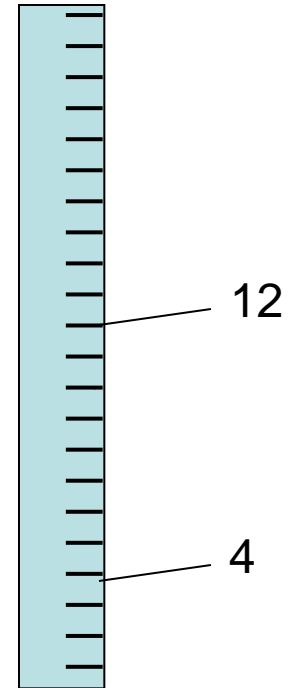
Overview

- I. The Concept & Content Validity
- II. Measurement Options
- III. The Unique Case of Rare Diseases
Challenges & Opportunities
- IV. Conclusions



Measurement & PROs

- **Goal**
 - Accuracy
 - Measure what it's supposed to measure
 - Measure this consistently
 - Ease of use
 - Consistent with the context
 - Useful for communication
 - Common language
 - Interpretable
- **“What” Drives “How”!!**
 - Concept clarification is critical!





Concept Clarification

- What is the target patient population?
 - Diagnosis, stage of disease, age group
- What is the clinical problem?
 - Biologic, physiologic, symptomatic, functional
- How is this problem to be addressed?
 - Intervention - Product or product line
- What is the intended outcome/concept/claim?
 - Improve? Stabilize? Prevent?
- How is this outcome currently defined?
 - Empirically? Clinically?
- How is this outcome (concept) currently measured?
 - Instrument? Other?
- Is this approach or instrument appropriate?
 - Fit for purpose? Sufficiently sensitive?



Content Validity

- The extent to which scores produced by a research instrument represent the target concept(s).
 - contains the relevant & important aspects of the concept.
 - contains a sufficient sampling of content to represent the concept



Evidence (Documentation)

- Evaluation - Based on the methods used to develop and select items and determine the instrument structure
 - the relevant & important aspects of the concept
 - sufficient sampling of content



Measurement Options

Existing versus New Instruments



Measurement Options

- Use an existing instrument
- Adapt an existing instrument
- Develop a new instrument



Measurement Options

- Use an existing instrument
- Adapt an existing instrument
- Develop a new instrument



Addressing Content Validity of an Existing Instrument

- Rothman, M, Burke, L, Erickson, P, Leidy NK, Patrick D, Petrie CD. (2009). Use of existing patient-reported outcome (PRO) instruments and their modification: the ISPOR good research practices for evaluating and documenting content validity for the use of existing instruments and their modification PRO task force report. Value in Health, 12 (8): 1075-83; Epub 2008 Sept 25.



Threats to Validity of Existing Instruments (Rothman et al, 2009)

- Absent or unclear conceptual match between the instrument & claim
- Lack of direct patient input into item content from the target population.
- Lack of evidence regarding saturation – no evidence that the most relevant and important item content is contained in the instrument
- Modification (Adaptation) of an instrument



Existing Instruments

- Rarely have documentation of content validity
 - Generally
 - Target purpose
 - Concept, population
 - Medical product labeling
 - May not be “fit for purpose”



Adapting Instruments

- “Adaptation” includes:
 - Content – Item stems or response options
 - Change, add, or delete
 - Instructions
 - Recall
 - Mode of administration



Adapting Instruments

- “Adaptation” means:
 - The “score” changes:
 - Meaning – content validity
 - Properties
 - validity, reliability, sensitivity
 - Interpretation



Adapting Instruments

- “Adaptation: has implications:
 - Insensitivity
 - effect size?, sample size?
 - Treatment effect?
 - Documentation (labeling claim)



Content Validity??

- The extent to which scores produced by a research instrument represent the target concept(s).
 - contains the relevant & important aspects of the concept.
 - contains a sufficient sampling of content to represent the concept



Qualitative Methods: Evaluating Existing or Adapting Instruments

Concept Elicitation – Content Mapping

- Focus Groups and/or Interviews
 - Sample size varies based on concept and a priori knowledge
 - To saturation
 - Possible Range: 15-30 patients, more or less

Cognitive Interviewing - Evaluation & Understanding

- Interviews
 - Sample size varies – to assure comprehensiveness & clarity
 - Possible Range: 10 to 20 patients, more or less



Measurement Options

- Use an existing instrument
- Adapt an existing instrument
- **Develop a new instrument**



Addressing Content Validity of a New Instrument

- Patrick D, Burke L, Gwaltney C, Leidy NK, Martin M, Ring L. Establishing and reporting evidence of the content validity of newly-developed patient-reported outcomes (PRO) instruments for medical product evaluation: Good research practices, Part 1 – Eliciting concepts for a new PRO instrument. ISPOR Task Force Report under submission, Value in Health.
- Patrick D, Burke L, Gwaltney C, Leidy NK, Martin M, Ring L. Establishing and reporting evidence of the content validity of newly-developed patient-reported outcomes (PRO) instruments for medical product evaluation: Good research practices, Part 2 – Assessing respondent understanding. Task Force Report under submission, Value in Health.



Qualitative Methods: Developing a New Instrument

Concept Elicitation

- Focus Groups:
 - Generally, 4 to 8 groups of 5 to 8 people
- Interviews
 - Often 15 to 40 people
- Broad concepts require more participants

Evaluation & Understanding

- Interviews
 - Generally 5 to 20 people



Challenges

The Unique Case of Rare Disease



Challenges – Trials of Orphan Drugs

- Prevalence: Rare
 - Definition: <200,000 people in the U.S.
- Clinical trial designs (Kesselheim et al., *JAMA*, 2011)
 - Sample size
 - Randomization
 - Masking (blinding)
 - Endpoints
 - Statistical analyses
 - Adverse events



Challenges – Content Validity

- Knowledge
 - Unknowns – disease & patient experience
- Prevalence
 - Fewer patients/participants available
 - Fewer still when excluding those enrolled or eligible for trials
- Access
 - Geographic distribution
 - Across US or global
 - Specialty clinics
 - Patients travel for appointments
- Disease characteristics
 - Rare or acute events, relapses, etc



Implications

- Knowledge
 - Existing disease models, qualitative research, instruments
- Prevalence & Access
 - Patient recruitment & enrollment
 - Focus group feasibility
 - Costs – time and travel for interviewers/focus group leaders
- Disease characteristics
 - Timing to capture acute events, relapses, etc.



Opportunities

The Unique Case of Rare Disease



Plan Early

- Factor challenges into product development planning
- Consider target PRO endpoint early
- Select/develop instrument using sound methods
- Use your sample(s) wisely
- Validate through Phase II trials or registries



Know the Disease & Experience

- Disease attributes & expression
- Publications
- Clinician expertise
- Patient and caregivers groups



Select Focused Outcomes

- Example
 - “function” versus range of motion or muscle strength
 - “fatigue” versus muscle strength/weakness
 - “health-related quality of life” versus pain
- Advantages
 - Easier to understand and communicate
 - Less qualitative data required to achieve saturation
 - Likely to be less variable – within and between patients



Use or Adapt Existing Instruments

- Develop a disease model (Patrick et al, *Value Health*)
- Match content (Rothman et al., *Value Health, 2009*)
- Select/decide carefully
 - Existing \neq Good
- If match, document content validity
 - Cognitive interviewing
 - Elicitation & cognitive interviewing



Consider Alternative Methods

Be creative and scientific

- “Modes” of data collection
 - Telephone Interview
 - Virtual focus groups – conference call, web camera
- Sample/respondents
 - Excellent informants describing patient experiences
- Existing resources
 - Registries, Patient advocacy group
 - Exit interviews in clinical trials
- Validation studies
 - Phase II, patient registries?
- Option B
 - Post-approval PRO labeling?



Collaborate

- Multi-sponsor consortia – outcome measures
 - Examples:
 - EXACT-PRO Initiative <http://www.exactproinitiative.com>
 - Critical Path PRO Initiative <http://www.c-path.org/index.cfm>
- Patient advocacy groups and foundations



Conclusions

Content Validity and Research with Rare Diseases



Patient-Reported Outcomes

- Represent the patient's voice in research.
- Content validity = the accuracy of the voice
 - Scores represent the content (voice)
- Patients with rare disease deserve an accurate voice.
- Optimizing content validity is challenging.
- There are opportunities to address these challenges.



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