

Measurement Issues with Rare Diseases

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Measurement in Clinical Trials: Review & Qualification of
Clinical Outcome Assessments;
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Overview

- I. Rare Diseases
- II. Challenges
- II. Measurement Options
- III. Opportunities/Approaches
- IV. Conclusions

Rare Diseases

- Rare Diseases
 - Definition: <200,000 people in the U.S.
 - Orphan Product: A drug, biologic, device or medical food that is used for the prevention, diagnosis, or treatment of a rare disease.
- Prevalence
 - A disease that is rare in some populations may be common in others.
 - Europe - European Organization for Rare Diseases (EURORDIS)
 - » 5,000 to 7,000 distinct rare disease
 - » 6 to 7% of the EU population are affected by a rare disease
- Perspective
 - “Rare diseases are rare, but rare disease patients are numerous” (Orpha.net)
 - » Orphanet database: 5,954 disease and 4,942 expert centers
 - “Our diseases may be “rare”, but our voices are strong” (A. Kennedy, 2011, Quest)

Rare Diseases - Examples

Name	Estimated Prevalence (/100,000) in Europe
Alpha-1 Antitrypsin Deficiency	25
Cutaneous T-Cell Lymphoma	15
Cystic Fibrosis (CF)	13
Hemophilia A	11
Amyotrophic Lateral Sclerosis (ALS)	5
Mesothelioma	3
Hereditary Angioedema	1
Wolfram Syndrome	0.57
Tay Sachs Disease	0.30
Goucher Disease Type 3	0.05

Orphanet Report Series, Rare Diseases Collection, May 2011 #2

⁴ http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_decreasing_prevalence_or_cases

Rare Diseases - Examples

Name	# Published Cases in Europe
Whipple Disease	1,000
Castleman Disease	400
Marinesco-Sjogren Syndrome	200
Wells Syndrome	80
Rapp-Hodgkin Syndrome	72
Marden-Walker Syndrome	30

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Rare Diseases

- All ages
 - Adults, children, elderly
 - Broad age range
- Multi-faceted
 - Multiple systems
 - May be associated with impaired cognition or communication
- Variable
 - Expression may vary from person to person
 - Within a person over time

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Challenges of Clinical Trial Design

- Sample size
- Randomization
- Masking (blinding)
- **Endpoints**
- Statistical analyses
- Adverse events

Kesselheim et al., Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer *JAMA*, 305, 22: 2320-2326, 2011

Measurement Challenges in Rare Diseases

Challenge	Implications
<u>Knowledge</u> Unknowns: disease & experience	Using existing instruments, disease models, qualitative research
<u>Availability</u> Case and site identification Acute illness Fewer experts Patients, caregivers, clinicians	Recruitment & enrollment Onsite interviews or focus groups
<u>Access</u> Geography - US or global Patients & clinics	Recruitment, enrollment, participation
<u>Variability</u> Age & disease Cognition or communication Rare or acute events	Selecting outcome & respondent Combining data Timing

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Measurement Options – PRO, ObsRO, CliniRo

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

Measurement Options

- Use an existing instrument
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- Develop a new instrument

Addressing Content Validity of an Existing PRO Instrument

- Rothman, M, Burke, L, Erickson, P, Leidy NK, Patrick D, Petrie CD. 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, 2009.

Threats to Validity of Existing Instruments

PROs (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 (PRO, ClinRO, ObsRO)

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

Adapting Instruments

- Includes:
 - Content – Item stems or response options
 - » Change, add, or delete
 - Instructions
 - Recall
 - Mode of administration
- Means:
 - The “score” changes:
 - » Meaning – content validity
 - » Properties
 - validity, reliability, sensitivity
 - » Interpretation

Adapting Instruments

- Implications:
 - Score
 - » History
 - » Meaning – **content validity**
 - » Sensitivity
 - Effect size, Sample size
 - Testing
 - » **Content validity**
 - » Reliability, validity, sensitivity, interpretation, responder definitions
 - Documentation (labeling claim)
 - » Rationale and testing the adaptation
 - » Context of use

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
- PROs, ClinRO, ObsRO

Qualitative Methods - PROs: 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**

Developing a New Instrument

- Target concept
- Structure
 - Recall, response options (checklist, ordinal scaling, ratio scaling)
 - Content
 - Instructions
 - Scoring
- Expert input (patients, observers, clinicians)
- Pilot testing (inter-rater reliability)
- Refinement
- Quantitative testing
 - Score meaning

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Addressing Content Validity of a New PRO 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, 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, Value in Health.

Content Validity: Developing a New PRO 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

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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 ≠ 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
- Existing resources for patient recruitment
 - Registries, Patient advocacy group
 - Exit interviews in clinical trials to document content validity
- Sample/respondents – content validity assessment
 - Excellent informants – patients, caregivers, clinicians
- Highly variable conditions
 - Between patients: Select the outcome/attribute most common across patients
 - Within patients: Daily versus periodic assessment
- Variable age groups
 - Standardize outcome – observed versus self-report
 - Composite measurement of signs and symptoms
 - » Rules: well-defined and reliable

Consider Alternative Methods

- Validation studies
 - Phase II data, patient registries
- Option B
 - Post-approval PRO labeling

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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

Opportunities - Summary

- Plan early
- Know the disease and experience
- Select focused outcomes
- Use or adapt existing instruments
- Consider alternative methods
- Collaborate

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Conclusions

- Measurement (& clinical trials) in rare diseases can be challenging
- Consider the measurement options
 - Select, adapt, develop
 - Minimize threats to validity - sound science still applies
- Take advantage of opportunities to optimize accuracy
 - Plan early, know the disease and experience, select focused outcomes, use or adapt existing instruments, consider alternative methods, collaborate
 - Accuracy
 - » Precision & confidence
 - » Should yield stronger effect sizes
 - Smaller sample sizes to yield statistical significance
- Communicate measurement methods clearly
 - Target concept, measurement method
 - Score meaning and interpretation



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