Development of Validated Instruments

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Overview

• Define Patient Reported Outcomes (PROs)
• Factors to Consider when Developing PROs
• FDA Guidance for PROs
• Use of PROs in FDA Clinical Trials
Patient Reported Outcomes (PROs)

• Any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.

• Can be measured in absolute terms (e.g., severity of a symptom) or as a change from a previous measure.

• In trials, measures the effect of a medical intervention on one or more concepts.
  – Concept is the thing being measured (e.g., symptom, effects on function, severity of health condition).
Concepts a PRO May Capture

- Symptoms
- Symptom impact and functioning
- Disability/handicap
- Adverse events
- Treatment tolerability
- Treatment satisfaction
- Health-related quality of life
Criteria to Consider in PRO Development

• Appropriateness
  – Does the content address the relevant questions for the device?

• Acceptability
  – Is the questionnaire acceptable to patients?

• Feasibility
  – Is it easy to administer and process/analyze?

• Interpretability
  – Are the scores interpretable?

Abstracted from (1) Patient Reported Outcomes Measurement Group: University of Oxford
(2) NIH PROMIS Instrument Development and Validation Standards
Criteria to Consider in PRO Development

• Precision
  – How precise are the scores?

• Reliability
  – Does it produce results that are reproducible and internally consistent?

• Validity
  – Does the questionnaire measure what it claims to measure?

• Responsiveness
  – Does the questionnaire detect changes over time that matter to patients?
Criteria to Consider: Appropriateness (Concepts Measured)

• Conceptual framework to support measurement of the concept of interest
  – Patient interviews, focus groups, qualitative cognitive interviewing inform this process
  – Will evolve with acquisition of empirical data

• Recall period appropriate for population, disease state, or application of the questionnaire
Criteria to Consider: Acceptability

- Administration
  - Mode (self vs. interviewer; paper vs. computer)
  - Time (length of time it takes to complete; frequency of administration)
  - Format of the instrument (layout, appearance, legibility)
  - Language (considering associated idioms and cultural norms)
  - Costs (training of staff, printing of questionnaires, electronic devices)
Criteria to Consider: Interpretability

- The meaningfulness of scores produced by the questionnaire
  - What does a score mean?
  - What is the minimal clinically important difference (minimum score changed deemed beneficial to patients)?
  - Should an overall score be computed and presented to support a given claim?
Criteria to Consider: Precision

• How is the questionnaire scaled?
  – Binary (yes vs. no)
  – Likert/adjectival (e.g., strongly agree, agree, disagree, strongly disagree)
  – Visual analogue
  – Pictoral
  – Weighting of items

• Are there large floor or ceiling effects on the score?
  – Limits discriminatory power and responsiveness
Criteria to Consider: Reliability & Reproducibility

- Internally consistent or reproducible and degree to which questionnaire is free from measurement error
  - Proportion of score that is signal rather than noise
  - As measurement error increases ≥ sample size increases to obtain precise estimates of intervention effect
    - Target 0.7-0.9 in many studies

- Questionnaire yields same results on repeated administrations without any intervention
  - Test-retest reliability (e.g., 2-14 days)
Criteria to Consider: Validity

• Extent to which a questionnaire measures what is intended
  – Qualitative research with the targeted patient population is needed to ensure developmental appropriateness of the measure
    » Face validity (appears to measure concept of interest)
    » Content validity in context of use (adequately covers concept/domain of interest)
  – Quantitative
    » Criterion validity (correlates with another measure considered more accurate. May or may not be available)
    » Construct validity
Establishing Content Validity

• Literature review
• Expert opinion
• Qualitative research (essential)
  – Input from target population of patients to document understandability and comprehensiveness of measure
  – Diversity in demographic & disease characteristics of target population
• Quantitative analyses
  – Rasch
  – Factor analysis
  – Does not eliminate need for high quality cognitive debriefing of the final instrument in the relevant patient population

Establishing Content Validity (cont.)

• Determined after confirmation that the concept and the context of use are appropriate

• Empirical evidence that the instrument measures the targeted concept in the context of use
  – If existing instrument is used for a new context of use, additional content validity evidence may need to be developed

• Content validity must be established before other evidence of construct validity, reliability or sensitivity to change can be interpreted
Criteria to Consider: Responsiveness

• Captures health changes
  – before and after the intervention OR
  – in different disease or treatment states

• Evaluated within specific populations and not a fixed/inherent property of the questionnaire

• Determine the relevant, clinically meaningful effect size
FDA Guidance on PROs

- FDA-wide guidance
- Acknowledges the importance of appropriately and effectively incorporating the patient’s voice into the evaluation of medical products
- Final: December 2009

PRO Development is Iterative

• Reasons for changing items during development
  – Clarity or relevance
  – Response range
  – Variability
  – Reproducibility
  – Inter-item correlation
  – Ability to detect change
  – Item discrimination
  – Redundancy
  – Recall period
Outcome Measure

• The impact of treatment on how patients see, feel, and function in their daily lives
  – Must be well-defined and reliably measured
  – Can be assessed directly (e.g., visual symptoms)
  – Can be assessed indirectly (e.g., visual acuity)
FDA Review of Clinical Trial Outcome Assessments

- Identify the measurement concepts
  - Does the instrument measure the concept it was intended to measure?
  - Does the instrument measure the concept claimed?

- Identify the context of use
  - Primary or secondary endpoints?
  - Trial inclusion criteria?

Designing Clinical Trial Consider use of PROs

• Step 1: Define the diseased population

• Step 2: Define the context of use

• Step 3: Select concepts of measurement that will define treatment benefit or safety concern
Designing Clinical Trial Consider use of PROs (cont.)

• Step 4: Select or develop a well-defined and reliable outcome assessment to measure each concept for the proposed context of use
  – If not observable, need a PRO
  – Observable but does not need clinical judgment may need PRO as well
  – Self-report of symptoms provides direct evidence of treatment benefit or harm and should be used whenever possible
Elements of PRO Submissions Reviewed by FDA

- Concepts being measured
- Number of items
- Conceptual framework of the instrument
- Medical condition and population for intended use
- Data collection method
- Administration mode
- Response options
- Recall period
- Scoring (weighting of items or domains)
- Format
- Translation or cultural adaptation availability

Measurement Properties of PRO

- Should be well established before enrollment in pivotal clinical trial
- Requests for FDA input
  - Need information about labeling goals
  - Hypothesized PRO instrument conceptual framework
  - Relationship of PRO endpoints to clinical trial
Summary

- PROs should be
  - Valid with respect to content in the intended population
  - Psychometrically evaluated
  - Well-developed before utilization in the pivotal clinical trial
  - Considered during the design and planning of the clinical trial
  - Developed with early FDA input
Thank you