FDA Perspectives on IRT/CAT

DIA Workshop on Advances in Health Outcomes Measurement: Exploring the Current State and the Future Applications of Item Response Theory, Item Banks, and Computer-adaptive Testing
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Definitions

- Patient-reported outcome
  - Information relevant to health and treatment as perceived and reported by a study subject
  - PROs may be knowable and reportable by the patient only (e.g., pain severity) or may represent the patient's perspective of otherwise observable information (e.g., sleep time)
  - Each PRO represents specific concept that may be general or specific in nature
    - health-related quality of life
    - functional abilities (e.g., activities of daily living)
    - individual symptoms (e.g., pain severity or nasal symptom complex)
    - health-related events (e.g., sleep time or use of rescue therapy)
- Proxy-reported outcome
  - The same type of information as perceived and reported by another person
  - Generally reserved for situations where the patient is unable to respond or report (e.g., infants, cognitively impaired)

More definitions

- *Quality of Life:* A general concept that implies a personal evaluation of the impact of any or all aspects of life experience on the perception of general well-being. Since this term implies the evaluation of non-health-related aspects of life, it is too broad to be considered appropriate for a medical product claim. "QOL" is often used as an term to refer to the entire subset of endpoints that may be noticeable to patients and may impact their state of well-being, whether or not the endpoints are patient-reported. (See Johnson and Temple, Cancer Trt Rep, 1985; Beitz, Gnecco & Justice, JNCI Monographs, 1996.)
- *Health-related quality of life (HRQL): HRQL* is a multidimensional concept that includes, at a minimum, the domains of physical, psychological (including emotional and cognitive) and social effects of an illness and its treatment.
  - An "HRQL" claim implies the measurement of the overall impact of a medical condition and its treatment on a patient's perception of well-being.
  - Claiming a statistical and meaningful improvement in "HRQL" implies
    - the instrument measures all HRQL domains that are important to the study population with the disease or condition of interest and that may be affected by the treatment under study
    - improvement was demonstrated in all of the domains.

PRO ≠ HRQL

QOL ≠ HRQL

Do definitions matter in clinical trials?

- Absolutely—because FDA thinks in terms of claims
- Certainly, if you measure a difference with any endpoint, you may believe a difference exists.
- The challenge arises when study results appear in the label or in promotion.
- General claims that imply multiple dimensions of a general measurement concept are misleading if the implied dimensions are not measured
- A PRO's conceptual framework and demonstrated psychometric attributes drives study interpretation and the language used to describe study results.

FDA drug approvals, 1997-2002

- 30% (n=214) of new molecular entity labels contained PROs; this proportion was fairly constant over that time period
- About half (n=64) of the labels with PROs mentioned multidimensional PRO instruments
- About 2/3 mentioned unidimensional PRO instruments
- About half mentioned patient-reported event logs

Begin with the end in mind

- A PRO measure is only as useful as it was developed to be
- Success depends on the alignment of product development, clinical trial, and PRO development objectives
- If PRO claim intended, seek an agreement at End of Phase 2 meeting with FDA clinical and statistical disciplines
- Randomized study essential, blinded study preferable

FDA Mission: Better Information for Decision-makers

"....The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines, medical devices and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health."

Streamlining the "Critical Path"

"There is an urgent need to improve the efficiency and effectiveness of the clinical trial process, including trial design, endpoints, and analyses…much more attention and creativity need to be applied to disease-specific trial design and endpoints intended to evaluate the effects of medical products."

http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

Streamlining the "Critical Path"

"*For many therapeutics, effectiveness criteria are best defined by the practitioners and patients who use the products.* ***Much work needs to be done on clinical trial design and patient-driven outcome measures to ensure that endpoints in new therapeutic areas accurately reflect patient needs and values****. Community (health professional and patient) consensus on appropriate outcome measures and therapeutic claims can lay a clear development path for new therapeutics, especially when there is international regulatory harmonization."*

http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

Challenges for the Critical Path Initiative

- New therapeutics with novel mechanisms targeting unique pathways or even diseases may demand novel assessments
- As new endpoints emerge, “validation” requires that we understand not only how these endpoints perform, but what they mean clinically
- Amongst the important considerations in interpreting the clinical meaning of an endpoint (i.e., assessing risk-benefit) is having an idea of the level of change that is important to the patient (i.e., the MID)

Measurement concept

- "Improvement in patient-reported outcomes" is not helpful.
- "Improvement in ABCQOL" is not helpful unless decision-makers are familiar with the instrument and how to interpret results
- We have the ability to demonstrate treatment impact very precisely, but what "concept" are we measuring, and is that concept important to decision-makers?
- FDA always looks at study results in terms of the unidimensional components of multidimensional measures
- Concept definition and domain identification/coverage complications are not solved by IRT
- Use of IRT/CAT in daily clinical practice will increase decision-maker familiarity and therefore the usefulness of resultant measures in clinical trials.

PRO use in clinical trials depends on the instruments demonstrated ability to function as expected in all patient subgroups

- Consideration for all known and possible patient differences that may influence PRO results, e.g., age group, sex, language, culture, disease severity, co-morbidities, etc.
- If patient subgroup specific versions are created, FDA considers whether each version conforms to the pre-specified conceptual framework and whether a version functions similarly between groups
- DIF analysis may offer a convenient contribution for validation studies.

eSource

- Direct electronic data capture technology enables transmission of data from the patient to a centralized databank, bypassing the direct control of the clinical investigator.
- FDA regulations meant to assure data quality require investigators to maintain case histories that record all observations and other data pertinent to the investigation on each study patient including all source documents.
- FDA's acceptance of data from electronic sources depends on the ability to verify the quality and integrity of such data during onsite inspections and audits. Data should be attributable, original, accurate, contemporaneous, and legible.
- When data is transmitted directly from the source to the sponsor, FDA has data integrity concerns since there is no way to inspect independent source data and to verify the authenticity of data submitted to FDA by the sponsor. FDA considers these issues on a case by case basis. Early discussions with FDA are recommended. This is will be a topic of future guidance from the agency.

Summary

- Use of PROs in clinical trials has always had a key role in drug development
- Patients demand better information about treatments
- Many challenges exist with PRO endpoints—item response theory and computer adaptive testing has the potential to both resolve and add to those challenges