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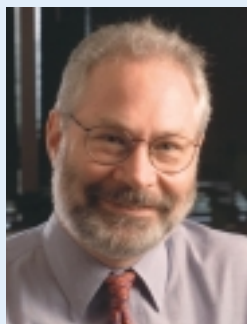
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SCIENCE & POLICY OPINION



The Importance of PROs and the FDA Draft Guidance

By Dennis A. Revicki, PhD

Patient-reported outcomes (PROs) are frequently incorporated into clinical trials comparing health interventions for chronic diseases. These PROs include measures of health-related quality of life (HRQL), health status and functioning, symptom severity and burden, treatment satisfaction, and other patient-derived outcome measures. Their primary value is in providing the patient's perspective on the effects of treatment and disease, and for many chronic diseases represents one of the most important health outcomes for evaluating the effectiveness of treatments. Clearly, the application of relevant and psychometrically sound PROs in clinical trials assist patients, their family members and clinicians in understanding the comprehensive impact of treatment on patient functioning and well-being.

The release of the FDA draft "Guidance for Industry — Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" represents both a challenge and opportunity for the pharmaceutical and medical device industries. For now, the evolving FDA thinking on PROs and evidence requirement for supporting PRO labeling and promotional claims has been exposed to the light. In fact, Laurie Burke and her FDA colleagues should be commended for successfully taking on this activity and for providing insight into the evidence standards for PROs

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Documenting the Rationale and Psychometric Characteristics of Patient-Reported Outcomes for Labeling and Promotional Claims: The PRO Evidence Dossier

By Dennis A. Revicki, PhD and Lori Frank, PhD

A key feature of the FDA draft guidance on PROs is its focus on the types of evidence required for PRO-based measures used within a regulatory submission. The operationalization of the guidance document can be considered a "PRO Evidence Dossier" with specific content. The purpose of this dossier is to summarize as completely as possible the planned PRO assessment strategy, the evidence on the psychometric qualities of the selected PRO instruments (i.e., reliability, content validity, construct validity, responsiveness), interpretation guidelines (i.e., MID), summary of clinical trial results, and requested PRO labeling language.

Typically the documentation of necessary evidence, if available at all, is provided across a number of different documents associated with the clinical development plan and clinical trial program, including the end of Phase II-related documents, clinical trial protocols, independent reports, filed statistical analysis plans, and once the clinical trial program is completed, the clinical study reports. This dispersion of relevant PRO-related information complicates regulatory review. Thus, it seems reasonable to develop an approach that includes all the relevant evidence in a single summary document. This is the essence of the PRO Evidence Dossier.

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The EXACT-PRO Initiative: An Innovative Approach to PRO Instrument Development

By Nancy Kline Leidy, PhD & The EXACT-PRO Team



A new approach for developing PRO instruments for evaluating treatment outcomes in pharmaceutical trials is underway! The EXACT-PRO initiative is bringing together experts in instrument development and validation, specialists in clinical practice and research, and dedicated division and Study Endpoints and Label Development (SEALD) staff from the U.S. Food and Drug Administration (FDA) to develop a single, validated, and accepted patient-reported outcome (PRO) measure for use in drug development trials. A key element of the project has been the interest, enthusiasm, and sponsorship of pharmaceutical companies committed to improving PRO evaluation in chronic pulmonary disease through this innovative cooperative program.

The EXACT (**EX**acerbations of **Ch**ronic pulmonary disease **T**ool) project involves the development of a measure for evaluating the frequency, severity and duration of acute exacerbations of chronic obstructive pulmonary disease (COPD) in general, and chronic bronchitis specifically. Exacerbations are an important feature of COPD, leading to significant morbidity and mortality. Despite widespread interest in understanding the effect of treatment on exacerbations, there is no consensus on its definition or evaluation. A variety of outcome measures, often with areas of overlapping content and/or different structure, have been used in clinical trials, with no single, validated, accepted "gold" standard. This has created problems for the industry, regulatory agencies, and clinical decision makers as they attempt to evaluate the absolute and relative efficacy of new treatments for this important health problem. The EXACT-PRO initiative brings experts together to address these problems.

The EXACT measure will be structured to indicate the presence of an acute exacerbation in order to evaluate exacerbation frequency as an outcome in trials of COPD. In addition, it will be designed to evaluate the effect of treatment in terms of severity, duration and resolution of exacerbations from the perspective of the patients themselves. The outcome of the project will be a single instrument sponsors can use as an efficacy endpoint in clinical trials of investigational drugs to be submitted to the FDA for review and approval and to communicate patient-reported outcomes of treatment to decision makers.

The project is being conducted in two phases: Phase I involves a literature summary and analysis; patient focus groups and one-on-one interviews; an expert panel meeting to address the patient's perspective of exacerbations, the item pool and response options, and the draft questionnaire; translation and cognitive debriefing; and validation protocol development with expert review. Phase I of the project is on target for completion by the fall of 2007. The direction and timeline for Phase II, including the breadth and depth of empirical validation, will be determined with input from project sponsors, instrumentation and clinical research experts, and the FDA.

To make certain sponsors, experts, and the FDA have access to comprehensive, up-to-the minute information from and about the project, the EXACT-PRO initiative includes a limited access web site (www.exactproinitiative.com). Log-in passwords give sponsors, experts, and the FDA access to the project's comprehensive bibliography on acute exacerbations of chronic bronchitis and COPD, instrument analysis tables, study protocols and interview guides, and updates on study progress and results. A dialogue page serves as a medium for asking questions and sharing ideas about the PRO instrument development process.

UBC's EXACT-PRO team includes Nancy Kline Leidy PhD, Director and Principal Investigator of the project, Terry Wilcox PhD, Kellee Howard, Jennifer Petrillo, Elizabeth Allan, and Alise Nacson, with support from M.A. O'Donnell, Julia Dixon, Laurie Smith and other members of the UBC staff. Drs. Paul Jones and Sanjay Sethi are serving as Senior Clinical Research Consultants. The EXACT-PRO expert panelists include experts in PROs, pulmonary research, and members of the FDA.

The EXACT-PRO Initiative is possible through the commitment of the following sponsors: Adams Respiratory, Astra-Zeneca, Bayer, Boehringer-Ingelheim, Forest Laboratories, Merck, Novartis, Ortho-McNeil, Pfizer, and Schering-Plough.

Dr. Leidy is also President of UBC's Health Care Analytics Group, overseeing UBC's Health Outcomes, Economics, Pricing and Reimbursement, and Meta-Analysis services in the U.S. and Europe.

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Use of PROs by Oncology Clinicians

By Kevin Knopf, MD

Oncologists use the term “quality of life” frequently and informally, but most would not be familiar with the methodology of PROs in the academic sense. However, PROs are part and parcel of our daily practice.

For patients with curable cancers, we have traditionally accepted that short term decrements in quality of life, even if they are large, are acceptable given the chance of cure. For example, adjuvant chemotherapy for breast or colon cancer is associated with moderate decrements in quality of life for three to six months, as is curative chemotherapy for non-Hodgkin’s lymphoma, Hodgkin’s disease, and testicular cancer. Bone marrow transplants involve a much greater and more prolonged detriment to quality of life, but is felt justified if there is curative potential.

Much of day to day practice, however, involves non-curative situations where the goal is both prolongation of survival and maximizing quality of life. There is a balance between toxicity caused by treatment and potential benefit that is challenging. Typically we have utilized “on the spot” patient-reported outcomes — e.g., patients will be asked to rate their level of pain, appetite, and/or energy level on a score of one to ten. Specific toxicities will also be graded when appropriate, such as nerve damage related to chemotherapy agents.

Other medical specialties adapt PROs specific to their area as needed to practice effectively. For example, an orthopedic surgeon who specializes in joints would ask focused questions on functional capacity; a neurologist treating patients with Parkinson’s disease would ask questions related to mobility and neurologic function; a cardiologist might focus on exercise tolerance, shortness of breath, and chest pain in a patient with coronary artery disease.

Specific PROs such as the SF-36, the EORTC QLQ-C30 or the FACT are challenging for oncologists to interpret. Lack of familiarity with these instruments has hindered our ability to interpret scores and what constitutes a meaningful change. Part of the recent FDA recommendations on PROs asks for more specificity in PRO instruments, and this will enable oncologists (and other clinicians) to incorporate PROs in their day to day practice with greater ease. Collection of PROs will likely increase over time and be part of the clinical data base. Technological advances will make collection of data easier — e.g., a portable computer “tablet” where PRO data can be entered by patients in the waiting room.

There is greater acceptance of formal PROs in clinical trials. Again, the problem of what constitutes a meaningful change in score is pervasive. However, in this area we are looking for quality of life differences in two arms of a randomized trial (whether it is drug A vs. drug B or drug A vs. best supportive

Upcoming Meetings focusing on PROs:

ISPOR 11TH ANNUAL INTERNATIONAL MEETING Third Plenary Session: The Patient Voice in Medical Product Evaluation: FDA Draft Guidance on Measuring Patient-Reported Outcomes

May 20-24, 2006 – Philadelphia, PA
<http://www.ispor.org/meetings/phila0506/index.asp>

ISOQOL Patient-Reported Outcomes and FDA Regulatory Guidance Meeting

June 29, 2006 – Washington, DC area
<http://www.isoqol.org/June06meetingflyer.pdf>

Building Tomorrow’s Patient-Reported Outcome Measures: The Inaugural PROMIS Conference

September 11-13, 2006 – Gaithersburg, MD
<http://meetings.promis.iqsolutions.com>

Patient-Reported Outcomes Assessment in Cancer Trials: Evaluating and Enhancing the Payoff to Decision Making

(sponsored by the National Cancer Institute)
September 20-21, 2006 – Bethesda, MD
<http://www.scgcorp.com/PROACT/>

ISOQOL PRO Regulatory Issues in Europe and the USA: Methods Analysis and Measurement

October 10, 2006 – Lisbon, Portugal
<http://www.isoqol.org/FDAPortugal.htm>

13th Annual ISOQOL Conference

October 11-14, 2006 – Lisbon, Portugal
<http://www.isoqol.org>

care). These have traditionally used the National Cancer Institute’s Common Toxicity Criteria which grades specific side effects on a score of one to four. However, PROs such as the SF-36, EORTC QLQC30 and subscales, and FACT score and its subscales have become more common in clinical trials and the oncology literature. Indeed, two pharmacologic agents were approved by the FDA on the basis of randomized trials showing an improvement in quality (but not quantity) of life, and these agents were adopted widely in clinical practice.

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How Did the Evidence Get to the Other Side? The PRO Message in the Real World

By Teresa Wilcox, RPh, PhD

Achieving a labeling and/or claim based on a PRO is a huge accomplishment. However, the effort is all for naught if the information is not used. Several articles in this newsletter discuss possible target audiences for the results, e.g., clinicians, payers, etc. To effectively communicate with these groups, one must evaluate what messages from the PRO data are important to them and what do they want, or need, to understand about the PRO instrument. The need to understand the science behind the message may influence their assessment of the results as credible evidence.

One must be prepared to address the customers' need for scientific evidence regarding the development of the PRO instrument. It is critical to consider at what level external audiences will require scientific information on the validation of the instrument, what format will be used to deliver affirmative messages and responses to questions, and who within the company will deliver the information. Thoughtful time should be spent to consider the depth of information needed. For example, a primary care practitioner may only want to know that the instrument has been validated, while a national thought leader may require the peer-reviewed publication of the instrument validation as well as a scientific interchange on PRO development terminology and standards.

A variety of tools and venues could be used to deliver the message and respond to unsolicited queries. All tools must effectively translate the rigorous science into an understandable language for the clinician. For example, a clinician might intuitively know that assessing the internal consistency of

questions is important but have limited knowledge of the appropriate statistical assessment and interpretation. Possible tools might include medical information letters and targeted slide decks.

“Patients have the right to know how a drug will affect them — how they will feel and function.”

— Laurie Burke, MPH, RPh, Director, Study Endpoints and Label Dev., Office of New Drugs, CDER, FDA, DIA Webinar “New PRO Draft Guidance Issued by FDA”, April 5, 2006.

Lastly, the company should equip their team with necessary tools to accurately respond to development and validation questions and to properly respond to customers queries. Communication could occur through various team members, including: health outcomes scientists, medical information specialists, medical liaisons and commercial colleagues (e.g., sales, account managers, etc.). Again, it is important to

understand what messages and key issues or questions each person would address. Like the external clinician, many of the team members will have limited background in instrument development; however, they will be asked to deliver affirmative messages and to credibly respond to questions. Formal training and education of this team will build their communication effectiveness.

Delivery of an effective message always begins with a well-designed communication plan. Messages built on data from PROs are no exception. In fact, greater detail may be necessary because of limited clinician experience and comfort with these endpoints. Effective communication of the scientific support for the PRO endpoints builds the customer's confidence for integrating the results into their decision making process for using the product or device.

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Translation and Cultural Adaptation of PROs

By Emuella Flood, BA

Multinational clinical trials have become a necessity in today's global economy to expedite testing and approval of new pharmaceutical treatments. As most clinical trials are now international in scope, it is often necessary to have multiple translations and cultural adaptations of the instruments required for the trials. The challenge is to develop new language versions of PRO measures that are equivalent in meaning, interpretation, valuation and relevance. This is especially difficult given the limitations of language, as well as the differences that exist among countries and cultures in terms of values, expectations, experiences, and attitudes toward health.

Recently, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force for Translation and Cultural Adaptation published guidelines on developing translations and cultural adaptations of PRO measures. The guidelines describe a 10-step process, which includes multiple forward translations, reconciliation of the multiple forwards, back translation, harmonization of all new versions, and cognitive debriefings of the new versions with a small sample representing each target population. Following this methodology reduces the risk of inaccurate translations and invalid study data.

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SCIENCE & POLICY OPINION

PROs and the FDA Draft Guidance

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in the drug application review and approval process. The availability of the draft guidance allows the FDA and sponsors to have a dialogue based on a framework for evidentiary requirements. While there may not be complete agreement about all of the content in the guidance, it does enable a discussion, based on the science of PROs and standards of psychometric evidence, which may help move relevant and important claims for treatment benefit forward.

PROs, like other health and clinical outcomes, must demonstrate acceptable measurement qualities (i.e., reliability, validity) to be most useful in clinical trials. To achieve a successful PRO labeling claim, it is necessary to articulate a conceptual framework underlying the PRO, select and document the development and measurement qualities of the PRO instruments, design and implement good clinical trials, specify *a priori* the key PRO endpoints and a statistical analysis plan, provide guidelines for interpreting statistically significant PRO results, and provide fair and complete reporting of the PRO results. The specification of a conceptual framework represents good science and can really be considered developing a ‘small theory’ as to the associations between the mechanisms of the disease and treatment intervention and the PRO domains of interest, including defining the content of the PROs. It is clear that the FDA is most comfortable with PROs that are proximal to the underlying and recognized pathophysiological mechanism and measures that are simple and straightforward. This does not, however, mean that the FDA may not consider multi-item and multi-dimensional PRO measures (i.e., HRQL); it only means that more evidence will need to be supplied to justify and support more complicated PROs. Consideration also needs to be given to how distal from the disease mechanism the PROs may be in respect to the conceptual model. For example, for studies in chronic pain, clearly pain intensity is a relevant and simple PRO that is essential to measure in clinical trials. Less proximal but still meaningful PRO domains include fatigue, sleep quality and physical functioning, all which have direct linkages with the pain experience. More distal domains, such as psychological well-being and social activities are important to patients, but may be too far from the direct impact of treatment to be considered primary PRO endpoints for a clinical trial. Regardless, decisions need to be made as to the targeted PRO domains and measures and the strength of the evidence needed and available to support their inclusion in a product label.

The specification of a conceptual framework represents good science and can really be considered developing a ‘small theory’...

Clearly, good measurement characteristics are important for clinical and PRO instruments, and increasingly there are studies focused on the development and psychometric (or clinimetric) evaluation of clinical endpoints. The FDA seems to be interested in ensuring that any endpoint, based on patient reports (and perhaps even clinician reports) will have acceptable evidence on reliability, validity and responsiveness. Where necessary, information will need to be provided on interpretation guidelines, and we are seeing different regulatory agencies requesting information on the clinical significance of observed clinical trial results, especially when the treatment differences seem small (i.e., less than 20%). There will be greater focus on quality measurement and requirements for demonstrating good measurement characteristics. This represents the opportunity for sponsors and the FDA to more clearly understand the patient benefits of new treatments. Good measurement is likely to maximize the possibility of observing treatment benefits when the treatment is actually effective. Clinical trial results based on endpoints with strong psychometric characteristics will provide useful information for patients, their families, clinicians and the health care system. This is the basis for evidence-based medicine and represents the way forward for understanding the benefits of new health care interventions.

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The PRO Evidence Dossier

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The draft guidance document provides an outline for this evidence dossier and the key features are noted below. The combination of all the relevant information and evidence into a single document simplifies the review and evaluation of the PRO evidence for the clinical division and study endpoint reviewers within the FDA. Another advantage of collecting the required evidence into a single document is clarification for industry researchers of any gaps in existing information that need to be addressed in order to support the clinical development program and targeted PRO claims.

Rationale for Measuring PRO Endpoints: The PRO Evidence Dossier must include clear and specific language documenting the specific target labeling statements desired. From that,

...the relationship between the labeling statement and the PRO measures used must be clearly specified.

the relationship between the labeling statement and the PRO measures used must be clearly specified. The rationale for use of specific PROs must include the relationship between the “conceptual framework” underlying the

targeted label statements and the PRO used to operationalize that framework. It is essential to include a conceptual framework for understanding the proximal and distal nature of the relationships between the clinical and PRO measures within treatment and disease progression context. Importantly, documentation from qualitative research on involved stakeholder groups (i.e., patients and their families, clinicians, others) is considered part of this rationale. This section of the dossier should also provide some insight into the important domains of health outcomes for the targeted disease population.

Rationale and Selection of PRO Instruments: In many cases, multiple PRO instruments may be available for assessing the domains identified during the previous stage in planning the PRO strategy for a clinical development program. In this section it is necessary to summarize the rationale for the selection of specific PRO measures, with reference to the match between the objectives of the clinical trial program and the important domains that need to be measured and the content of the PRO measures. Consideration also needs to be taken in

selecting instruments that assess the relevant part of the health outcome continuum in the targeted patient population, psychometric characteristics (i.e., reliability, validity, responsiveness), language translations for international studies, relevant recall period for the population and disease, and the timing of PRO assessment in the clinical trials. Enough support and rationale needs to be provided so that it is convincing for a health outcomes researcher and demonstrates that there is some justification for selecting one or more PRO instruments.

Background on the Development of the PRO Instruments:

Based on the instrument manual, publications on the development of the PRO instrument, and if needed, contacts with the instrument developer(s), a brief summary should be developed documenting the instrument development methods and procedures. This section should cover the methods used to identify the key outcome domains, item generation and reduction procedures, and scoring subscale and total scores. Since the FDA view is that PRO instruments should be based on significant patient input, there should be evidence that the content, domains and items in the PRO instrument has some basis in information derived from patient focus groups and/or interviews.

Summary of Psychometric Characteristics of the PRO Instruments:

The measurement qualities of the PRO instruments that will be used as the foundation for the PRO labeling or promotional claim need to be summarized in sufficient detail to allow an experienced researcher to fully understand the psychometric characteristics of the selected instruments. This section of the evidence dossier should include a summary of the available evidence on the content validity, reliability, construct validity, and responsiveness of the PRO measures. It is important to include relevant information on psychometric qualities of the measure(s) from samples of patients that are comparable to those in the planned clinical trials, or at least similar enough that relevant generalizations can be made about the psychometric qualities of the PRO measures.

Evaluation of content validity is more qualitative and the evidence supplied needs to be sufficient enough to demonstrate that the content of the construct or domain is covered adequately. Content validity—the coverage of the construct or domain—differs from face validity.

Reliability for PRO measures is demonstrated through internal consistency reliability and test-retest reliability data. While reliability evidence across populations is of interest, the real focus should be on showing reliability in the targeted patient population.

Next, the construct validity of the PRO instruments needs to be summarized for the target patient population. The evidence supporting the construct validity of the PRO

measure should include attention to convergent, divergent, discriminant, and known groups validity. Enough information needs to be provided to convince the reviewers that the PRO instrument is operating as expected; that is, it is related to clinical and other PRO measures in meaningful ways and that the direction and magnitude of these associations are as hypothesized. In addition, it is important to show that the PRO measures are not related to concepts that the PRO should not be related to.

Responsiveness is a component of validity and represents the PRO measure's capability to detect changes related to changes in clinical status or other relevant outcome measures. This part of the document needs to summarize the evidence that the PRO scores are responsive or sensitive to changes in clinical status.

An assessment of the completeness of the psychometric information on the selected PRO measures will help in planning any additional independent studies that may be needed to provide additional needed measurement evidence. For example, often new disease-specific instruments have little data available as to responsiveness and MID. Therefore, it may be necessary to plan and complete an observational study designed to provide responsiveness and MID information as well as additional information on reliability and validity. It also may be possible to conduct blinded secondary analyses of the PRO data collected in Phase II studies to examine psychometric characteristics and MID.

Interpretation Guidelines and MID: Related to the responsiveness of PRO measures is the concept of MID and guidance to those reviewing the clinical trial results as to whether the statistically significant group differences or changes are meaningful and important. The MID is the smallest change that patients perceive as beneficial and/or which would require a change in clinical management. The section of the dossier on MID should specify a number value for the MID and summarize the rationale and evidence supporting this MID.

Summary of Clinical Trial Results: The intent of this section is to provide a summary of the PRO findings from the clinical trials, with most emphasis on information and results that may assist the reviewer in evaluating whether or not the PRO results are scientifically adequate enough (i.e., substantive evidence) to support a labeling or promotional claim. When the PRO Evidence Dossier is initially developed, this section will understandably be absent.

Requested PRO Labeling Statements: The final section of the evidence dossier should contain the desired labeling or promotional claim statements related to the PRO endpoints based on the clinical research program. The claims language should be derived directly based on the content of the

primary PRO endpoints pre-specified in the clinical trial protocol and statistical analysis plan. The claim statements need to be clear and unambiguous and are intended to communicate the PRO findings to physicians and patients.

Summary: A PRO Evidence Dossier provides a single document to gather relevant evidence regarding selection and use of PRO measures for regulatory submission. It should be considered a living document in that it will function to record the key elements in the PRO assessment and development strategy. When prepared carefully, the evidence dossier may help industry researchers in identifying information that will need to be further developed to support the clinical development program and targeted PRO claims, and when completed, it can serve as a useful guide for regulatory review.

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Translation and Cultural Adaptation of PROs

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The newly released FDA draft guidance acknowledges the need to follow "accepted standards" for translation and cultural adaptation and to provide support for the accuracy of translated PRO measures and the validity of the resulting data. The draft guidance does not specifically state what the "accepted standards" are, though it mentions the need for experienced translators to carry out the translations, an adequate translation/adaptation methodology, harmonization of the various versions, and evidence that the measurement properties are similar across versions. This last point suggests that a psychometric validation study would be required for each new version. This is not in line with current practice for translation and cultural adaptation and would represent a heavy additional burden for sponsors. The guidance would benefit from a clear statement as to what type of "evidence" would be required or considered sufficient to show that measurement properties of various versions are comparable. Also, it would be important to state whether existing translations which have been used widely but have not been psychometrically validated, would need to undergo this type of evaluation to meet FDA guidelines.

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Effective Training in PRO Collection

By Adam Butler

Clinician-Rated Scales are selected as pivotal endpoints in clinical research across a wide range of diseases. However, often these scales rely on clinical subjectivity which can cause substantial variability in scores across research clinicians. Effective training applied consistently to raters across a wide range of rating instruments has been shown to increase scoring standardization and precision with Clinician-Rated Scales, translating into successful study design and effective study implementation.

PRO instruments can also be used as effective endpoints in clinical research. However, because the amount and type of evidence required by the FDA to support labeling claims measured by PRO instruments is no different than any other endpoint, inter-patient variability, like inter-rater variability, must be minimized. In its recent draft guidance for industry,

the FDA indicates that increased training for both clinicians and patients will be critical to ensure the effective use and application of PRO assessments.

The FDA suggests that study quality can be optimized at the design stage by specifying procedures to minimize inconsistencies in trial conduct through standardized instruction and training for clinicians and their patients. The draft guidance outlines three specific areas for training support of PROs:

- Standardized training and instructions for patients regarding self-administered PROs;
- Standardized interviewer training and interview format for PRO instruments administered in an interview format; and
- Standardized instructions for investigators regarding patient supervision, timing and order of questionnaire administration during or outside the office visit, processes and rules for questionnaire review for completeness, and documentation of how and when data are filed, stored, and transmitted to or from the study site.

Many of the same principles associated with rater training designed to improve inter-rater reliability across Clinician-Rated Scales can be applied to PRO measures. A training program designed to satisfy the draft guidance could include:

- Disease specific didactic training, administered either online or live, for investigators and site personnel regarding the influence of the targeted disease on patient comprehension and PRO reporting;
- Protocol-specific didactic training, administered either online or live, for clinicians regarding the instruments;
- Robust patient education materials, delivered not only at study initiation, but ongoing and available on-demand throughout the duration of a subject's participation in a study.

For example:

- Patient Starter Toolkits consisting of patient education printed and video materials highlighting the disease, PRO completion guidelines, and background information on reporting symptoms;
- Outbound patient education communications to remind patients to complete required PRO instruments in compliance with the protocol schedule.
- Trainer's Toolkits for sites designed to standardize patient education across sites participating in a trial. The Trainer's Toolkit could include all materials included in the Patient Starter Toolkit plus:
 - Training video demonstrating how to conduct effective patient education;
 - Syllabus for conducting site-based Patient Training Sessions;
 - Powerpoint presentation and speaker's notes for trainers;

Building Tomorrow's Patient-Reported Outcome Measures: THE INAUGURAL PROMIS CONFERENCE

September 11-13, 2006
Gaithersburg Marriott Washingtonian Center
Gaithersburg, Maryland USA
<http://meetings.promis.iqsolutions.com>

What Is PROMIS?

The Patient-Reported Outcomes Measurement Information System (PROMIS) initiative establishes a collaborative relationship between NIH and individual research teams through a cooperative agreement mechanism. The broad objectives of the PROMIS network are to:

- Develop and test a large bank of items measuring patient-reported outcomes
- Create a computerized adaptive testing system that allows for efficient, psychometrically robust assessment of patient-reported outcomes in clinical research involving a wide range of chronic diseases
- Create a publicly available system that can be added to and modified periodically and that allows clinical researchers to access a common repository of items and computerized adaptive tests.

The network will collaborate on the collection of self-reported data from diverse populations of individuals with a variety of chronic diseases, using agreed-upon methods, modes, and questionnaires.

For more information on PROMIS, visit <http://www.nihpromis.org>.

- Reminder postcards to review and distribute to patients; and
- Patient Assessment Quizzes to be completed at the end of site training sessions to confirm patients' understanding of the training content.

The FDA has been paying special attention to PRO data collected electronically, and this draft guidance addresses the rapidly increasing use of electronic collection of PRO data. Studies that rely on patient use of an electronic device to report data — even if that device is a phone — will especially benefit from patient education videos and multimedia presentations. Patient education videos and multimedia training have been shown to increase patient understanding of clinical trial concepts and responsibilities¹ — and as research continues to rely on patients' reports of their symptoms, effective and consistent patient reports of symptoms and outcomes are critical. Many subjects — including elderly patients, patients with dementia, patients with psychosis, adolescent or pediatric patients, and those naïve to research — will benefit from training videos that demonstrate the use of electronic diaries and reporting devices.

Based on this guidance, any protocol design that includes an endpoint that is patient-reported will need to consider not only the validation and development issues raised in the draft guidance, but will also need to ensure that comprehensive and effective training is designed and implemented.

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¹ Weston J, et al. Evaluating the benefits of a patient information video during the informed consent process. *Patient Education and Counseling* March 1997; 30(3):239-245.

Implementing Electronic Solutions to Improve Patient Compliance and Recall Bias in Patient-Reported Outcomes

By Kimberly Sierk

PRO tools have long been used in clinical trials for capturing data unique to each individual patient's perspective of how they are functioning, feeling, and in some instances, responding to an investigational product as it relates to their health. Traditionally, paper diaries were used to collect patient-reported outcomes to be used in primary and secondary endpoint analysis for clinical trials, but in recent



years the introduction of electronic capture of diaries (ePRO) has been on the rise.

In February of 2006, the FDA released the draft guidance which focuses on PRO instruments and their use to determine effectiveness endpoints in clinical trials. In part, the draft guidance discusses the various decision making factors to consider during the creation, selection and implementation of any PRO instrument.

These factors include elements such as:

- Medium: paper-based, interactive voice response system (IVRS), web, etc.
- Recall Period: event driven, regular intervals, baseline and end of treatment
- Response Options: Visual Analog Scale, Likert Scale, Numeric Rating Scale, etc.

A recent Phase III trial used a six-week patient-reported diary to determine if the primary endpoint of the trial was achieved. The diaries were collected via patient interaction twice daily by IVRS and/or a web-based diary system. The patients were trained by the investigative site on accessing the diary system and frequency and timing of submissions, as well as being provided with an instruction card listing the diary questions.

Of the 714 patients who participated in the trial, 640 completed with an overall diary compliance rate of 93%. The compliance

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PROS IN SPECIAL POPULATIONS

Choosing and Developing Pediatric PRO Measures

By Louis Matza, PhD

As stated in the FDA draft guidance document, development and validation of pediatric PRO instruments should follow the same rigorous steps recommended for adult PRO measures. However, measures used with children or adolescents should first be validated within the target age groups, and there are conceptual and methodological issues to keep in mind when choosing, developing, or validating pediatric PRO measures. The draft guidance document recommends careful development of a conceptual framework prior to creating a measure. When conceptualizing pediatric PROs, it is particularly important to remember that children are embedded within multiple social contexts including the family, the child's peer group, the classroom, and the community¹. Each of these contexts is likely to mediate the impact of disease and treatment on the child. For example, asthma has been shown to impair health-related quality of life (HRQL) in both children and adults², but the specific effects of asthma are likely to be different for children because of their context. Asthma could limit a child's participation in play and athletics with peers, leading to social and emotional consequences that are different from those experienced by adults with the same disease. An asthma-specific measure developed for adults would not capture these contextual aspects of disease impact.

The relationship between children and their social context is complex, involving simultaneous mutual influences among children and multiple contexts^{1,3}. Children are active agents exerting an influence upon their context while simultaneously being shaped by their context^{4,5}. In addition, contextual factors have been shown to have a long-term influence on children's social and psychological development. For example, peer rejection in childhood is associated with numerous long-term negative outcomes including delinquency and school drop-out⁶. In sum, because context plays a different and possibly more important role for children than for adults, pediatric PRO measures must assess health status within a conceptual framework that considers the relevant contextual variables.

There are also methodological issues that must be considered when designing a pediatric PRO measure, including identification of the youngest age at which children can reliably report a given outcome⁷. Researchers have made recommendations regarding the youngest age at which children can reliably report their health status and HRQL. Opinions vary, but it is generally estimated that children can begin reporting on the more concrete domains such as pain between 4 and 6-years-old^{2,8-9}, although assessment of more subjective

domains will require a somewhat older sample. The lower age limit for child self-report will vary according to the complexity of the constructs; the level of vocabulary and terminology; and individual differences in children's cognitive development and language skills.

A related issue is the decision regarding the most appropriate respondent¹⁰. The decision of whether to use child self-report, parent proxy-report, or both requires consideration of the child's age, the domains of health status that may be addressed, the disease area, the study design, and the intended use of the data. A growing body of literature is examining many additional pediatric PRO issues such as age-appropriate instrument formatting and design; optimal recall periods; advantages and disadvantages of creating multiple forms of a measure corresponding to different age groups; and avoidance of child response sets^{7-9,11-13}.

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¹ Cox MJ, Paley B. Families as systems. *Annu Rev Psychol.* 1997; 48:243-267.

² Juniper EF. Health-related quality of life in asthma. *Curr Opin Pulm Med.* 1999; 5(2):105-110.

³ Bronfenbrenner U. *The Ecology of Human Development.* Cambridge, MA: Harvard University Press; 1979.

⁴ Cook WL. Interpersonal influence in family systems: A social relations model analysis. *Child Dev.* 2001; 72(4):1179-1197.

⁵ Cummings EM, Davies PT. Maternal depression and child development. *J Child Psychol Psychiatry* 1994; 35(1):73-112.

⁶ Kupersmidt JB, Coie JD, Dodge KA. The Role of Poor Peer Relationships in the Development of Disorder. In: Asher SR, Coie JD, eds. *Peer Rejection in Childhood* New York: Cambridge University Press; 1990; 274-305.

⁷ Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. *Value in Health* 2004; (1):79-92.

⁸ Annett RD. Assessment of health status and quality of life outcomes for children with asthma. *J Allergy Clin Immunol.* 2001; 107(Suppl 5):S473-481.

⁹ Connolly MA, Johnson JA. Measuring quality of life in paediatric patients. *Pharmacoeconomics* 1999; 16(6):605-625.

¹⁰ Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. *Qual Life Res.* 2001; 10(4):347-357.

¹¹ Eiser C, Mohay H, Morse R. The measurement of quality of life in young children. *Child Care Health Dev.* 2000; 26(5):401-414.

¹² Landgraf JM, Abetz LN. Measuring Health Outcomes in Pediatric Populations: Issue in Psychometrics and Application. In: Spilker B, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials.* Philadelphia: Lippincott-Raven Publishers; 1996:793-802.

¹³ Rebok G, Riley A, Forrest C, et al. Elementary school-aged children's reports of their health: A cognitive interviewing study. *Qual Life Res.* 2001; 10(1):59-70.

What Do You Do When the Patient is Cognitively Impaired? PROs in Cognition Research

By Lori Frank, PhD

A range of disorders like Alzheimer's Disease are associated with decline in cognitive function and for some treatments, cognitive impairment can be an important side effect ("chemo brain" from chemotherapy, for example). How do you address patient-based measurement when the patient may not be an accurate respondent? And why should you?

Section IV.E.2 of the draft guidance references cognitive impairment (CI) of the respondent and suggests inclusion of proxy reports in addition to patient reports, with examination of correspondence between the two. No further specific guidance is provided but several additional points require attention for PRO-based assessment in CI. PRO measurement is "worth it" in CI as it can expand capture to meaningful areas beyond basic neuropsychological functioning and can help with interpretation of clinician-based measures. To date, however, PROs are under-used in CI research.

Because a key contribution of PROs is measurement of relevant aspects of the disease experience beyond those that are clinically objective, PROs can be extremely meaningful for characterizing CI and its response to intervention.

As noted in the draft guidance, in addition to valuing the patient perspective, PROs may provide a more reliable form of measurement than clinician interview-based measurement. Certainly clinician-based measures in CI research, such as the clinician interview-based impressions of change (CIBIC)^{1,2}, are key to disorder quantification and evaluation of interventions. Recent work has begun to explore clinical meaning of CIBIC ratings^{3,4} but interpretation of CIBIC data in terms of meaning to clinicians as well as patients is still problematic⁵. Joffres and colleagues note that "clinicians appear to be skeptical of cognitive changes not supported by like changes in function or behaviour." PROs offer a way to capture functioning and behavior — and more.

The potential for PROs in CI research is vast and under-recognized. Clinical measures of CI do not capture the range of concerns of patients and caregivers. PROs fill this gap both through the emphasis on the individual's perspective and on the content of domains PROs address. At lower levels of CI severity, where measurement sensitivity of existing scales is limited, turning to formal PRO assessment of functioning can be particularly valuable. There are measurement issues to remain aware of, however. For PROs, clinical measures may relate meaningfully to some aspects of disorder impact on the patient but relate minimally to others, and the relationship may vary by level of CI and over time. Selection of comparison measures used for establishing validity or as anchors for

minimally important difference (MID) determination must therefore be made thoughtfully.

By moving beyond neuropsychological definitions of functioning, PROs can substantially expand capture of key aspects of the disorder and the impact of interventions by addressing reaction to symptoms, the experience of diagnosis, the impact on social relationships and family, ability to complete work or usual activities, use of coping strategies, and specific fears and concerns. Recent qualitative work supports the collection of some disease-related information directly from individuals with mild to moderate CI⁶, indicating meaningful expression of disease experience and self-report not entirely discordant from proxy report. While specific memory complaints may be prominent clinically, the consequences for ability to complete everyday activities may be of more concern to consumers. Higher order executive functioning and complex ADL performance may be difficult for a clinician to accurately measure within the clinical interaction; PROs can address this measurement gap. Work showing detectable personality changes extremely early in the course of diagnosable dementia⁷ supports this view.

Cognitive impairment has substantial impact on the daily lives of those who suffer from it and their loved ones. PROs offer a way to quantify this impact comprehensively, and with immediate meaning to clinical researchers as well as patients and families.

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¹ Schneider LS, Olin JT. Clinical Global Impressions in clinical trials. *Int Psychogeriatr* 1996; 8:277-280.

² Knopman DS, Knapp MJ, Gracon SI, Davis CS. The clinician interview-based impression (CIBI): A clinician's global change rating scale in Alzheimer's disease. *Neurology* 1994; 44:2315-2321.

³ Rockwood K, Black SE, Robillard A, Lussier I. Potential treatment effects of donepezil not detected in Alzheimer's disease clinical trials: a physician survey. *Int J Geriatr Psychiatry* 2004; 19:954-960.

⁴ Joffres C, Bucks RS, Haworth J, Wilcock GK, Rockwood K. Patterns of clinically detectable treatment effects with galantamine: a qualitative analysis. *Dement Geriatr Cogn Disord*. 2003; 15(1):26-33.

⁵ Frank L. Commentary: "Meta-analysis of memantine: summary and commentary on the Cochrane Collaboration's systematic review" — Meaning and measurement in cognitive impairment. *Alzheimer's & Dementia* 2006; 2(2), In Press.

⁶ Frank L, Lloyd A, Flynn J, Kleinman L, Matza L, Margolis MK, Bowman L, Bullock R. Impact of cognitive impairment on mild dementia patients and Mild Cognitive Impairment patients and their informants. *Int Psychogeriatr* 2006:1-12.

⁷ Balsis S, Carpenter, BD, Storandt M. Personality change precedes clinical diagnosis of Dementia of the Alzheimer Type. *J Geriatr Psych* 2005; 60B(2):P98-P101.

DIFFERENT VIEWS OF MID

Responsiveness and Minimal Important Differences for Patient-Reported Outcomes: Why Bother?

By Dennis A. Revicki, PhD

Patient-reported outcomes (PROs) provide the patient's perspective on the effectiveness of treatment, and for many diseases the patient is really the only source of health outcome data¹. For clinical trials evaluating new pharmaceuticals, PROs need to be based on a clear conceptual framework, have evidence supporting content validity (i.e., the instrument content reflects the key characteristics of the construct from the patient's perspective), and must have demonstrated acceptable psychometric qualities (e.g., reliability, validity). Clearly, to be useful effectiveness endpoints in clinical trials, the PROs must also have evidence documenting responsiveness to changes in health or clinical status. Without evidence that the PRO can detect meaningful changes in health status, using the PRO in a clinical trial may be risky. Responsiveness is an aspect of construct validity and is determined by evaluating the relationship between changes in clinical and other endpoints, and changes in the PRO scores over time. Responsiveness can also be based on the application of a treatment of known and demonstrated efficacy, in either observational studies or in clinical trials^{2,3}.

Demonstrating responsiveness is necessary, but additional information is needed to determine the minimal important difference (MID) for a PRO measure. Responsiveness represents the instrument's ability to detect changes in health status, while the MID is used to interpret whether the observed change is important from the patient's or clinician's perspective⁴. Increasingly in health outcomes research, the MID is based primarily on the patient's perspective with the clinician's viewpoint serving to confirm the findings on MID. The MID value is used to interpret statistically significant PRO results from clinical trials in those situations where differences may be small (i.e., < 0.50 standard deviation units).

Increasingly in health outcomes research, the MID is based primarily on the patient's perspective with the clinician's viewpoint serving to confirm the findings on MID.

The MID has been defined as the smallest change in a PRO measure that is perceived by patients as beneficial or that would result in a change in treatment². There are a number of anchor-based and distribution-based methods that have been used to determine the MID for PRO measures^{2,5,6}. However, the current situation for determining the MID is fluid and evolving, and there is no clear consensus as to the recommended, best practice approach for determining the MID². The recommended approach is to estimate the MID based on several anchor-based methods, with relevant clinical or patient-based

indicators, and to examine various distribution-based estimates (i.e., effect size, standardized response mean, standard error of measurement) as supportive information, and then to triangulate on a single value or small range of values for the MID. Confidence in a specific MID value evolves over time and is confirmed by additional research evidence, including clinical trial evidence.

Responsiveness and MID may vary by population and contextual characteristics, and there may not be a single MID value for a PRO instrument across all applications and patient samples. There is likely a range in MID estimates that vary across patient population and clinical study context. It should be appreciated and accepted that aspects of PRO assessment include some measurement error and that no PRO measure is perfect, and should not be expected to be perfect, in order to be used in clinical trials. There does, however, need to be evidence supporting the psychometric characteristics of the PRO instrument such that there is confidence that changes in scores over time, with the application of treatments with some efficacy, can be detected, and the measurement error (or noise) is not so large that it is problematic to observe meaningful changes in patient health status.

For PRO endpoint data to be accepted as evidence of treatment effectiveness, there must be evidence documenting the instrument's conceptual framework, content validity, and psychometric qualities, including reliability, validity and responsiveness. Responsiveness is necessary to demonstrate that the PRO scores are sensitive to actual changes in clinical or health status. While demonstrating responsiveness is a key component to establishing an instrument's

construct validity, it is also important to determine the MID to assist in interpreting statistical significant PRO results in clinical trials. The MID may vary by population and context, and no one MID may be valid for all study applications involving a PRO instrument. Responsiveness and MID must be demonstrated and documented for the particular study population, and these measurement characteristics are needed for PRO labeling and promotional claims.

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¹Revicki DA, Osoba D, Fairclough D, Barofsky I, Berzon R, Leidy NK, Rothman M. Recommendations on health-related quality of life research to support labeling and promotional claims in the United States. *Qual Life Res* 2000; 9:887-900.

²Guyatt G, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. *Mayo Clinic Proceed* 2002; 77:371-383.

³Hays R, Revicki DA. Reliability and validity (including responsiveness). In Fayers P, Hays R (eds.). *Assessing Quality of Life in Clinical Trials*, Second Edition. New York: Oxford University Press, 2005.

⁴Osoba D. The clinical value and meaning of health-related quality-of-life outcomes in oncology. In Lipscomb J, Gotay CC, Snyder C (eds.). *Outcomes Assessment in Cancer: Measures, Methods, and Applications*. Cambridge: Cambridge University Press, 2005.

⁵Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol* 2003; 56:395-407.

⁶Wyrwich KW, Bullinger M, Aaronson N, Hays RD, Patrick DL, Symonds T, Sloan JA. Estimating clinically significant differences in quality of life outcomes. *Qual Life Res* 2005; 14: 285-295.

Limits of MID: Why We Should Focus on Importance

By Lori Frank, PhD

The FDA is looking for comment on minimal important difference (MID) and responder definitions. While certainly basic psychometric performance must be demonstrated for new measures or for use of existing measures with new populations, focus on the MID as part of the “checklist” of properties to obtain may obscure the more important issue of determining the appropriate “decision threshold” for the research question at hand. There are many methods for establishing that threshold and MID is just one. Therefore, in Section IV.C. 4, the guidance document should clarify that there are multiple methods for aiding in interpretation of results prior to the statement that this section presents” some of the methods that have helped sponsors and the FDA interpret clinical trial results...” (lines 534-5). Discussion of the MID and responder analyses can remain, but should be supplemented by discussion of effect size and mention of methods for examining distribution separation. Broadening the section in this way should avoid the rush for research on the MID of specific measures without consideration of the range of interpretation aids that should be brought to bear for the specific use of a specific measure.

Despite the disadvantages of sole focus on anchor- and distribution-based MID methods, the MID as a concept has advanced thinking about measurement of treatment effects and comparisons between groups¹⁻³. MID is useful to improve interpretation of statistically significant differences and in that vein is used in a logical chain of

point estimates compared
via statistic

statistical significance
established

MID established as lower
end threshold of clinical
significance.

In this way it implicitly endorses the statistical testing as necessary but potentially insufficient for interpretation of specific data. The main value of the MID concept is in assisting with placing arbitrary metrics into a context likely of more use to a clinical audience, when determined using an anchor-based approach. The risk is reification of those anchors, which are themselves generally artificially scaled. In some cases, qualitative distinctions provide the basis for the anchor metric, and relating those back to otherwise hard to interpret point

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PRO Guidance in Europe — the European Medicines Agency (EMA)

By Andrew Lloyd, DPhil

In November 2004, the Efficacy Working Party at the EMA produced a draft document outlining their views regarding the role of health-related quality of life (HRQL) as an outcome measure for use in regulatory submissions. This document was entitled a “Reflection Paper” on regulatory guidance for the use of HRQL data in the evaluation of medicinal products. The EMA invited comment on this draft document, and after reviewing the comments from various bodies, a revised version of the “Reflection Paper” was released in July 2005¹. This document restricts comment to HRQL only and does not include other PROs.

The reflection paper is specifically not designed as a guidance regarding the methodology of HRQL assessment. Rather, it is intended to describe how HRQL can be incorporated into trials and the way it can be used in submissions to support products.

The document makes many clear statements which should be considered:

- HRQL is considered to be a multi-dimensional construct, and as such, only multi-dimensional measures should be used.
- HRQL should be clearly differentiated from symptoms. So HRQL cannot be captured by merely measuring the sum total of symptoms that people experience.
- HRQL data should be considered to go beyond and be distinct from the efficacy and safety endpoints. HRQL may be useful for interpreting how a drug affects the primary efficacy endpoints.
- A label claim regarding improvement in HRQL needs to be supported by data collected by instruments validated for use in the corresponding condition. Instruments should not be validated using data from the same pivotal studies that are used to support the license, although confirmatory testing is allowed. This is in line with the FDA’s position.
- The EMA does not rule out approving global claims for improvement in HRQL as the FDA virtually has. Such a claim would need to be supported by improvements in all or most domains.
- Alternatively, claims based on specific domains of HRQL are also possible as long as they are specified *a priori* in the statistical analysis plan (SAP). This should also be supported by independent data regarding what is a clinically meaningful change on that measure. The SAP should indicate which domains will change and which will not change.

- If the HRQL measure is included in the Phase 3 study as a co-primary endpoint, then the trial must be powered for this measure.
- If efficacy and safety are already established, then it is still possible to get an HRQL claim through a supplementary head to head non-inferiority type study.

The success of any application for a label claim will be based on:

- The rationale and justification for choice of HRQL assessment
- The hypotheses regarding HRQL changes
- The proven validity of the instruments
- Evidence of cultural adaptation/translation if applicable
- The adequacy of the SAP, and the relevance of observed changes. Recommendations regarding SAPs are broadly in line with those from the FDA. This includes appropriate means of handling missing data and describing methods for handling multiplicity of endpoints. MID should be estimated using multiple methods.

We are in broad agreement with the guidance issued by the EMA. However, there are two areas which we think could be looked at again. We are unsure about the stated willingness of the EMA to accept global HRQL claims. No single measure covers everything that contributes to HRQL and so making a claim that product X improves HRQL seems like too bold a step to make. It may be preferable to approve claims related to specific aspects of HRQL—such as physical functioning.

We also believe that the EMA should require that HRQL improvements related to a health technology be demonstrated in two independent studies. While this may seem like a conservative position, the verification that a second study provides is clearly powerful.

The EMA’s guidance on the use of HRQL data is a clear document which explicitly lays out the issues to consider when attempting to secure a label claim. The EMA and FDA have an ongoing dialogue regarding these issues which may result in greater alignment over time.

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¹ European Medicines Agency Reflection Paper on the Regulatory Guidance for the Use of Health Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products Committee For Medicinal Products For Human Use (CHMP) Doc. Ref. Ema/Chmp/Ewp/139391/2004; London 2005

Including the Patient's Perspective in Medical Device Trials

By Kathy Beusterien, MPH and Nancy Kline Leidy, PhD

Recent technological advances have led to a wide range of diagnostic and therapeutic products that offer primary preventive and first-line therapeutic alternatives for patients with a variety of health conditions. Understanding the process of care and outcomes of treatment from the patient's perspective is an essential component of a comprehensive assessment of these new alternatives. PROs can provide important data on the advantages and disadvantages of therapeutic options not captured through non-PRO clinical endpoints, improving the decision-making process for physicians, payers, and the patients themselves, as they choose among devices or, with increasing frequency, between drugs and devices.

PRO measures for medical devices are similar to those used to evaluate outcomes of pharmacologic treatment, including symptom frequency or severity, function, psychological well-being, patient preference and treatment satisfaction. Evaluating outcomes of devices designed to improve survival, for example, should include data on the nature of the survival benefit, that is, both the quantity and *quality* of life. A health utility instrument can be used to estimate patient preference for different health states and compute quality-adjusted life years associated with the various treatment alternatives. Satisfaction with the process and outcome of care is another useful PRO for device evaluation, providing data on the effect of the new technology from the patient's perspective.

As in the case of pharmaceutical trials, the use of PROs in device trials is associated with practical, methodological and regulatory challenges that need to be addressed in order to maximize their scientific validity and enhance their utility as data sources for health care decision making. An important and somewhat unique consideration in device trials is the nature of the treatment/device itself, making it difficult, and some cases impossible, for trials to include a placebo or sham treatment control group or for clinical investigators or patients to be blinded to treatment. This can lead to bias of various forms, including subtle differences in the approach investigators take with their patients, their appraisal of treatment effect, and the patient's perception of treatment and treatment effects. Study design should include carefully constructed methods for minimizing and/or describing this bias, including careful respondent training, independent observation or evaluation, statistical control variables, such as social desirability indicators, and sensitivity analyses.

For a number of reasons, device trials are also characterized by relatively small sample sizes, making it difficult to achieve statistical significance in PROs, even in the presence of

relatively large, clinically meaningful effects. To overcome this challenge, studies must be carefully designed with precise PRO measurement, including highly reliable instruments administered at carefully selected intervals with no missing data to optimize sample size. Realistic a priori power and sample size estimates can provide insight into the probability of success in any given trial and assist with trial design. Although large sample sizes to meet PRO needs may not be feasible in device evaluation, small, well-designed PRO studies can provide an important building block for understanding the impact of treatment from the patient's perspective.

Methodological challenges in device studies highlight the need for consensus on the best (valid, reliable, sensitive) PRO assessment tools for specific therapeutic areas. These measures should be sensitive enough to capture the health effects attributable to the device, but generic enough to apply to outcomes across treatment options. Using the same measures across studies would facilitate cross-study comparisons and meta-analysis and contribute to evidence-based decision making.

Given the diversity in the types of medical devices and the speed with which innovations are introduced, effective assessment of the patient's perspective of new health technologies requires a cooperative effort between industry, the clinical community, and regulatory agencies to maximize efficiency and expedite the development of new technologies with an understanding of their absolute and relative value in improving health and enhancing the quality and/or cost-effectiveness of health care delivery. To fully capture the risks and benefits of treatment, device evaluation should incorporate all aspects of the device's function, safety, and effectiveness, including the patient's experience and perspective.

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BIBLIOGRAPHY

- Borer JS. Development of cardiovascular drugs: the U.S. regulatory milieu from the perspective of a participating nonregulator. *J Am Coll Cardiol* 2004; 44(12):2285-92.
- Buckman PM. Spine instrumentation and the FDA: what spine surgeons should know. *J Spinal Disord* 1989; 2(4):292-5.
- Chen L, Keane AT, Every NR. The Food and Drug Administration and atrial defibrillation devices. *Am J Manag Care* 1999; 5(7):899-909.
- Kaganov AL. Medical device development: innovation versus regulation. *Ann Thorac Surg* 1980; 29(4):331-5.
- Lewis C, U.S. Food and Drug Administration. Emerging trends in medical device technology: home is where the heart monitor is. Available at: http://www.pueblo.gsa.gov/cic_text/health/med-device/mdt.html—Accessed 4/7/06
- Wang SS, Mendelson DN, Schulman KA, et al. Exploring options for improving healthcare. *Am Heart J* 2004; 147(1):23-30.
- Windhover Information Inc. Looking Good: Are Lifestyle Devices the Future of Medical Technology? In Vivo: The Business & Medicine Report, March 2003; pg. 52.

The Patient's Voice:

Patients will be speaking at 16 conference symposia at this year's American Thoracic Society International Conference in San Diego (May 21-24). Patients will discuss their personal experiences with their diagnosis, disease, and treatment and how these have altered their lifestyles, families, social relationships, and careers. They will also offer insight into what patients would like health care providers and researchers to know about their experiences with the health care process and the importance of research to understand the patient's perspective.

Recall Period in Patient-Reported Outcomes — What is the True “Bias” Issue?

By Donald E. Stull, PhD & Nancy Kline Leidy PhD

As the role and importance of PROs for understanding the effect of new pharmaceuticals and devices increase, the validity and reliability of PRO measures and data come under greater regulatory scrutiny. Agencies such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) must consider the underlying psychometric properties of PRO measures as they review and interpret clinical trial data during the approval and labeling process. One issue that has been raised is the “best” or “most appropriate” recall period for capturing PROs in these trials (See FDA draft guidance, Section IV.B.3).

For the most part, the intent of PRO instruments, and the purpose of including PRO measurement in clinical trials, is to quantify the patients' subjective experiences with their condition or disease and the effect of treatment on these experiences. In some cases, they are asked to give their appraisal of the treatment process. In these instances, then, the patient is the only valid source of this information (cf. FDA draft guidance, Section III.A.1).

When patients are asked to describe or rate their health or specific aspects of their health, including events, symptoms, function, or well-being, it is usually with reference to a particular time period, i.e., immediate (now), the past day, week, a month, or longer. The extent to which their recall is “accurate” is an interesting question. Recall of health care events or utilization patterns involves a verifiable report of an objective event. But what constitutes “accurate” rating of subjective experience? What is “over” and “under” reporting

of experiences such as pain? And what are the implications of variation in the estimation of subjective phenomena, particularly in clinical trials?

Unfortunately, an in-depth discussion of the factors affecting respondent recall is beyond the scope of this piece. However there are several general guidelines that can assist investigators as they design instruments and the PRO component of clinical trials to optimize precision.

First, because memory can be imperfect and respondents can have difficulty recalling health events, behaviors, experiences, or appraisals, the recall period for any given instrument or measurement should be sufficiently proximal to the experience to enhance/ease recall without burdening the patient or research staff.

Second, the recall period of the instrument should match the concept of interest. Interest in day-to-day symptom variability requires daily evaluation, while a one-week recall may adequately capture patient's overall perception of symptom severity. If a decision is made to change the recall period for a given instrument, the structure of the measure has changed and the ‘new’ instrument's reliability and validity will need to be tested.

Third, the recall period should match the study timeline, with consideration given to the duration of treatment. For example, a trial design involving a 7-day run-in period followed by 7 days of treatment that uses the SF-36 standard version (four-week recall), recall at day 14 will be asking respondents to think back to the run-in period. Consequently, the investigators will be unable to isolate change that may have occurred during the course of treatment.

The extent to which patient recall can introduce error or bias into clinical trials and lead to erroneous conclusions is an important question with implications for instrument development and evaluation as well as clinical trial design. For example, under what circumstances would patient underestimation or failure to recall certain health events, behaviors, or experiences in a clinical trial evaluation result in the conclusion that an intervention had little or no impact (a Type II error). Alternatively, when might patient overestimation lead to a conclusion that an intervention had a profound effect, when, in fact, it did not (a Type I error)? Finally, and important for randomized, multi-group clinical trials — if the under- or over-estimation is small and/or equally distributed across both treatment groups, will this estimation error change the outcome of the trial, i.e., the magnitude of the difference between groups?

There is no doubt that an appropriate recall period is an important aspect of instrumentation. Applying clear logic,

knowledge from previous empirical work in this area, and sound psychometric principles are essential steps in the selection of a recall period that will maximize the reliability and validity of the measure and the trial data. In addition, careful consideration must be given to understanding the magnitude of patient subjective estimation 'error,' the extent to which the 'under-' or 'over-' estimation is differentially or equally applied across treatment groups and, ultimately, whether and how this influences or biases the test of the effect of treatment on the PRO.

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SELECTED BIBLIOGRAPHY

Bradburn NM, Rips LJ, Shevell SK. Answering autobiographical questions: the impact of memory and inference on surveys. *Science* 1987; 236(4798):157-161.

Sudman S, Bradburn NM. *Response Effects in Surveys: A Review and Synthesis* 1974. Chicago: Aldine.

Worsley A. Effects of varying recall periods on reported food intakes. *Appetite* 1991; 16(1):69-82.

Stone AA, Schwartz JE, Broderick JE, Shiffman SS. Variability of momentary pain predicts recall of weekly pain: a consequence of the peak (or salience) memory heuristic. *Pers Soc Psychol Bull.* 2005; 31(10):1340-1346.

Kreulen GJ, Stommel M, Gutek BA, Burns LR, Braden CJ. Utility of retrospective pretest ratings of patient satisfaction with health status. *Res Nurs Health* 2002; 25(3):233-241.

Day N, McKeown N, Wong M, Welch A, Bingham S. Epidemiological assessment of diet: a comparison of a 7-day diary with a food frequency questionnaire using urinary markers of nitrogen, potassium and sodium. *Int J Epidemiol.* 2001; 30(2):309-317.

commonly used for qualitative data collection for item generation are focus groups and cognitive debriefing interviews. Focus groups are group discussions among individuals with similar health conditions who are guided through discussions solicited by open-ended questions¹. Cognitive debriefing interviews are structured one-on-one interviews with individuals focusing on a topic of interest (usually questionnaire items). Both approaches of qualitative data collection are useful and the selection of each approach should be based upon the desired outcome.

Focus groups are particularly useful for generating items and conceptual frameworks as well as to gain understanding about aspects of specific health conditions. Should focus groups not be the ideal method of data collection due to topic sensitivity (e.g., HIV, sexual dysfunction), one-on-one patient interviews can also be utilized. Qualitative methods assist the researcher in discovering the vocabulary and thinking patterns of the target group to assist in the development of quantitative standardized items for questionnaires. Hearing patients describe specific symptoms or how a condition impacts one's life allows the researcher to generate items that are meaningful and measurable to patients. Using the words spoken by patients rather than by researchers or clinicians is essential.

Cognitive debriefing interviews are ideal for reviewing item content, wording, response options, format, and other questionnaire issues. The cognitive interviewing process generally consists of questions to ascertain the comprehension, relevance, readability, and response processes of a questionnaire. Cognitive interviewing methods fall into two sub-groups: think-aloud and verbal probing. In the think-aloud approach, the interviewer asks the participant to "think out-loud" while responding to a question so that one gains an understanding of the cognitive processes used when responding to the question (i.e., how a participant thinks when answering the question). With the verbal-probing approach, the participant initially completes the questionnaire. Upon completion, the interviewer will then ask specific questions regarding the participant's interpretation and understanding of the questionnaire². Both cognitive debriefing approaches provide the data needed; however, the approach that best meets one's research objectives should be chosen. The verbal-probing approach is useful as it represents the typical patient self-administration approach that will be used in later stages of questionnaire development.

Qualitative data collection should proceed until saturation (i.e., when no new thoughts or insights are noted) is achieved. Thus, the sample size will vary depending upon the topic and research needs. When analyzing qualitative data, descriptive statistics are used to summarize the data and characterize

The Importance of Qualitative Data in PROs

By Karin Coyne, PhD, MPH

While the FDA draft guidance document states: "PRO instrument item generation is incomplete without patient involvement" (p 10, line 295), the usefulness of qualitative data extends far beyond item generation. Qualitative data, which is usually in the form of words rather than numbers, is essential in patient-reported outcome research as such data places meaning and genuineness to a health condition. Qualitative data are a rich source of patient descriptions and explanations of thoughts, feelings, and processes of living with a health condition. Additionally, qualitative research can be used to generate theories and conceptual frameworks of disease impact.

Importantly, the same rigor applied to quantitative research must also be applied to qualitative research. Methods

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Qualitative Data in PROs

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the sample. Content analysis is typically performed to identify recurrent themes, patterns, and processes in the data. This is a time-intensive and critical process which can be done manually or with a qualitative data software package (e.g., Atlas.ti, Ethnograph, Nudist)⁵.

Qualitative data provide a rich source of information not only for item generation but also to enhance clinician and researcher understanding of the impact of health conditions or treatments on patient lives.

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¹ Krueger RA. (1994). *Focus Groups. A Practical Guide for Applied Research* (2nd ed). Thousand Oaks, CA: Sage Publications.

² Willis, G.B. (1999). *Cognitive Interviewing: A "How To" Guide*. From the short course "Reducing Survey Error through Research on the Cognitive and Decision Processes in Surveys," presented at the Meeting of the American Statistical Association.

³ Miles MB, and Huberman AM. 1994. *Qualitative Data Analysis*. Thousand Oaks, CA: Sage Publications.

Implementing Electronic Solutions

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achieved in this trial is in contrast to rates reported for paper-based diaries, which can be as low as 11%. Paper-based diary non-compliance is largely due to the lack of adequate patient recall stop-gaps and negligible day to day oversight of adherence to protocol timeframes.

Complete data for analysis in this trial was achieved by implementing a patient diary system that was user-friendly and provided acceptable diary recording timeframe restrictions and alerts for overdue or missing diaries. By offering patients the choice of using the IVRS or web to record their diaries, each patient was able to select a medium that was most conducive to their lifestyle. In addition, due to the system enforced time restrictions for diary entry, the data reflected patient response at a verifiable time and based on a controlled recall period. As a result, confidence in the accuracy of the data and in the consistency of PRO administration was enhanced. Detailed reporting was provided to the investigative site of non-compliant patients for re-education or evaluation for continuing participation in the trial.

Many of the points discussed in the FDA's draft guidance are being implemented and considered in current ePRO systems and are continuously being refined and improved. As shown in this trial, ePRO use can significantly improve the completion rates for PROs, using the latest technology to avoid the pitfalls found in paper based diaries such as un-enforced diary completion windows and time lag in monitoring non-compliant patients by the investigative site.

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⁵ Stone A et al, Patient non-compliance with paper diaries, *British Medical Journal* 2002; 325:1193-1194.

UBC's Database on Patient-Reported Outcomes in Approved Pharmaceutical Labeling

By M.A. O'Donnell, BA

Over the years, UBC staff has developed a database of information on patient-reported outcomes (PRO) in approved pharmaceutical labeling. The PRO database has over 110 FDA-approved labels (as well as some examples of PRO claims that were not approved by the FDA) and is growing. It evolved from searches conducted in a variety of sources, including labels posted on the FDA website, Drugs@FDA; the Physician's Desk Reference® Electronic Library (Thomson PDR, Montvale, NJ); and through PRO claims known by the staff or identified in previously published articles.^{1,2,3} The database also includes text in regulatory documents for over 80 medicinal products approved by the European Medicines Agency (EMA), based on published research on PROs in the European drug regulatory process.⁴

Building the database is an interesting process. PRO information can be embedded in a label, making it difficult to uncover. When text searches are conducted, emphasis is placed on breadth and depth, looking for concept terms such as "quality of life," "patient-reported," and "subjective evaluation," and methodologic terms such as "daily diary," "visual analog scale," "global assessment" and other terms common to the PRO field. Care is taken to exclude clinician-reported assessments of patient experiences and adverse events. As expected, the database includes labeling information such as patient-reported symptoms recorded in diaries, visual analog scales assessing satisfaction, and multi-item, multi-domain scales measuring health-related quality of life — with the PRO serving as primary or secondary endpoints in the trials.

It is important to remember that the past actions of the FDA are not necessarily predictors of future actions, and that PRO claims are evolving. Chopra and colleagues' review of quality of life labeling, for example, concluded that "In more recent cases, approved QoL labeling claims were more narrowly defined and more rigorously worded [than in the past] with respect to trial results and specific patient-reported instruments."⁵ Clearly the new PRO draft guidance⁶ will have an effect on future labeling. Also, the new guidance for industry on the "Clinical Studies Section of Labeling for Prescription Drug and Biological Products"⁷ specifically highlights the importance of providing information that is most useful to prescribers treating patients and suggests that this emphasis could "warrant significant departures from past labeling practices."

Previous label information is one small piece of the puzzle that can help inform a successful PRO development and communication strategy for pharmaceuticals or devices. The UBC PRO database helps staff identify and evaluate concepts, measures, and claims used in the past in similar disease areas or treatment — including questions such as "What concepts have previously been used in measuring GERD?" or "What PRO labels have included a 100 mm visual analog scale or daily patient diary?" or "What labels for products with an insomnia indication include data on subjective perceptions of sleep?" Staff use the labeling data together with knowledge of the therapeutic area, scientific literature, instrument development and validation, FDA requirements, the information needs of consumers (patients, providers,

payers), and the health care environment to develop strategic and scientific product development plans involving PROs.

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For more information about UBC's experience in PRO strategy and/or the PRO database, please contact Dr. Lori Frank via email at Lori.Frank@unitedbiosource.com. Dr. Frank is the Deputy Director of UBC's Center for Health Outcomes Research.

¹ Willke RJ, Burke LB, Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy end-points in approved product labels. *Control Clin Trials* 2004; 25:535-552.

² Shah SN, Sesti AM, Copley-Merriman K, Plante M. Quality of life terminology included in package inserts for US approved medications. *Qual Life Res* 2003; 12:1107-1117.

³ Symonds T, Berzon R, Marquis P, Rummins TA, Clinical Significance Consensus Meeting Group. The clinical significance of quality of life results: practical considerations for specific audiences. *Mayo Clin Proc* 2002; 77:572-583.

⁴ Szende A, Leidy NK, Revicki D. Health-related quality of life and other patient-reported outcomes in the European centralized drug regulatory process: a review of guidance documents and performed authorizations of medicinal products 1995 to 2003. *Value in Health* 2005; 8(5):534-548.

⁵ Chopra T, Shah SN, McLaughlin-Miley C, Hinton J. Quality of life in product labeling: a review of marketed drug products. *Value in Health* 2001; 4:51.

⁶ Draft Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *Federal Register*, February 3, 2006; 71(23):5862-5863.

⁷ Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. *Federal Register*, January 24, 2006; 71(15): 3921-3997.

THE PRO INSTRUMENT DEVELOPMENT AND MODIFICATION PROCESS

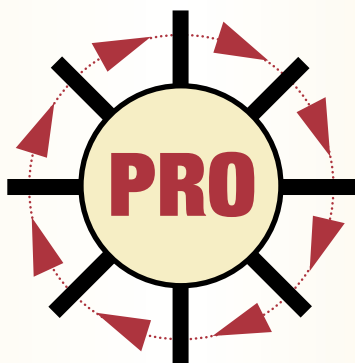
FDA draft "Guidance for Industry — Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," Figure 1, Page 11.

I. Identify Concepts and Develop Conceptual Framework

Identify concepts and domains that are important to patients.
Determine intended population and research application.
Hypothesize expected relationships among concepts.

IV. Modify Instrument

Change concepts measured, populations studied, research application, instrumentation, or method of administration.



II. Create Instrument

Generate items.
Choose administration method, recall period, and response scales. Draft instructions. Format instrument. Draft procedures for scoring and administration. Pilot test draft instrument. Refine instrument and procedures.

III. Assess Measurement Properties

Assess score reliability, validity, and ability to detect change. Evaluate administrative and respondent burden. Add, delete, or revise items. Identify meaningful differences in scores. Finalize instrument formats, scoring, procedures, and training materials.

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scores can be valuable. In most cases, however, face valid distinctions between levels is all that anchors can provide. The distribution-based methods for establishing MID avoid this logic problem by relying on the strengths of classical test theory to aid interpretation. These methods have merit as well although specific shortcomings include sample-dependence, a serious limitation to what should be a generalizable value.

Part of the limitation of the MID concept, at risk of being downplayed given current draft guidance language, is that the MID is an estimate with limited generalizability as it can be sample-dependent and method-dependent with some unhelpfully wide variation in value depending on the method used to calculate it. Instead, one can think of a range of tools to use as decision threshold determinants — one of which is statistical significance. In this case the “I” in MID is the importance of statistically measurable group separation. Consideration may need to be made of power for detection of important effects, not just statistically significant effects. It is of interest that the FDA is endorsing use of other methods for examining group differences, such as cumulative frequency distribution, in guidance language (see Section E and Appendix of Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biologic Products — Content and Format, January 2006⁴). It may be possible to make reasonable and defensible decisions about treatment effects without a prior specification but instead through inspection of group distributions.

Establishing MID presents logic issues similar to those involved in establishing PRO validity. What is the basis for a gold standard, particularly when many PROs are created to measure previously unmeasured concepts? Post-hoc review of data, while not ideal, can be useful for some validation purposes. Similarly, post-hoc review of data to help determine if group differences are meaningful may need to be accepted as part of the PRO validation process.

There are many ways to determine “I” — what is important. As with MID or statistical significance, the determination of importance is dependent on the uses of the information or measurement goals. The goal should determine selection of method, not the other way around.

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¹ Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol* 2003; 56:395-407.

² Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Medical Care* 2003; 41 (5): 582-592.

³ Hays RD, Farivar SS, Liu H. Approaches and recommendations for estimating MID in health-related quality of life measures. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2005; 2:63-67.

⁴ Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biologic Products — Content and Format, January 2006; <http://www.fda.gov/cder/guidance/5534fn1.htm>

The FDA draft “Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” was released on February 2, 2006 for comment purposes. This draft can be found at:

<http://www.fda.gov/cder/guidance/5460dft.pdf>

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