

Incorporating the Patient's Perspective into Drug Development and Communication: An Ad Hoc Task Force Report of the Patient-Reported Outcomes (PRO) Harmonization Group Meeting at the Food and Drug Administration, February 16, 2001

Catherine Acquadro, MD,¹ Rick Berzon, DrPH,² Dominique Dubois, MD,³ Nancy Kline Leidy, PhD,⁴ Patrick Marquis, MD,⁵ Dennis Revicki, PhD,⁴ Margaret Rothman, PhD,⁶ for the PRO Harmonization Group

¹MAPI Research Institute, Lyon, France; ²Boehringer Ingelheim GmbH, Ridgefield, CT, USA; ³Janssen Pharmaceutica, Beerse, Belgium; ⁴MEDTAP, Bethesda, MD, USA; ⁵MAPI Values, Boston, MA, USA; ⁶Johnson & Johnson, Raritan, NJ, USA

ABSTRACT

Background: The extent to which patient-based outcomes can be used to evaluate and communicate the effect of new drugs and devices is a subject of much debate. Criteria for evaluating the scientific quality of data to support health-related quality of life (HRQL) and other patient-based labeling and promotional claims in the United States and Europe have been proposed by various scientists and organizations. Since March 2000, a working group composed of members of the International Society for Quality of Life Research (ISOQOL), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the Pharmaceutical Manufacturer's Association Health Outcomes Committee (PhRMA-HOC), and the European Regulatory Issues on Quality of Life Assessment (ERIQA) met to discuss and coordinate the various recommendations by their respective groups and address the need to harmonize outcomes review criteria within and across United States and European regulatory agencies. Over time, the discussion expanded from HRQL outcomes to include any outcome based on data provided by the patient or patient proxy, that is, patient-reported outcomes (PROs). The working group therefore became known as the PRO Harmonization Group.

Methods: Working with a member of the US Food and Drug Administration (FDA), four key issues requiring clarification were identified: how PROs are defined and

put into operation for research purposes; the added value of PROs in the drug review and evaluation process; selected questions related to the PRO measurement and research methodology; and the interest and demand for PRO information by decision makers. On February 15, 2001, all members of the PRO Harmonization Group attended a meeting in Rockville, Maryland, to discuss these four issues further, and on February 16, 2001, a formal presentation was made to representatives from various departments and reviewing divisions of the FDA. These presentations are summarized in this report.

Results: All participants agreed that PROs are important for understanding the impact of treatment on patient functioning and well-being. They also stressed the need to communicate PRO information to key decision makers, including regulatory agencies, clinicians, patients and their families, and payers. Finally, the meeting resulted in plans for continuing the dialogue on PRO measurement and interpretation.

Summary: The February 16, 2001, meeting represented an important step in harmonizing efforts across various organizations and in opening a dialogue with the FDA around major issues related to methodologic standards for measuring and interpreting PROs in the drug evaluation process.

Keywords: claims, health-related quality of life (HRQL), patient-reported outcomes (PRO), regulatory issues.

Address correspondence to: Catherine Acquadro, MAPI Research Institute, 27 rue de la Villette, 69003 Lyon, France. E-mail: cacquadro@mapi.fr

Introduction

Health-related quality of life (HRQL) and other patient-based assessments are important for understanding the impact of treatment on patient functioning and well-being [1,2]. The extent to which

these outcomes can be used to evaluate and communicate the effect of new drugs and devices is a subject of much debate. In the United States, a number of products have been reviewed at the US Food and Drug Administration (FDA) for approval to communicate HRQL outcomes in labeling and promotion. Along with these submissions have come questions about the underlying methodology of HRQL research and its application to the drug approval process.

To address the need for additional information, criteria for evaluating the scientific quality of data to support HRQL labeling and promotional claims in the United States have been proposed by independent scientists [3] and organizations, including International Society for Quality of Life Research (ISOQOL) [4] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (<http://www.ispor.org>), with ongoing discussions by the Pharmaceutical Research and Manufacturer's Association Health Outcomes Committee (PhRMA-HOC) [5]. At the same time, the European Regulatory Issues on Quality of Life Assessment (ERIQA) group assessed the use of HRQL outcomes in regulatory reviews conducted in Europe [6].

In an effort to coordinate the various recommendations provided by these groups and to formulate principles to guide HRQL outcomes review criteria within and across regulatory agencies in the United States and Europe, a working group of members from the four organizations was convened. Over time, the discussion expanded from HRQL outcomes to include any outcome based on data provided by patients or patient proxy as opposed to data provided from other sources (Fig. 1). The FDA proposed the term "patient-reported outcomes" (PRO) to represent these types of outcomes in the regulatory review process [7]. The working group subsequently became known as the PRO Harmonization Group.

Based on the results of previous discussions and input from the FDA, the PRO Harmonization Group identified and focused on four key issues requiring clarification within the context of drug evaluation: 1) the definition and operation of PROs for research purposes; 2) the added value of PROs in the drug review and evaluation process; 3) specific questions related to the PRO methodology; and 4) interest and demand for PRO information by decision makers. Participants from the four groups were divided into task groups to address each of the issues identified above and to make recommendations to the PRO Harmonization Group. After sub-

stantial deliberations, the PRO Harmonization Group presented results and recommendations on these four issues to the FDA on February 16, 2001.

Objectives and Scope

The objective of the meeting was to open a dialogue between the FDA and organizations interested and/or engaged in PRO research. Four presentations were made: 1) PRO Concept and Definition, Team Leader, Margaret Rothman, PhD; 2) Value of PROs, Team Leader, Nancy Kline Leidy, PhD; 3) Methodological Considerations for PRO Data in Clinical Trials, Team Leader, Patrick Marquis, MD; and 4) Interest in and Demand for PRO Information, Team Leader, Rick Berzon, DrPH. The contents of these presentations are summarized in this report.

Concept and Definition of PRO

Group 1 presented a framework for and a conceptual definition of HRQL and PROs. Definitional clarity is important to any scientific endeavor. Lack of clarity around definitions related to PROs, especially HRQL, impedes development of the field, hampers communication with patients and clinicians, and hinders discussion and policy development. Whereas it is generally agreed that HRQL is an important concept, there is no universally agreed upon definition or clearly developed conceptual framework for understanding the relationship between HRQL and PROs.

One approach to categorizing data collected in clinical trials is to consider the source of information. There are several potential sources of data to evaluate the safety and efficacy of a new drug (Fig. 1), i.e., patients, clinicians, and caregivers. Each source shown in Fig. 1 serves as an umbrella term for the types of data that may be provided by that source. It is generally acknowledged that each source may provide a unique and valuable perspective on the disease and the efficacy of a therapy. For example, patients may focus on the changes in their own health; families may react not only to the impact on the patients, but also to the impact on family life; and clinicians and researchers view disease and its treatment from a clinical perspective.

The proposed framework and definition are based on two guiding principles. First, PRO assessment, especially in the context of drug evaluation, is an evolving field. Any proposed framework and definition should be broad rather than prescriptive, thus fostering rather than hindering the growth of the field. Second, the framework and definition are proposed for use within the context of the drug

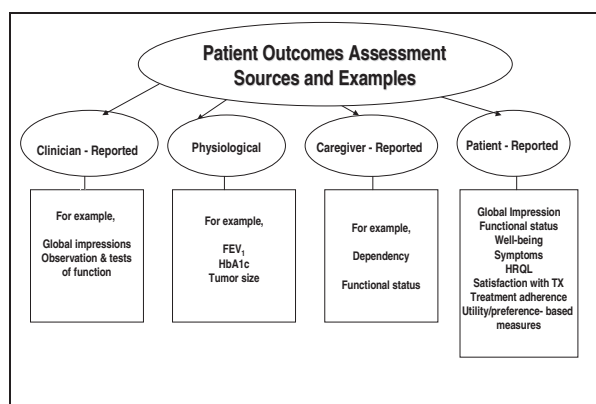


Figure 1 Patient outcomes assessment: sources and examples.

approval and regulatory process. Appropriateness for use beyond this context must be evaluated separately.

Initial discussion began with a delineation of those issues on which there appeared to be broad general agreement including the information provided by the patient is inherently subjective; the patient's subjective experience provides a unique and valuable contribution to the drug development process; scientific methods for assessing subjective outcomes, e.g., psychometrics and utility measurement, are well developed and provide the basis for PRO assessment; the design of PRO studies follows the rules defined for clinical trials, e.g., clear specification of hypotheses and standard methods of analysis and interpretation; and the HRQL represents the patient's report of the impact of a health condition, varies by disease or health condition and over time, consists of multiple domains, and includes the concept of the value placed on the assessed outcome.

HRQL is one of several types of PRO data that may be collected in the context of a clinical trial. Other PROs include, but are not limited to, symptoms, patient satisfaction with treatment, functional status, psychological well-being, and treatment adherence (Fig. 1). The following definitions evolved: patient-reported outcomes represent the patient's report of a health condition and its treatment, and HRQL represents the patient's evaluation of the impact of a health condition and its treatment on daily life.

Patient's evaluation implies that the patient is the preferred respondent for HRQL data. It is recognized that at the present time, not all patients can provide such information, e.g., very young children and persons with severe dementia. Information provided by other sources, generally referred to as

proxy or surrogate respondents, is not equivalent to that which would be provided by the patient. Research findings suggest that the degree of association between patient and proxy data varies according to the extent to which a behavior is observable. In those cases where the behavior is unobservable, data may be biased by characteristics of the proxy respondent [2,8].

Impact on daily life implies that the domains assessed are relevant to the patient and indicates that the assessment goes beyond mere counting of events. For example, the number of times a patient reports an episode of heartburn, or symptom frequency, over a defined period of time does not provide an evaluation of the impact of heartburn on the patient's daily life and, hence, can only be considered a symptom inventory, but not a domain of an HRQL instrument. In contrast, an assessment of heartburn-related symptom distress experienced by the patient does provide an impact component and thus may represent a HRQL domain. Research suggests that frequency and distress evaluations may yield different information; thus the impact component provides unique information [9,10].

The notion of multidimensionality is a key component of definitions of HRQL. A single domain, e.g., physical function, cannot be considered as a HRQL measure, even though it is a patient-reported outcome. The type and number of domains required for an HRQL instrument are not specified in this definition as the group, and the committee as a whole by its adoption of the definition believed that this varies by health condition and treatment. It is incumbent on the researcher or sponsor to provide evidence that sufficient coverage of domains relevant to the target population are included in the assessment to uphold a HRQL claim.

The group did not specifically endorse any of the paradigms that attempt to delineate the relationships among types of PROs and other variables, e.g., Wilson and Cleary [11], as there appeared to be insufficient evidence to support hypothesized relationships. Further research into the relationships among PROs is required to enhance our understanding of illness and treatment from the patient's perspective.

The Value of PROs

Group 2 introduced the value of the patient's perspective and structured its argumentation around four key points: 1) a unique indicator of the impact of disease; 2) essential for evaluating treatment efficacy; 3) useful for interpreting clinical outcomes; and 4) a key element in treatment decision making.

A unique indicator of the impact of disease. The patient's report of symptoms, side effects, and other health-related data gathered during history taking are important entries in the multifactorial database that is the foundation for accurate medical diagnosis and treatment. In many situations, the physician relies almost entirely on patient reports in evaluating disease activity. The management of conditions such as functional gastrointestinal disorders, sexual dysfunction, benign prostatic hypertrophy, and insomnia, for example, is based almost entirely on the patient's report of symptoms and their impact on daily functioning and well-being. Successful treatment of migraine headache is defined by two patient-reported outcomes: pain relief and return to normal daily activities. Similarly, the optimal dose of antihistamines for the treatment of seasonal allergic rhinitis is based on achieving symptom relief to the point of tolerability, that is, symptom relief with minimal side effects resulting in optimal functioning and well-being.

There are many situations in which patient-reported data and objective physiologic markers of disease activity are used concomitantly to determine the severity of disease, monitor the trajectory of illness and select or adjust the optimal treatment regimen. Diagnosis and treatment of chronic obstructive pulmonary disease (COPD), for example, include a considered evaluation of the patient's history of respiratory symptoms along with laboratory and spirometric evaluation [12,13]. The goals of management in COPD are to: 1) reduce airflow limitation; 2) prevent and treat secondary medical complications; and 3) decrease respiratory symptoms and improve quality of life [12].

The historically weak empirical relationship among pulmonary function, symptoms, and HRQL supports the need for simultaneously considering each of these clinical parameters in understanding the impact of disease and treatment [14,15]. The fact that some treatments can reduce symptoms and improve HRQL with minimal change in FEV₁ further highlights the important and complementary nature of subjective and objective parameters of disease activity in this population [16].

Change in the patient's report of functional limitations is an important, and often a primary, clinical indicator of disease progression and treatment effectiveness for chronic conditions such as rheumatoid arthritis, Parkinson's disease, multiple sclerosis, stroke, and traumatic brain injury. Although objective tests of performance, such as muscle strength and joint function, provide data on the patient's functional capacity, these indicators do

not assess daily functioning in and around the home or work setting [17,18]. Treatment guidelines provided by a number of different professional organizations recommend that these data be gathered directly from the patient. Assessing HRQL is considered part of the standard of care in the treatment of allergy [19], COPD [12], and gastroesophageal reflux disease [20] and in rheumatology [21,22]. By definition, treatments for chronic diseases are palliative rather than curative. Thus, PROs of all types, e.g., HRQL, preference or satisfaction with treatment, or health status, are appropriate indicators of disease activity and progression.

Essential for evaluating treatment efficacy. In clinical trials, as in practice, patient report is the sole source of data on frequency and severity of symptoms and side effects and the impact of treatment on functioning and well-being. Consistent with the definition of a scientific instrument, PRO measures provide precise, reliable, valid, and reproducible data. The data represent the quantification of the patient perspective of the impact of disease and treatment.

PROs are essential endpoints in any clinical trial in which: 1) the patient's self-report is the primary or sole indicator of disease activity; 2) the treatment has a small impact on survival but may have a significant impact, positive or negative, on HRQL; 3) the treatment may adversely affect patient functioning and well-being; 4) the treatment arms offer equal clinical efficacy but differential PRO benefits; and 5) treatment-related decisions are based on a combination of objective and patient-reported subjective parameters.

Useful for interpreting clinical outcomes. PRO data from clinical trials contribute to the comprehensive evaluation of the benefits of new treatment. The result of a trial examining the efficacy of levetiracetam in reducing seizure frequency in patients with epilepsy is a case in point [23]. In this study, the HRQL outcomes of patients categorized as "responders," that is, patients for whom the treatment was efficacious, differed across the three treatment groups, suggesting a differential HRQL benefit of treatment distinct from the primary endpoint (Fig. 2).

Results of a trial examining the efficacy of rizatriptan for the treatment of migraine is an example of the importance of data provided by the patient in evaluating optimal dosing regimens [24]. In this trial, the 5- and 10-mg doses of rizatriptan were each found to be significantly more efficacious than placebo in relieving pain. However, patients randomly assigned to the 10-mg group showed

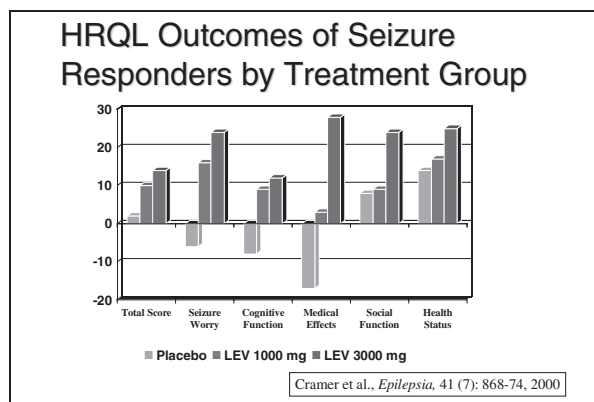


Figure 2 HRQL outcomes of seizure—responders by treatment group.

significantly better responses on three of five domains of HRQL assessed in the study (Fig. 3). These additional data suggest that 10 mg is the dose of choice for achieving pain relief sufficient to improve functioning and well-being.

A key element in treatment decision making. A number of specialty groups and organizations recommend the use of PROs in clinical trials and have published guidelines for selecting outcome measures specific to the unique characteristics and evaluation needs of the underlying disease. The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Group has recommended that clinical trials include a comprehensive appraisal of symptoms such as pain and joint stiffness, and the HRQL effects of treatment [21,22]. The systemic lupus erythematosus subgroup specifi-

cally recommended the inclusion of the patient-reported measure of health status, disability, and HRQL [21]. The Group for the Respect of Ethics and Excellence in Science (GREES) recommendations for the registration of drugs used in the treatment of rheumatoid arthritis suggests that generic and disease-specific measures of HRQL be included as secondary efficacy end points for clinical trials of symptom-modifying drugs [25]. In oncology, according to Johnson and Temple, “parameters of efficacy for advanced metastatic disease are survival, quality of life (performance status or pain), objective tumor response, and time to treatment failure” [26].

The goal of evidence-based medicine is to improve the quality and efficiency of medical care by basing treatment on sound scientific rationale. Any treatment designed to improve symptoms, functioning, well-being, or other PROs should also be based on scientific evidence, which is data from well-controlled clinical trials. PROs of clinical trials are particularly important for decision makers faced with limited resources and/or confronted with the evaluation of tradeoffs between efficacy, toxicity, and costs. Sound, scientific PRO data for any medical treatment, including pharmacologic therapies, is key to evidence-based decision making. A summary of the key points on the value of PROs is presented in Table 1.

Methodologic Considerations in Assessing PROs in Clinical Trials

Group 3 focused on selected methodologic issues associated with PRO assessment. Two key aspects were presented: the scientific value of PRO measures and the standards and procedures to follow for assessing PROs in clinical trials. PRO measures are scientifically valid insofar as: 1) the outcomes can be conceptually defined; 2) they can be put into operation through questionnaires; and 3) the questionnaires can be demonstrated to be reliable, valid, and responsive [27].

PRO measures have been primarily developed and validated based on psychometric theory although other approaches are used, e.g., utility [28]. Psychometrics has a long history in the human sciences [29–31]. Current HRQL questionnaires benefit from the experience accumulated over the past 50 years in this field. Empiric validation supports their status as scientific measures [32]. The validation process consists of different aspects that are well defined. The Harmonization Group adopted standard definitions and methods for assessing reliability, validity, and responsiveness

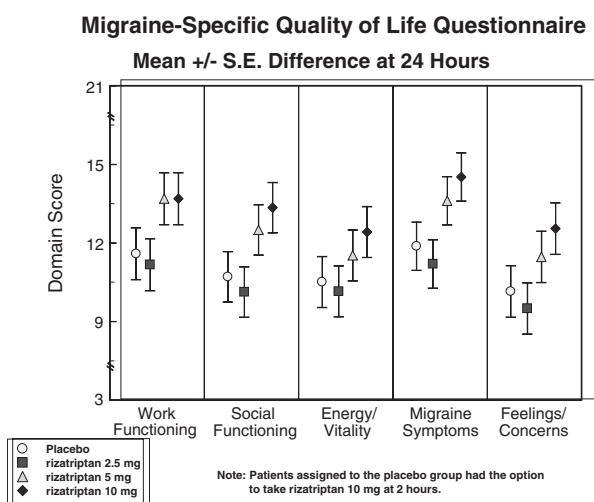


Figure 3 Efficacy of rizatriptan in migraine.

Table 1 Summary of key points on the value of PROs

- The patient's perspective is a key element in medical diagnosis and treatment.
- Patient-reported data are unique and complementary indicators of disease activity and treatment effectiveness.
- Professional organizations recognize the key role patient-reported data play in diagnosis and treatment, as evidenced by professional practice guidelines.
- PROs in clinical trials provide important data for evaluating the effectiveness of new treatment.
- Consistent with the definition of a scientific instrument, patient-reported outcome measures provide precise, reliable, valid, and reproducible data.
- The inclusion of PROs in clinical trials is sanctioned by professional organizations, as evidenced by trial guidelines put forth by professional organizations.
- PRO data are essential for evidence-based practice.
- For new pharmaceuticals, PRO data from clinical trials support evidence-based practice.

Abbreviation: PROs, patient-reported outcomes.

[2–6,27–32]. These measurement characteristics are widely accepted and considered essential for assuring that a PRO instrument is meaningful to patients and clinicians and provides accurate and valid measurements of the intended domains.

For PROs to be incorporated as evaluation criteria in the drug approval process and as support for promotional or labeling claims, they must meet the same standards as traditional clinical measures [6,33]. More specifically, several methodologic issues are important: 1) specification of the PRO research question and end point; 2) selection/development and validation of PRO questionnaire; 3) study design and PRO evaluation; 4) data analysis; and 5) interpretation and reporting.

Decisions about the incorporation of a PRO strategy into a clinical trial should be made with the research design and intended claim in mind. It is important to address questions such as “what is the claim you are hoping to achieve?” and “what are the research questions and the measures that address that claim?” PRO research and clinical trials should be driven by hypotheses, and appropriate hypothesis testing requires attention to research design, data collection procedures, and conduct of the clinical trial.

The selection of the PRO measure should be justified, based on the domains of interest for the patients, the drug profile, and the hypotheses being tested. The development of the questionnaire should be based on patient interviews and it should provide adequate assessment of the domains of interest. Psychometric evidence of the questionnaire's reliability and validity must be provided. Ideally, responsiveness for the domains on which the hypotheses are tested should be demonstrated before the clinical trial.

The evaluation must follow clinical research standards and be designed in such a way that it adequately addresses the hypotheses being tested. The study design should address any issues that might negatively affect or compromise the integrity of the study, such as randomization, mode and timing of questionnaire administration, and prevention of missing data. Each of these research design considerations is linked to the target disease and patient population under study and the effects of treatment on the targeted disease.

The specific statistical analysis procedures must be outlined and developed to relate to the prespecified hypotheses and the targeted claim, even when the PRO is a secondary end point. A full analysis plan must be developed a priori to include the scoring method, the adjustment procedure for multiple testing, and a scientific procedure to handle missing data. A specification of the data analysis strategy and statistical models is required.

Interpretation should be made in the light of the clinical findings and should go beyond statistical significance. The consistency of PRO findings with other variables reported in the clinical trial and how this information can supplement clinical end points should be discussed. Full disclosure of all results should be provided and must include compliance with questionnaire completion, in relation to the loss of patients to follow-up, and score distribution, both at baseline and over time [34,35].

In conclusion, PROs are scientific measures that can evaluate change in outcomes. They must be handled like any other effectiveness end point in clinical trials. Methods for selecting, developing, validating, measuring, and reporting PROs are similar to those for other clinical effectiveness measures. PROs focus attention on the patient's perspective because patient information is derived from focus groups or individual interviews used to identify relevant content and domains.

Interest in and Demand for PRO Information

Group 4 was charged with reporting the reasons driving the interest in and demand for PRO information.

Over the past decade, a variety of demographic, social, and technologic phenomena have been driving the interest in and demand for PRO information. Specific trends include an increasing prevalence in chronic illnesses [36,37], patient empowerment [38], and advances in information technology [39–42].

Chronic illnesses are increasing in prevalence; and people with these conditions are living longer

fuller lives. Current US census demographic data reveal that 13% of the US population is age 65 or older [43]. Over the next 30 years that number will increase to 20%. According to US Census Bureau projections [43], the largest increases in the elderly population will be in people over the age of 85. In 1994, this group represented 10% of the elderly and 1% of the overall population; by 2050, those percentages are expected to rise to 24 and 5%, respectively [43].

Chronic illnesses are incurable by definition; therefore, improving patient HRQL and providing PRO information has become a reasonable assessment of a drug's value. Improving the patients' well-being and ability to function are important new end points for many chronic illnesses.

Patient empowerment is a primary driver of demand for PRO information. The increasing interest of patients and their ability to actively understand, participate in, and influence their health-care decisions has changed the traditional doctor/patient relationship. Findings from HRQL assessments provide more complete and relevant information to patients in ways that have intuitive value to them. Patients gain insights and a more comprehensive understanding of treatment risks and benefits. Furthermore, this information may increase patients' participation in their own treatment and gives them a voice in health-care decision making that, until recent years, has been lacking.

People with chronic conditions have begun to realize that by learning more about their illness, it is possible to live life with a sense of continuity and control. According to Segal [38], "... capacity for self-care is central to the management of chronic diseases ... and health education is a central element in the best practice protocols for the management of these conditions." Technologic tools, such as the Internet, contribute to individual empowerment and make it easier for health-care information to be communicated to those who are ill. Patients can discover the strengths and weaknesses of therapeutic regimens through use of the Internet, HRQL, PRO data and through more traditional means. All of these developments foster communication with health-care providers and reinforce patients' feelings of empowerment.

Physicians use PRO information in their discussions with patients to recommend treatments that are efficacious and have minimum adverse side effects. The addition of PRO data in labeling can help clinicians present the value of treatment alternatives to patients. Patient-relevant data includes information concerning any change in the ability,

for example, to perform activities of daily living or instrumental activities of daily living. This information should be as readily available as data related to adverse events. More importantly, PRO information increases clinician-patient communications and encourages patients to become self-reliant. According to one clinician [29], "... For centuries, the medical profession ... perpetrated a paternalism that deprived patients of the self-esteem that comes from self-reliance." Today, the age-old adage that knowledge is power has new meaning for health-care consumers. Better clinician-patient communications and patient empowerment have affected the entire health-care system, encouraging health-care businesses to provide patients with pertinent, patient-friendly information on their health status. Patient information sheets provided by clinicians at the time of emergency room discharge translate clinical findings into relevant information that can be understood by patients. Translating degree of improved lung capacity into the ability to walk without impaired breathing is another illustration of this ideal.

In breast cancer, PRO information can influence how patients perceive the condition and how clinicians treat it. Kiebert *et al.* [44] reviewed the breast cancer literature and found that in mastectomy versus breast-conserving surgery, where survival outcomes are similar, a clinician's treatment regimen is dependent on the patient's perception of specific aspects of HRQL. Kiebert and colleagues found that in 10 of 18 studies, patients experienced a more positive outcome with respect to body image after surgery with breast-conserving treatment. These and other findings caused the authors to conclude that the more a patient is involved in the treatment decision-making process, the more likely it is that surgery will be limited [44].

Epilepsy is a chronic illness with serious physical and social consequences for patients. It is a diverse disorder, characterized by transient disturbances of brain function manifested as altered consciousness or episodic impairment of function. The seizures are often not satisfactorily controlled even after antiepileptic drugs are initiated [45]. In addition to the physical aspect of the illness, the emotional and social issues must be considered. Lack of self-esteem, embarrassment, and a reduced ability to perform normal social activities such as driving and participating in sports are all pertinent HRQL issues for subjects with this diagnosis [46]. As is the case with breast cancer, epilepsy can demonstrate the value of PRO data in influencing clinician-recommended treatment regimens. Increased

patient participation in the treatment process affects the way therapies for the disease are mutually selected by providers and patients and adhered to by patients.

In conclusion, demographic, social, and technologic trends will continue to drive the interest in and demand for PRO information. The increase in methods of communication will continue to modify the doctor/patient relationship, empowering patients and affecting not only the means by which information is conveyed, but also the very nature of the information itself. PROs, and HRQL information in particular, will play an increasingly vital role in these events.

Discussion

PRO measures extend patient outcome assessment beyond survival, traditional clinical efficacy, and adverse effects and most importantly represent the patient's perspective on the impact of disease and its treatment on her/his everyday functioning and well-being. Whereas PROs have been incorporated into clinical trials over the past 20 years, there remains concern about the value and application of these measurements in the evaluation of new therapies. The focus of the PRO harmonization effort is on addressing the application of PRO end points in the evaluation and review of new therapies for approval by the FDA and other regulatory agencies. The primary intent is to clarify areas of ambiguity and provide regulatory agencies with recommendations on the best practices in PRO assessment. This effort also identified unresolved research issues associated with the use of PROs in evaluating new medical treatments. There is no intent to provide overall guidance and recommendations on the development and use of PROs for other applications, such as monitoring the health status of population, evaluating the quality of medical services delivery, or evaluating other health interventions.

Several other PRO research issues were raised during the meeting held at the FDA in February 2001 including:

1. What are the scientific standards associated with PRO instrument development?
2. What are the issues associated with PRO instrument selection, including rationale and hypotheses, relationships with clinical end points?
3. What is the state of the science in handling missing data in PRO statistical analyses?
4. How can PRO results be interpreted, especially when there are inconsistencies between outcomes?

These four issues were addressed in a PRO harmonization meeting held in March 2002. The results of this meeting are the focus of a forthcoming article. In addition, FDA participants raised issues related to recommendations for substantiating evidence supporting PRO labeling or promotional claims and presentation of PRO results in the product label. These issues will be addressed in a future PRO Harmonization Group meeting.

The PRO Harmonization Group represents an unprecedented level of communication between the FDA and pharmaceutical and academic researchers. It has contributed to understanding the value of the patient perspective and the best practices for incorporating it into the drug evaluation process.

Clearly, more research is needed and future meetings are needed to further develop understanding of the PRO assessment in the evaluation and regulatory review process. While complete consensus may not be reached on all issues, improving the understanding of researchers from industry, academia, and regulatory agencies will ensure that clinical trials will include state-of-the-art measures and methods. In addition, identifying areas for future research that will assist the FDA and other regulatory agencies in incorporating PRO end points into their decision making is useful. The intent of conducting clinical trials and reviewing treatment effectiveness and safety data is to communicate information about the risks and benefits of new therapies to physicians, patients, and their families in terms that may be used to make individual health-care decisions. PROs, including HRQL, are an important component of this process.

The PRO Harmonization Group thanks Laurie B. Burke, RPh, MPH (Director, Study Endpoints and Label Development, Office of New Drugs, CDER, FDA); Robert J. Meyer, MD (Director, Office of Drug Evaluation II, Office of New Drugs, CDER, FDA); Robert Temple, MD (Director, Office of Medical Policy, CDER, FDA); and other FDA representatives who attended the February 16, 2001, meeting. We also thank ERIQA, ISOQOL, ISPOR, PhRMA-HOC, and Dr Jean Paul Gagnon. We acknowledge the membership of the PRO Harmonization Group by organization: ERIQA—Catherine Acquadro, MD, MAPI Research Institute, France; Olivier Chassany, MD, PhD, AP-HP, France; Dominique Dubois, MD, Janssen Pharmaceutica, Belgium; Asha Hareendran, PhD, Pfizer, UK; Patrick Marquis, MD, MAPI Values, USA; Pierre Sagnier, MD, Bayer, UK; Ingela Wiklund, PhD, AstraZeneca, Sweden; Rhys Williams, PhD, Bristol Myers—Squibb, USA. ISOQOL—Ivan Barofsky, PhD, Johns Hopkins University, MD, USA; Rick Berzon, DrPH, Boehringer Ingelheim, CT, USA; Donald Patrick,

PhD, MSPH, University of Washington, WA, USA; Dennis Revicki, PhD, MEDTAP International, MD, USA; Albert Wu, MD, PhD, Johns Hopkins University, MD, USA. ISPOR—Joyce Cramer, BS, Yale University School of Medicine, CT, USA; Pennifer Erickson, PhD, Pennsylvania State University, PA, USA; Paul Kind, M.Phil, University of York, UK; Nancy Kline Leidy, PhD, MEDTAP International, MD, USA. PhRMA-HOC—Greg Boyer, PhD, Pharmacia, USA; Catherine Copley-Merriman, MS, MBA, Pfizer, MI, USA; Joseph DiCesare, MPH, RPh, Novartis, NJ, USA; Haim Erder, PhD, Amgen, CA, USA; Jean-Paul Gagnon, PhD, Aventis, NJ, USA; Lou Garrison, PhD, Roche, Switzerland; Joseph Jackson, PhD, Bristol Myers Squibb, NJ, USA; David Miller, PhD, GSK, NC, USA; Margaret Rothman, PhD, Johnson & Johnson, NJ, USA; Nancy Santanello, MD, MS, Merck, PA, USA; Richard Willke, PhD, Pharmacia, NJ, USA.

Although members of each organization participated in the PRO Harmonization efforts, this report does not represent an official document, endorsement, or consensus view of the ISOQOL, ISPOR, PhRMA-HOC, ERIQA, or the FDA.

This report was financially supported by ERIQA, ISOQOL, ISPOR, and PhRMA-HOC.

References

- Bergner M. Quality of life, health status, and clinical research. *Med Care* 1989;27(Suppl):S148–56.
- Patrick DL, Erickson P. *Health Status and Health Policy: Allocating Resources to Health Care*. New York: Oxford University Press, 1993.
- Leidy NK, Revicki DA, Geneste B. Recommendations for evaluating the validity of quality of life claims for labeling and promotion. *Value Health* 1999;2:113–27.
- Revicki DA, Osoba D, Fairclough D, et al. 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.
- Santanello NC, Baker D, Cappelleri JC. Regulatory issues for health-related quality of life—PhRMA Health Outcomes Committee Workshop, 1999. *Value Health* 2002;5:14–25.
- Chassany O, Sagnier P, Marquis P, et al. Patient-reported outcomes: the example of health-related quality of life—A European guidance document for the improved integration of health-related quality of life assessment in the drug regulatory process. *DIA J* 2002;36:209–38.
- Burke L. Acceptable evidence for pharmaceutical advertising and labeling. *DIA Workshop on Pharmacoeconomics and Quality of Life Labeling and Marketing Claims*. 2000 Oct 3; New Orleans (LA). Horsham (PA): Drug Information Association; 2000.
- Rothman ML, Hedrick SC, Bulcroft KA, et al. Effects of adult day health care on health outcomes and satisfaction with care. *Med Care* 1993;31:38–49.
- Rothman M, Farup C, Stewart W, et al. Symptoms associated with gastroesophageal reflux disease: development of a questionnaire for use in clinical trials. *Dig Dis Sci*, 2001;46:1540–48.
- Portenoy RK, Thaler HT, Kornblith AB, et al. The memorial symptom assessment scale. an instrument for the evaluation of symptom prevalence, characteristics and distress. *Eur J Cancer* 1994;30A:1326–36.
- Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes. *JAMA* 1995;273:59–65.
- American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;152(Suppl):S77–120.
- National Heart, Lung and Blood Institute & World Health Organization. Global Initiative for Chronic Obstructive Lung Disease [Internet]. Publication No. 2701A. Bethesda (MD): US Department of Health and Human Services, Public Health Service, National Institutes of Health; 2001. Available from: <http://www.goldcopd.com/workshop/index.html>.
- Eltayara L, Becklace MR, Volta CA, et al. Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;154(6 Pt 1):1726–34.
- Hajiro T, Nishimura K, Tsukino M, et al. Comparison of discriminative properties among disease-specific questionnaires for measuring health-related quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157(3 Pt 1):785–90.
- O'Donnell DE. Assessment of bronchodilator efficacy in symptomatic COPD: is spirometry useful? *Chest* 2000;117:S42–7.
- Bostrom C. Shoulder rotational strength, movement, pain and joint tenderness as indicators of upper-extremity activity limitation in moderate rheumatoid arthritis. *Scand J Rehab Med* 2000;32:134–9.
- Lee CE, Simmonds MJ, Novy DM, et al. Self-reports and clinician-measured physical function among patients with low back pain: a comparison. *Arch Phys Med Rehabil* 2001;82:227–31.
- Kaliner M. Allergy care in the next millennium: guidelines for the specialty. Presidential Address. *J Allergy Clin Immunol* 1997;99:729–34.
- An evidence-based appraisal of reflux disease management—Genval Workshop Report. *Gut* 1999;44(Suppl 2):S1–16.
- Boers M, Brooks P, Strand V, et al. The OMER-

- ACT filter for outcome measures in rheumatology. *J Rheumatol* 1998;25:198–9.
- 22 Strand V, Gladman D, Isenber D, et al. Endpoints: consensus recommendations from OMERACT IV. *Lupus* 2000;9:322–7.
- 23 Cramer JA, Arrigo C, Van Hammee G, et al. The effect of levetiracetam on epilepsy-related quality of life. *Epilepsia* 2000;41:868–74.
- 24 Santanello NC, Polis AB, Hartmaier SL, et al. Improvement in migraine-specific quality of life in a clinical trial of rizatriptan. *Cephalalgia* 1997;17:867–72.
- 25 Group for the Respect of Ethics and Excellence in Science (GREES) Rheumatoid Arthritis Section. Recommendations for the registration of drugs used in the treatment of rheumatoid arthritis. *Br J Rheumatol* 1998;37:211–5.
- 26 Johnson JR, Temple R. Food and Drug Administration requirements for approval of new anticancer drugs. *Cancer Treat Rep* 1985;69:155–9.
- 27 Lohr KN, Aaronson NK, Alonso J, et al. Evaluating quality-of-life and health status instruments: development of scientific review criteria. *Clin Ther* 1996;18:979–92.
- 28 Von Neumann J, Morgenstern O. *Theory of Games and Economic Behavior*. Princeton: Princeton University Press, 1944.
- 29 Likert R. A technique for the measurement of attitudes. *Arch Psychol* 1932;140:1–55.
- 30 Cronbach L, Meehl P. Construct validity in psychological tests. *Psychol Bull* 1955;281–302.
- 31 Nunnally J, Bernstein I. *Psychometric Theory* (3rd ed.). New York: McGraw-Hill, 1994.
- 32 Hays R, Anderson R, Revicki DA. Assessing reliability and validity of measurement in clinical trials. In: Staquet MJ, Hays RD, Fayers PM, eds. *Quality of Life Assessment in Clinical Trials*. New York: Oxford University Press, 1998.
- 33 Fayers PM, Hopwood P, Harvey A, et al. Quality of life assessment in clinical trials—guidelines and a checklist for protocol writers: the UK medical research council experience. *Eur J Cancer* 1997;33:20–8.
- 34 Machin D, Weeden S. Suggestions for presentation of quality of life data from clinical trials. *Stat Med* 1998;17:711–24.
- 35 Sanders C, Egger M, Donovan J, et al. Reporting on quality of life in randomised controlled trials: bibliographic study. *Br Med J* 1998;317:1191–4.
- 36 Prevalence of disability and associated health conditions—United States, 1991–1992. *Morb Mortal Wkly Rep* 1994;43:730–1,737–9.
- 37 CDC Chronic Disease Prevention. *The Burden of Chronic Diseases and Their Risk Factor—National and State Perspectives*. Washington: U.S. Department of Health and Human Services, 2002.
- 38 Segal L. The importance of patient empowerment in health system reform. *Health Policy* 1998;44:31–44.
- 39 Eysenbach G, Diepgen TL. The role of e-health and consumer health informatics for evidence-based patient choice in the 21st century. *Clin Dermatol* 2001;19:11–7.
- 40 Ball MJ, Lillis J. E-health: transforming the physician/patient relationship. *Int J Med Inf* 2001;61:1–10.
- 41 Coile RC Jr. The digital transformation of health care. *Physician Exec* 2000;26:8–15.
- 42 Coile RC Jr. E-health: reinventing healthcare in the information age. *J Healthc Manag* 2000;45:206–10.
- 43 U.S. Census Bureau. *Population Projections of the United States by Age, Sex, Race, Hispanic Origin, and Nativity: 1999 to 2100* [Internet]. Washington: The Bureau, 2000 Feb 14. <http://www.census.gov/population/www/projections/natsum-T3.html>.
- 44 Kiebert GM, de Haes JCJM, van de Velde CJH. The impact of breast-conserving treatment and mastectomy on the quality of life of early-stage breast cancer patients: a review. *J Clin Oncol* 1991;9:1059–70.
- 45 Cramer JA. Quality of life assessment for people with epilepsy. In: Spilker B, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials* (2nd ed.). Philadelphia: Lippincott-Raven, 1996.
- 46 Arunkumar G, Wyllie E, Kotagal P, et al. Parent- and patient-validated content of pediatric epilepsy quality-of-life assessment. *Epilepsia* 2000;41:1474–84.