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The Mayo Clinic Manuscript Series Relative to the Discussion, Dissemination, and Operationalization of the Food and Drug Administration Guidance on Patient-Reported Outcomes

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ABSTRACT

Patient-reported outcomes (PROs) have become increasingly prevalent in clinical research and practice. On February 2, 2006, the Food and Drug Administration (FDA) released a draft guidance document with respect to incorporating PROs into clinical research endeavors which include FDA involvement. Researchers at the Mayo Clinic worked with FDA personnel and experts from academia, industry, clinical research, and clinical practice to facilitate discussion, dissemination, and operationalization of the FDA guidance document. This article introduces a manuscript series that resulted from this collective effort. Basic terms are defined and a précis of each article in the manuscript series is given. The ultimate conclusion to be drawn from this series is that, while the goals of assessing and analyzing PRO elements of clinical practice and research are challenging, there now exists a scientific foundation that makes achieving these goals feasible and the results credible. This is vitally important because after all, at the heart of all healthcare endeavors is the patient.

Keywords: FDA guidance, patient-reported outcomes, QOL, quality of life.

Introduction

Patient-reported outcomes (PROs) have become increasingly important in clinical research and practice in recent years with the advent of combination therapies and development of novel and targeted agents with limited but potentially acute side effects. In response to issues surrounding the measurement and interpretation of PROs within pharmaceutical industry-sponsored trials, drug approval applications, and labeling claims, the Food and Drug Administration (FDA) released a draft guidance document on February 2, 2006 (available at http://www.fda.gov/cder/guidance/5460dft.pdf) [1]. The draft guidance document outlines how the FDA evaluates PROs when used as efficacy end points in support of labeling claims.

The articles in this issue add to the draft guidance document in that methods are delineated to handle the various challenges associated with including PROs in FDA-related clinical trials. For example, in the article by Sloan et al. [2], methods for handling missing data and multiple end points are described. The articles of this issue do not represent a consensus view of all meeting participants. They do, however, represent an elaboration of the contents of the draft guidance document from the viewpoint of experts from academia, industry, clinical research, and clinical practice, informed by reviews from FDA representatives and 2 days of open discussion during a meeting held in February 2006. This meeting was intended to:

1. Provide a focused process to facilitate discussion of the recent FDA guidance among all stakeholders;
2. Educate stakeholders on the background, content, intent, and concerns surrounding the guidance;
3. Provide an opportunity for systematic review and discussion of the feedback that has been given to FDA on the guidance and its implications; and
4. Delineate ways to best operationalize the guidance so that PROs are incorporated into clinical trials using state-of-the-science knowledge.

Although the manuscripts deal specifically with issues related to FDA-related clinical trials, many of the findings and recommendations apply to virtually all research involving PRO assessments. Material

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related to the meeting and manuscript series can be obtained at http://www.qolpro.org.

PROs: A Primer

Origin of the Term PRO

The term "patient-reported outcome" appeared in literature after 1999, although terms such as "self-reported health outcomes" and "patient-generated outcomes" continue to be used [3,4]. The term PRO originated after the Harmonization Meeting in 2000 [5]. A working group met to discuss and coordinate recommendations and to address the need to harmonize outcomes review criteria in the US and European regulatory agencies. The discussion expanded from health-related quality of life (HRQOL) to include outcomes based on data provided by the patient (or PROs). The working group thereafter became known as the PRO Harmonization Group. PRO is now used with increasing frequency in the evaluation of new therapeutic products, quality-of-life literature, and reports tied to patient interviews and physician–patient communication.

PRO Data Capture

Collection of patient-generated information during a clinical encounter is usually elicited through questions to establish the history of the illness. Formalized PRO data gathering in support of product development and effectiveness is more systematic using standardized instruments and questions designed to capture explicit information about intensity or severity of symptoms, satisfaction with care, or impact on quality of life and function. In the context of patient care, the clinical staff must integrate the findings into a treatment plan, whereas researchers use the data to characterize benefits of a treatment.

Incorporation of PRO data is intended to result in improved understanding of the illness experience, and underscores evidence used for a product claim. The PRO should, in principle, facilitate the ability to predict changes in physical, mental, or social function. The PRO may enhance the understanding of the disease and treatment when the PRO is correlated with physiological changes (e.g., sleep patterns, eating habits, or elimination). Part of the challenge in using PRO data is the capacity to derive meaning from the synthesis of the data.

Types of PRO Data

Patient-reported outcome data captured through an oral history, a discussion, a cognitive interview, survey items, or electronic equipment can all be useful. For example, utilization of equipment such as the talking touch screen might provide a model to capture PRO data for low-literacy patients [6]. Whatever the collection method, the types of data are highly variable, ranging from very specific (e.g., symptom frequency) to more complex evaluations such as HRQOL assessments. Several examples are noted as follows:

1. The impact of the disease state on daily living and social functioning provide insight into the beliefs of the patient and the social network surrounding the patient. The relevance of the illness experience and the impact on the patient's life should help to determine whether, and to what extent, the complaints relate to or interfere with daily living or a patient's customary social role, self-esteem, and performance.
2. Symptom information includes descriptors of severity, intensity, bothersomeness, and the impact on everyday function. Symptoms such as pain, for example, serve a protective function by alerting the individual of impending tissue damage. Other symptoms may create a level of social discomfort, pressuring the individual to report inconvenience, bothersomeness, or dysfunction.
3. Satisfaction provides important feedback for the clinician, the researcher, and the health-care facility, and may help to substantiate a claim for a new product. Satisfaction information can lead to a deeper understanding of the patient's health problem, performance capacity, and potential disability, not only enhancing the care delivered but also providing insight into the desirability of the treatment. Medication satisfaction, a subset of PRO satisfaction, is often distinguished by its relationship with adherence. The patient's beliefs and values may change his or her willingness to adhere to medication recommendations. Beliefs not only influence satisfaction, but can change perceptions about symptom relief, medication efficacy, side effects, convenience, and ideas about the impact on quality of life [7].
4. The patient's assessment of HRQOL is considered an important indicator of treatment effectiveness and may influence recovery goals. HRQOL assessment is more complex than some PROs and may provide information about treatment outcomes in multiple domains.
5. Finally, PRO information has merit in and of itself, because PRO data can provide substantial rationale and scientific underpinning for the efficacy of other clinical end points. In addition, these outcomes can be useful to the pharmaceutical industry in rounding out the picture of the impact of treatment on health status and function. The industry may more effectively use the outcome information to communicate product value to the clinician and payers [8].

PRO Users

Patient-reported outcome data provides helpful documentation for a variety of users. There are times, for example, when the patient could be the user of these data. The patient's primary interest may concern the likelihood of improvement in daily life [5]. Changes important for self-care or those that alter the patient's personal outcome expectations contribute to critical judgments about care. Patients may be encouraged to keep track of changes in their care during follow-up visits, reinforcing the need to attend to changes in their health status [9].

The practicing clinician also stands to gain by improved insight into changes in performance status or physical symptoms paramount for medical decision-making (e.g., asthma symptoms reported by patients with newly exacerbated dyspnea on exertion). PROs may demarcate changes in health status relevant to treatment effectiveness, discharge, or for prescription changes. In practice, HRQOL could easily become the most prominent end point or outcome measure to show changes from the patient's perspective [10]. PROs have already become standard in chronic disease areas such as arthritis and erectile dysfunction.

Payer or managed-care organizations may be interested in the use of PRO information to predict outcomes. Other interests extend to the associated reduction in service use or cost of care resulting from changes in PRO [11]. Regulatory agency decision-makers also have a stake in PRO information as primary or secondary end points in a clinical trial, depending on the condition under study. The information could provide insight into the efficacy of new and existing products or technologies, to enhance or reinforce a product claim in the approval process.

Patient-reported outcomes in the framework of new product development include many of the same requirements as clinical use. These elements include specificity of the concept, a conceptual framework, documentation of data elements and collection methods, including validated instruments. PROs represent the perspective of the patient's experience with the disease state, and the impact on daily functioning and general well-being [5]. Capacity to reflect this fact in the reports of product development is essential for substantiation of a claim.

Project Etiology

The Cancer Outcomes Working Group was an initiative of the National Cancer Institute that produced a book published in 2005 which summarized key contributions to the literature of cancer patient outcomes research [12]. During the compilation of that text, it became apparent that concerns existed among individuals in the pharmaceutical industry regarding the viability of PRO assessments in labeling claim-related studies. Some companies were closing down outcomes research programs in response to a perceived shift in FDA opinion away from PRO assessments as end points in clinical trials. Whether this perception was real or imagined is open to debate. The point, however, was that in late 2004, there was real concern among QOL researchers that the then-pending release of the FDA guidance document on PROs would result in, at best, a serious curtailment of their use in clinical research, and at worst, "the death of QOL research." Individuals involved in this project from the Mayo Clinic approached the FDA Center for Drug Evaluation and Research group regarding this potential "storm on the horizon." The premise was to facilitate the discussion, dissemination, and operationalization of the pending guidance document by a collective effort. Writing teams were constructed to cover five major themes: Conceptual Issues; PRO Instrument Selection; PRO Instrument Development Issues; Validation of PROs; and Analysis, Interpretation, and Reporting Results Based on PROs. Writing team members came from a broad spectrum of stakeholders: academics, clinicians, pharmaceutical industry researchers, government and regulatory agency researchers, and patient advocates.

Team leaders were given a charge to produce an outline for each topic. Each outline was reviewed by all team members. The editorial process then moved forward to production of draft versions of the manuscripts. The manuscripts were then submitted to the Mayo Clinic team for central review. Extensive review processes were followed up to the date of the meeting in Chantilly, Virginia, February 23–25, 2006. More than 400 attendees spent 3 days discussing the FDA guidance document, the draft manuscripts, and other issues related to incorporating PRO assessments into clinical research. Detailed directions for revisions for all the manuscripts were derived from the discussions that were given to the writing teams. The postmeeting revision process then continued with input from all team members via further face-to-face and/or virtual meetings. The manuscripts were then submitted to *Value in Health* for peer-review.

Précis of Each Article

1. Patient-Reported Outcomes: Conceptual Issues [13]. This article covers such issues as:
   a. What is a PRO concept?
   b. What is an adequate conceptual framework?
   c. What are the consequences of proceeding with instrument development without a well-established conceptual framework?
   d. Do specific conceptual issues vary or evolve by phase of medical product development (i.e., Phase I, II, III, or IV trials)?

2. Patient-Reported Outcome Instrument Selection: Designing A Measurement Strategy [14] deals with:
   a. What is the recommended process for instrument selection?
   b. When is it appropriate to develop, modify, or adapt a PRO instrument?
   c. When is it appropriate to draw individual subscales or items out of assessments to be used separately as study end points?
   d. If you modify a PRO do you have to redo all validation? What can be used from the original validation?
   e. If you select an existing instrument, what do you do if the original development and validation documentation is inadequate?
3. Patient-Reported Outcomes: Instrument Development and Selection Issues [15] deals with:
   a. What are the basic qualitative research requirements during instrument development? For example, how much preliminary data is required to justify the aggregation of individual items into a domain score? How do you know when you have captured adequately all the requisite subconcepts?
   b. When can a single question serve as a PRO end point? When are multiple items required?
   c. What is the best method for constructing a summary score?
   d. How do you deal with respondent burden?
4. What Is Sufficient Evidence for the Reliability and Validity of Patient-Reported Outcome Measures? [16] deals with:
   a. What evidence of validity must you provide for a PRO assessment you plan to use in a clinical trial?
   b. What kinds of validation can be performed concurrently with different types of trials (i.e., Phase I, II, III, or IV clinical trials)?
   c. How do you validate the equivalence of translations or electronic versions of established questionnaires?
   d. What is the most appropriate use of item response theory during instrument development and validation?
5. Analysis and Interpretation of Results Based on PROs [2]:
   a. What are the analysis pitfalls with PRO data in clinical trials and how can they be avoided (e.g., missing data, multiplicity, etc.)?
   b. What are the best (alternative) methods to assess clinical significance of PROs?
6. Interpreting and reporting results based on PROs [17]:
   a. How should null results be interpreted?
   b. How do you present PRO data most effectively in an FDA application? In labeling?
7. Evaluating HRQOL in cancer clinical trials: the National Cancer Institute of Canada Clinical Trials Group experience [18] describes how PROs have been incorporated into cancer clinical trials in Canada.
8. Patient-reported outcomes to support medical product labeling claims [19] contains commentary from the FDA on the guidance document and how it relates to the other articles in this series; and finally,
9. A patient-reported observation [20] presents the most important perspective of all, that being a patient.

Conclusions

The goal of this project was to provide a supplement to the FDA guidance that would provide furnish detail and exposition that is impossible to communicate in the relatively brief 36-page document. We hope that readers will be able to use the recommendations provided in the accompanying manuscripts to facilitate incorporation of PRO assessments into the research process. As with anything worthwhile, assessing and analyzing PRO elements of clinical practice and research is challenging. We must do all that we can to make PRO assessment feasible and credible. If we fail in our task we will have left out the heart of all health-care research: the patient.

Laurie Burke, Jane Scott, and Donald Patrick were key in resolving the considerable administrative, political, and logistical challenges this Mayo/FDA joint endeavor entailed. Numerous members of the FDA who served as panelists throughout the meeting answered more than 300 individual questions relating to the guidance document over a period of 3 days. Steven Priori of the International Society for Pharmacoeconomics and Outcomes Research first suggested *Value in Health* as a venue for this series and worked tirelessly keeping us on target. Kristy Vierling and Kara Curry made the organization of the meeting run as smoothly as is humanly possible. Martha Hoag, Matthew Jenson, and Jeff Lobland of the Mayo School of Continuing Medical Education ensured that the meeting came off without a hitch. Vicki Schmidt is primarily responsible for all the articles getting submitted and managing the countless revisions. The writing team leaders devoted incredible energy and time in responding to our constant deadline pressures and keeping their individual teams on target. All of the writing team members contributed intellectual prowess so that the sum of the contributions was greater than the individuals. Reviewers donated their time and expertise to help the articles be as strong as they can be. All members of the Mayo QOL Team jumped in and more than made up for the deficits in their leader. Finally, I think we all owe a debt of thanks to the patients who have contributed their opinions over the years as the science of PROs has developed. Their patience with our ineptitude as we learned from our mistakes is unfathomable but totally vital to the scientific process.

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