Assessing the Symptoms of Cancer Using Patient-Reported Outcomes (ASCPRO): Searching for Standards

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Abstract
The U.S. Food and Drug Administration (FDA) 2006 draft guidance on “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” has engendered wide discussion about patient-reported outcome (PRO) domains that should be endpoints in clinical trials. Reducing the severity and impact of symptoms is a natural intervention endpoint for cancer, a condition associated with considerable symptom burden. Because symptoms are best described by patients who have them, including PROs as measures of treatment effectiveness or the differences among treatments provides essential information about the efficacy and toxicity of a treatment and its effects on function. The FDA guidance provides a framework for addressing such issues as clinical significance, study design, and statistical methods as they relate to applications for labeling claims; however, no set of recommended approaches for assessing specific symptoms by patient report in clinical trials exists, other than for pain. Accordingly, an interdisciplinary workgroup, Assessing the Symptoms of Cancer using Patient-Reported Outcomes (ASCPRO), has been formed to generate evidence-based recommendations for the assessment of patient-reported cancer-related symptoms and the use of that information to facilitate clinical research and decision making.

ASCPRO is among the first working groups to focus primarily on nonpain symptoms, including fatigue, sleep disturbance, appetite loss, depression, cognitive impairment, and shortness of breath. ASCPRO members are stakeholders in optimal symptom assessment, including patient advocates, academics, clinicians, those who pay for symptom control and monitor quality of care, and those who produce products that palliate cancer-related symptoms but that may also engender treatment-related symptoms.

Key Words
Patient report, outcomes, symptoms, quality of life, clinical trials
Introduction

The mandate of the U.S. Food and Drug Administration (FDA), in addition to assuring drug safety, is to ensure that the drug-approval process includes confirmation of clinical benefit. To be approved by the FDA, a drug must improve survival or make patients feel or function better. The effect of a treatment on how a person feels or functions is best known through patient self-report. Self-report of disease and/or treatment effects in clinical research is becoming known as a patient-reported outcome (PRO).

The FDA has a long history of approving drugs that ease symptoms such as pain, nausea and vomiting, depression, and insomnia. These drugs may have a direct effect on symptoms (e.g., relief of pain) and/or they may reduce disease burden, which indirectly provides a symptom-reduction benefit and may even prevent the development of symptoms. Because reduction of symptoms clearly provides a clinical benefit for persons with cancer, which in its more advanced stages is a highly symptomatic disease, a number of oncology medications have been approved by the FDA on the basis of symptom relief alone.

Taking into account the variations in how patients feel and how they function can inform the development of new therapies and provide a benchmark for appraising cancer treatments. The inclusion of PROs as means to measure differences among treatments is paramount for effectively evaluating the efficacy and toxicity of a treatment and the quality of survival. Furthermore, variation in the patient’s health status during the survival period has become a critical criterion in making final individualized treatment choices. When otherwise equally effective curative treatments differ in the severity of the symptoms they cause, the assessment of symptoms may help patients and clinicians choose between them; if two drugs produce fewer treatment-related symptoms (or side effects), then it can be thought of as having greater benefit to the patient.

The FDA Draft Guidance on the Use of PROs

In 2006, the FDA issued draft guidance for the pharmaceutical industry on “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.” The purpose of the draft guidelines (finalized in December 2009) was to describe how the FDA evaluates PRO instruments used as effectiveness endpoints in clinical trials and the agency’s current thinking on how sponsors can develop and use study results measured by PRO instruments to support claims in approved product labeling. Similar regulatory efforts are being made in Europe under the auspices of the European Medicines Agency (EMEA).

Industry and academic researchers attempting to adjust to the FDA draft guidance and the EMEA guidelines engaged in wide discussion about domains of PROs that should be considered as primary or secondary endpoints in clinical trials and for labeling purposes. Lipscomb et al., in a summary of the discussions that occurred during the year subsequent to the appearance of the FDA draft guidance, included a comprehensive discussion of the issues and a convenient linkage between each issue and relevant references summarizing the present state of the science. More recently, Bottomley et al. completed a comprehensive literature review of responses to these guidelines. The authors concluded that there were differences in approach between the U.S. and European guidelines, including a greater FDA emphasis on conceptual models and symptoms as well as more stringent design recommendations regarding recall bias and the degree of psychometric validation required.

When the draft guidance appeared, there was concern among stakeholders that rigid guidelines would hamper and perhaps make impractical the incorporation of PROs as endpoints in clinical trials for labeling purposes. These fears were largely unfounded, however, as the FDA draft guidance spurred healthy discussion and further research efforts to address the issues highlighted therein. Multiple academic societies (e.g., Drug Information Association, International Society for Quality of Life Research, American Society of Clinical Oncology, International Society For Pharmacoeconomics and Outcomes Research, and American Association of Pharmaceutical Scientists), governmental agencies (e.g., National Cancer Institute and FDA), and consulting companies (e.g., Center for Business Intelligence, MAPI Values, and
invivodata) held special sessions and workshops on how to interpret the FDA draft guidance and to incorporate it into trials with labeling claims. This focus on PROs also spurred multiple governmental initiatives to address some of the scientific issues. Most notably, the National Cancer Institute recently awarded a contract for the development of a patient-reported version of the Common Terminology Criteria for Adverse Events (CTCAE) and created a special symptom and quality of life (QOL) steering committee to facilitate incorporation of these endpoints into clinical trials under its auspices. Other initiatives, such as PROMIS (Patient-Reported Outcomes Measurement Information System) and CanCORS (Cancer Care Outcomes Research and Surveillance Consortium), continue to focus on the scientific issues surrounding PROs.

Nonetheless, the FDA guidance, as an evolving endeavor within the agency, is experiencing growing pains in terms of uneven and perhaps overly stringent interpretation and application. Although there is general agreement that consensus and concreteness are needed to firmly establish guidelines on the incorporation of PROs into clinical trials and for labeling purposes, unresolved differences of opinion as to how to achieve this goal still remain. And although symptom reduction is already used as a significant primary or secondary endpoint in oncology clinical trials, the several meetings responding to the FDA draft guidance have focused primarily on generic PROs. There has been little discussion of how the guidance might affect symptom assessment in oncology clinical trials. More importantly, despite a considerable body of literature, there has not been a coordinated effort to provide comprehensive guidance for symptom assessment in oncology clinical trials.

Here, we describe one effort to address these issues—the formation of an interdisciplinary workgroup called Assessing the Symptoms of Cancer using Patient-Reported Outcomes (ASCPRO) (www.ascpro.org).

**Definition of Terms**

A useful definition of “symptom” is provided by *Webster’s Third New International Dictionary,* which describes a symptom as “the subjective evidence of disease or physical disturbance observed by a patient.” Implicit in this definition is the negative nature of symptoms and, most importantly, that symptoms are observations of the person directly experiencing the evidence of disease or physical disturbance. In contrast to “signs” of disease (such as fever or high blood pressure), symptoms can only be known through patient report.

The nomenclature relating to PROs, QOL, health-related QOL (HRQOL), health status, patient well-being, and symptoms has often been confused in the literature. “PRO” has become an umbrella term encompassing any outcome that is derived from a patient report. This term thus encapsulates patient report of other outcomes such as QOL, health status, activities of daily living, and symptoms (Fig. 1). In the figure, symptoms and the functional impairment they cause are most proximal to the biological processes of disease and the interactions between disease and treatment. Because of this, changes in symptoms may be the most sensitive patient report of disease and response to treatment.

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**Fig. 1.** A measurement model for symptoms and overall HRQOL. Symptoms are not synonymous with HRQOL. HRQOL is an inclusive concept comprising many domains outside of those that are most likely to be affected by disease and treatment. Symptoms are patients’ perceptions of what is closest to the disease and treatment process. Symptoms and symptom interference are a subset of overall HRQOL domains, and knowing their status may be sufficient for making judgments about therapy effectiveness. © 2006 Charles S. Cleeland. Used by permission.
Symptoms as a Focus for Clinical Research

Therapies that have symptom control as a focus have become more prominent in the last few years, with several factors playing a role in this development. Increasing demands from patients and their significant others that the patient be more comfortable and functional are evident in the media and in the clinic. Some treatment-related symptoms, such as fatigue, depression, and neuropathic pain, can become so severe that optimal curative therapy must be delayed or terminated. The use of symptom scales in clinical trials, either alone or as components of other HRQOL measures, has demonstrated that some new drugs have unexpected positive benefits for symptom control. Finally, as we learn more about the biological bases of symptoms such as pain, nausea, vomiting, fatigue, and depression, the possibilities of symptom-focused interventions will expand.

Nonetheless, patient reports have not always been considered to be as credible as other, more “objective” outcome measures in either the clinic or clinical research, and this has been a major barrier to implementation of symptom ratings. Some have been concerned with “patient error” in reporting subjective systems, and considerable efforts have been made to assess, estimate, and incorporate the degree of “error” in subjective reports into analytical routines. Lost in these discussions is the acknowledgment that all measurements, be they objective or subjective, are susceptible to error. We too often place greater trust in so-called “objective” measures, which are surrogates for symptoms that are derived from laboratory or mechanistic sources or from clinician estimates of symptom severity and impact, rather than from the patients themselves. It is our assertion that patient-based “errors” are no more prevalent or problematic than errors associated with physician report or other surrogate sources.

PROs have sufficiently matured in recent years so that the utility of their assessments is demonstrable. Hence, for the purposes of ASCPRO initiatives (which focus on the assessment of symptoms), we will consider patient report as the sole targeted source of data. Although we acknowledge that measurement error is inherent in patient report (or indeed in any assay), we make the following assertions about symptom reporting:

- People are the only ones who experience and can report their symptoms.
- “Objective” measures of symptom status are only as successful as their correlation with self-report. The effort to define symptoms in terms of such objective measures as cortical imaging or electrophysiological measures is a circular exercise because the criterion—the “gold standard”—is always self-report.
- Clinical professionals are only moderately successful in estimating the symptoms of others and generally tend to underestimate symptom severity—unless they validate their estimates by asking the patient.
- People uniformly give more stable and informative estimates of symptom severity when given scales to report them rather than when given simple questions with dichotomous responses, such as “Do you have any symptoms (e.g., pain, fatigue)?”

One of the challenges of symptom assessment is to simultaneously measure the several symptoms a patient may have at any given time. Disease-related and treatment-related symptoms rarely occur in isolation, and the combined effect of multiple symptoms imposes a “symptom burden” that might be thought of as the subjective patient-reported counterpart of more objective constructs such as disease or tumor burden. This construct can only be made meaningful when the measurement of single and multiple symptoms is accepted and used.

Symptom Burden and HRQOL

Recognizing that symptoms do not occur in isolation and that patients typically experience multiple symptoms caused by disease or treatment, a measure of symptom burden might be a combination of the severity of the symptoms most associated with a disease or treatment and the patient’s perception of the impact of these same symptoms on daily living (Fig. 1). In contrast, QOL is best viewed as a subjective evaluation of life as a whole. In the conceptual model of HRQOL, the patient’s perception of the impact of symptoms...
goes beyond the reporting of symptom severity into the more abstract concepts included in the meaning of HRQOL, such as changes in social functioning because of disease and treatment or the spiritual meaning of the resulting experience. The symptom burden approach limits questioning of impact to the patient’s impressions of the impact of specific symptoms or symptom clusters.

The comprehensive nature of HRQOL is both one of its attractions and one of its difficulties as a PRO domain. Intuitively, a significant reduction in symptoms would be expected to bring improvement in other aspects of HRQOL, but does this necessarily occur? Jatoi et al.22 commented that if a symptom is significantly reduced by a given treatment even though a benefit is not demonstrated in more generic measures of HRQOL, it is imperative that the treatment should still be provided. A review of symptom management trials conducted under the auspices of the Community Clinical Oncology Program9 pointed out that the value added by including broader HRQOL measurement in symptom trials has yet to be demonstrated. The authors pointed out that HRQOL is often presented as a secondary endpoint without the benefit of a conceptual connection between symptom reduction and changes in HRQOL. They concluded that a variety of psychometrically sound symptom assessment scales are available to describe meaningful change in symptom severity and impact, and that symptom reduction in itself may be an entirely sufficient outcome for a trial.

Symptom Assessment and the CTCAE

The National Cancer Institute’s CTCAE, developed in the 1980s and revised in 2006,23 provides a system of identifying AE so as to guard the safety of patients participating in cancer clinical trials. Its stated purpose is to identify any unfavorable and unintended sign, symptom, or disease associated with the use of a treatment. Although extremely useful in protecting the safety of patients in clinical trials, the CTCAE was never intended to define endpoints for clinical trials in which symptoms are primary or secondary outcomes. In addition, the CTCAE is incomplete and insensitive in the reporting of symptoms that, though they may not be life threatening, are nonetheless important to patient well-being.24,25

A primary reason for the discrepancy between symptom assessment and the CTCAE is the latter’s dependence on clinician observation rather than patient self-report. A recent article suggested that physician estimate of symptoms is neither sensitive nor specific in detecting common adverse effects of chemotherapy.24 Another study demonstrated that clinically meaningful changes in PROs for the same symptoms are detectable months earlier than reported by physicians using CTCAE criteria.25 Because of this, the reporting of clinically meaningful events by means of the CTCAE criteria can underestimate symptomatic side effects that patients deem important. Conversely, the detection of PROs can prevent the evolution of serious AE.26 The National Cancer Institute supported the value of PRO-based CTCAE criteria by awarding a contract for the development of a PRO version of the CTCAE.27 Notably, several ASCPRO members are part of the consortium awarded that contract.

Seeking Answers Through Symptom Assessment in Clinical Trials

A primary impetus for the development of the FDA guidance was a concern for physician and patient understanding of the information presented in the labeling of drugs. The overarching issue is determining how we can best communicate results of trials to facilitate clinical decision making among patients, providers, and policy makers relative to cancer symptoms. It is thus imperative that labeling claims are based on the best science, which supports the use of PRO measures in clinical trials. Questions that need to be answered by clinical symptom studies include the following:

- How can we conclude that treatment X is indicated for relief of the symptoms of disease Y?
- How can we assert that cancer treatment X produces fewer treatment-related symptoms than treatment Y?
- How does one decide which symptoms are the most critical to patients for treatment X, disease Y, or stage Z?
- How much symptom relief is clinically meaningful to patients, and for which symptoms?
Which assessments and trial designs are best suited to investigate research questions related to symptoms?

Another set of questions relates to how symptom measurement and symptom clinical trial information will eventually be used in clinical transactions, including how symptom measurement will influence the practical constraints of the managed care clinic environment. Issues include the following:

- What will actually transpire between patient and provider and lead to a symptom-based treatment choice?
- How can clinical trial outcomes information meld with measurements that will be practical to use in the clinic?
- How can we create reliable and informative symptom assessments for routine clinical application with minimal burden on the patient and clinician?
- What type of technical or electronic enhancements (Web, telephone, or computer administration) might facilitate the gathering of symptom information before a clinic visit or the monitoring of patients with symptoms?
- What clinical pathways should be followed as a result of receiving data from symptom assessments?
- How do we handle potential dissimilarities between symptom assessments across various languages and cultures?

Ample evidence in the literature indicates that these questions have been tackled at least in part. People have been searching for consensus on many of the issues involved, such as clinical significance, study design, and statistical methods. The FDA guidance provides a general infrastructure for answering some of these issues as they relate to new drug applications for labeling claims. Some of the work that has been performed to construct clinical guidelines for various cancer-related symptoms, such as the National Comprehensive Cancer Network guidelines, is keyed to symptom assessment and bases treatment recommendations on patient ratings of symptom severity. To date, however, there is no general set of recommended approaches for assessing specific symptoms, with one exception: the issue of assessing pain in clinical trials.

**The IMMPACT Process for Consensus in Pain Measurement in Clinical Trials**

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) presents an excellent model of how a working group could address the clinical trial measurement of symptoms other than pain (e.g., fatigue, sleep disturbance, nausea, and depression) that affect patients with cancer. The IMMPACT initiative has taken the approach that the lack of an ideal assessment process for measuring pain should not deter us from assessing pain as an outcome in clinical trials. After doing substantial work to gather, collate, and summarize the existing information on pain assessment, IMMPACT developed recommendations answering a number of the questions listed above as they relate specifically to pain assessment.

To accomplish this work, IMMPACT formed a working group of specialists comprising academicians, clinicians, patient advocates, and representatives of the National Institutes of Health and the FDA. Included in their consensus recommendations is that clinical trials of chronic pain should assess outcomes representing six core domains: pain severity, pain interference, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and AE, and participant disposition. Not all domains would be necessary for all trials, but the working group advocated that the rationale for exclusion of any of the core domains should be specified when reporting any trial. Recommendations with respect to acceptable assessment methods and measures were given. Although the recommendations IMMPACT provided for pain assessment may not apply to all symptoms, the process by which consensus was achieved is completely portable and provides a precedent for refining the use of patients’ reports of cancer-related symptoms.

**Assessing the Symptoms of Cancer Using PROs**

ASCPRO’s primary goal is to generate scientifically sound recommendations for the assessment of patient-reported cancer-related symptoms and the use of that information to facilitate clinical research and decision
making. ASCPRO borrows heavily from the process used by IMMPACT to develop recommendations for trial assessment of pain but will apply the process primarily to other symptoms that are specific to cancer and its treatment. ASCPRO will disseminate its recommendations by means of position papers that will facilitate the measurement of both single and multiple symptoms within the context of a clinical trial. Specific steps to meet its goals include the following:

1. Prioritizing a list of common cancer-related symptoms for which there already exists substantive but scattered literature and for which it is most likely that consensus about assessment methods can be reached.

2. Constructing a measurement model that identifies relevant domains and describes the relationships to other clinical outcomes, synthesized from the current literature and the expert opinion of ASCPRO members.

3. Summarizing available assessments and approaches to measurement, including operational definitions of clinical significance for the measurement model. This includes a delineation of when unidimensional versus multidimensional assessment of the symptom is indicated.

4. Presenting alternative trial designs to answer questions related to the specific symptom under review.

The members of the ASCPRO working group are stakeholders in optimal symptom assessment and include patient advocates, academics, clinicians, those who pay for symptom control and monitor quality of care, and those who develop products that affect cancer-related symptoms. Individuals working for governmental agencies participate as advisors and provide input as independent scientists, but federal conflict-of-interest guidelines preclude them from formally endorsing any particular scientific group, including ASCPRO, or becoming official representatives of their governmental agencies. ASCPRO is cochaired by Charles S. Cleeland of The University of Texas MD Anderson Cancer Center and Jeff A. Sloan of the Mayo Clinic. A steering committee sets meeting schedules, sets the agendas and priorities for content meetings, identifies content experts, determines potential authors of articles, and develops group hypotheses.

ASCPRO Is Launched: The Charlottesville Meeting

In August 2006, the inaugural meeting of the ASCPRO organizing group was held in Charlottesville, Virginia, to review the status of symptom measurement in cancer clinical trials using PROs. The participants at the meeting strongly agreed that a number of issues related to symptom measurement in cancer need substantial review and discussion. These issues include the development of measurement and endpoint models of symptom assessment, a review of complex symptoms such as fatigue and emotional distress, and specific measurement issues such as appropriate recall period, development and validation of new and existing scales, and validation of translations of existing scales. We recognized that addressing these issues was a long-term process that would require a permanent working group on symptoms as outcomes in cancer clinical trials.

Follow-Up to the Charlottesville Meeting

Since the inaugural meeting, we have laid a foundation for continuing the working group. ASCPRO will develop a series of workshops to explore the use of PROs to measure potential symptom reduction benefits in cancer clinical trials.

A meeting of the steering committee was held in early 2007 in Washington, DC. At that meeting, the committee constructed a prioritized list of symptoms to address. It was decided that we would focus first on cancer-related fatigue. A subset of the ASCPRO membership was identified to initiate the evaluation process surrounding fatigue assessment. The Fatigue Task Force presented its first draft to the entire ASCPRO membership in October 2007. The ensuing review and discussion led to a second meeting of the Fatigue Task Force in June 2008, where comments from the October 2007 meeting were incorporated and the initial draft of a recommendation paper was produced. A procedure allowing for review of the draft by the entire ASCPRO membership and for incorporation of the larger group’s comments was established at that meeting. This allowed us to make progress in a timely fashion while testing our process along the way so it
can become increasingly efficient with each symptom considered.

At the October 2007 meeting, the ASCPRO membership also established the next two task force groups, which were commissioned to study cancer-related cognitive deficits and multisymptom outcomes.

**Conclusion**

The issuance of the FDA guidance for using PROs in labeling claims provides a needed impetus for careful scientific evaluation of the best way to gather data describing the symptom experience of cancer patients. ASCPRO is among the first working groups to treat symptom reporting as a primary focus and to make recommendations about standards and best practices for capturing changes in patient symptom experience in clinical research. For more information about ASCPRO, visit www.ascpro.org.

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