VOLUME 30 · NUMBER 34 · DECEMBER 1 2012

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Recommendations for Incorporating Patient-Reported Outcomes Into Clinical Comparative Effectiveness Research in Adult Oncology

Ethan Basch, Amy P. Abernethy, C. Daniel Mullins, Bryce B. Reeve, Mary Lou Smith, Stephen Joel Coons, Jeff Sloan, Keith Wenzel, Cynthia Chauhan, Wayland Eppard, Elizabeth S. Frank, Joseph Lipscomb, Stephen A. Raymond, Merianne Spencer, and Sean Tunis

Ethan Basch, Memorial Sloan-Kettering Cancer Center, New York, NY; Amy P. Abernethy, Duke University, Durham; Bryce B. Reeve, University of North Carolina at Chapel Hill, Chapel Hill, NC; C. Daniel Mullins, University of Maryland; Merianne Spencer and Sean Tunis, Center for Medical Technology Policy, Baltimore, MD; Mary Lou Smith, Research Advocacy Network, Plano, TX; Stephen Joel Coons, Critical Path Institute, Tucson, AZ; Jeff Sloan, Mayo Clinic; Cynthia Chauhan, Mayo Clinic Breast Specialized Programs of Research Excellence; Wayland Eppard, North Central Cancer Treatment Group Patient Advocacy Committee, Rochester, MN; Keith Wenzel, Perceptive Informatics; Elizabeth S. Frank, Dana-Farber Cancer Institute; Stephen A. Raymond, PHT Corporation, Boston, MA; and Joseph Lipscomb, Emory University, Atlanta, GA.

Submitted February 24, 2012; accepted June 19, 2012; published online ahead of print at www.jco.org on October 15, 2012.

Written on behalf of the Center for Medical Technology Policy, Baltimore, MD.

E.B. is a member of the Methodology Committee of the Patient-Centered Outcomes Research Institute (PCORI). The views expressed in this article do not necessarily reflect the views of PCORI.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Ethan Basch, MD, MSc, Health Outcomes Research Group, Department of Biostatistics, Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 307 East 63rd St, New York, NY 10065; e-mail: ebasch@mskcc.org.

0732-183X/12/3034-4249/$20.00

DOI: 10.1200/JCO.2012.42.5967

ABSTRACT

Examining the patient's subjective experience in prospective clinical comparative effectiveness research (CER) of oncology treatments or process interventions is essential for informing decision making. Patient-reported outcome (PRO) measures are the standard tools for directly eliciting the patient experience. There are currently no widely accepted standards for developing or implementing PRO measures in CER. Recommendations for the design and implementation of PRO measures in CER were developed via a standardized process including multistakeholder interviews, a technical working group, and public comments. Key recommendations are to include assessment of patient-reported symptoms as well as health-related quality of life in all prospective clinical CER studies in adult oncology; to identify symptoms relevant to a particular study population and context based on literature review and/or qualitative and quantitative methods; to assure that PRO measures used are valid, reliable, and sensitive in a comparable population (measures particularly recommended include EORTC QLQ-C30, FACT, MDASI, PRO-CTCAE, and PROMIS); to collect PRO data electronically whenever possible; to employ methods that minimize missing patient reports and include a plan for analyzing and reporting missing PRO data; to report the proportion of responders and cumulative distribution of responses in addition to mean changes in scores; and to publish results of PRO analyses simultaneously with other clinical outcomes. Twelve core symptoms are recommended for consideration in studies in advanced or metastatic cancers. Adherence to methodologic standards for the selection, implementation, and analysis/reporting of PRO measures will lead to an understanding of the patient experience that informs better decisions by patients, providers, regulators, and payers.

J Clin Oncol 30:4249-4255. © 2012 by American Society of Clinical Oncology

INTRODUCTION

The Center for Medical Technology Policy (CMTP) supports the development of effectiveness guidance documents (EGDs) to provide specific recommendations on the design and reporting of prospective clinical studies intended to inform decisions by patients, clinicians, policy makers, and payers. The recommendations are targeted to clinical investigators conducting studies of specific clinical interventions or health conditions. EGDs are intended to be analogous and complementary to US Food and Drug Administration (FDA) guidance documents and are generally focused on design elements that are relevant to clinical and health policy decision making. A summary of the EGD development process is available at http://www.cmtpnet.org, along with a detailed overview of the purpose of EGDs, target audiences, intended uses, topic selection, and related information. A previous oncology-focused EGD, "Recommendations for Clinical Trials of Off-Label Drugs Used to Treat Advanced-Stage Cancer," was published in *Journal of Clinical Oncology* in early 2012.[1]

The purpose of this CMTP EGD is to provide recommendations for the appropriate inclusion of patient-reported outcome (PRO) measures in the design and implementation of prospective clinical comparative effectiveness research (CER) in adult oncology, including but not limited to registries, prospective observational studies, randomized controlled trials, and pragmatic clinical trials.

Capturing the patient subjective experience is essential in prospective clinical CER, which aims to examine real-world outcomes related to existing treatments or process interventions. Without direct evidence reflecting the patient experience, stakeholders including patients, clinicians, payers, investigators, and regulators have incomplete information for decision making.

Information reported by clinical staff does not accurately reflect patients' experiences with care and generally cannot substitute for direct patient reporting.[2-4]

PROS

PRO measures are the standard tools for directly eliciting the patient experience, and their use has become the standard both in regulated and nonregulated clinical trials, particularly for assessment of symptoms and health-related quality of life (HRQOL). Systematic collection of PRO data has been shown to be feasible and efficient, to be more reflective of underlying health status than clinician reporting, to predict meaningful clinical outcomes including survival, to increase patient satisfaction with care, to be valued by clinicians for documentation and clinical decision making, and to improve symptom management as well as patients' overall health status.[2,5-12]

A widely accepted definition of PROs comes from the FDA guidance for industry titled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," which defines a PRO as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[13(p2)] Similar regulatory guidance has been published by the European Medicines Agency.[14]

US Regulatory Perspective

In the regulatory context, patient self-reporting is the standard approach for measuring symptom end points used to support drug approval and labeling claims. The FDA PRO guidance describes how the FDA evaluates PRO instruments used in clinical trials to assess treatment benefit when a PRO-based labeling claim is desired by a medical product manufacturer. The FDA PRO guidance does not specifically apply to CER or postapproval trials unless a sponsor is aiming to change a product label. Thus, there is a need for guidance when selecting or developing nonregulatory PRO end point measures for clinical research.

PROs in Oncology

Inclusion of PRO assessments is particularly salient in oncology, because it is common for the sequelae of cancer, its treatments, and associated psychosocial factors to affect the patient's subjective experience and functioning. The importance of incorporating PROs into cancer research and policy formation has been emphasized by major funding, policy making, standard setting, and regulatory entities,[15] including the National Cancer Institute (NCI),[16] American Cancer Society,[17] FDA,[13,18] Centers for Medicare and Medicaid Services,[19] and National Institutes of Health (NIH).[20]

Although there is a tradition of assessing PROs in cancer clinical trials, particularly for assessing HRQOL as a secondary end point in industry trials and NCI-sponsored cooperative group trials, and increasingly for assessing symptoms as primary or secondary end points, there are no widely accepted standards for the collection and reporting of this information outside of the regulatory context.

PATIENT-CENTERED OUTCOMES RESEARCH

Recognition of the importance of integrating the patient perspective into CER is reflected in the creation of the Patient-Centered Outcomes Research Institute (PCORI) under the US Patient Protection and Affordable Care Act.[21] This legislation specifies that clinical CER shall be designed to take into account patients' QOL preferences. Moreover, the scope of the work of PCORI, and of PCOR in general, includes identifying methods for incorporating the patient perspective at every step of CER, including prioritization of research topics, refinement of research questions, design of research studies, and dissemination/implementation of research results.[21a] Consideration of the patient perspective via PRO measurement plays a central role in the design of patient-centered CER.

METHODS FOR DEVELOPING THIS EGD

The principles and recommendations in this EGD were formulated based on an a priori–defined multistep process. Initially, 15 semi-structured interviews were conducted by CMTP staff with representatives of payers/health plans, compendia developers, regulatory agencies, product developers, community oncology, academic cancer clinical research, patients/patient advocates, and consultants providing PRO methodologic and logistical services for research to identify thematic and priority areas. Next, a 13-member technical working group including patient advocates, PRO methodologists, CER methodologists, medical oncologists, and clinical investigators (represented by the author list) was assembled and met in Baltimore, Maryland, on December 8, 2010, with five subsequent telephone meetings, to develop draft recommendations from the identified thematic areas.[22] Interviewees and technical working group members received no compensation.

The draft recommendations were refined based on a period of public comment between December 12, 2011, and February 1, 2012, with structured commentary received from individuals representing regulatory agencies, universities, cancer centers, NCI cooperative groups, patient advocacy organizations, health publishing firms, and oncology private practice networks, as well as formal input from organizations including the American Society of Clinical Oncology, European Organisation for Research and Treatment of Cancer (EORTC), Friends of Cancer Research, International Society for Quality of Life Research, Patient Advocates in Research, PatientsLikeMe, GlaxoSmithKline, and Pfizer. Ratings from public responses were elicited for each EGD recommendation for whether it was clear, reasonable, feasible, useful, and impactful, with overall agreement across categories for each recommendation ranging from 80% to 94%. Comments were collected for input on content and were not meant to serve as formal endorsement. This article is an abbreviated version of the full EGD, available at http://cmtpnet.org.

EGD RECOMMENDATIONS

Fifteen specific EGD recommendations are listed in Table 1 and discussed here. They are divided into three categories: selection of measures, implementation methods, and data analysis and reporting.

Selection of Measures

Recommendation 1. Include PRO measures in all prospective clinical CER studies in adult oncology.

ISSN 1990-3219 169-97

Table 1. Recommendations for Incorporating Patient-Reported Outcomes Into the Design of CER in Adult Oncology

Recommendation
Selection of Measures
1. Include patient-reported outcome measures in all prospective clinical CER studies in adult oncology
2. Include patient-reported symptoms that are appropriate to the study population, intervention, context, objectives, and setting
3. Include an assessment of health-related quality of life
4. Consider a measure that enables cost-utility analysis
5. Assure that measures have demonstrated validity (based on qualitative and quantitative research), reliability, and sensitivity in a comparable patient population (including assessment of meaningfulness of score changes and ability to detect change over time), as well as an appropriate recall period
Implementation Methods
6. Limit data collection so that the average patient can complete the process as quickly as possible (ideally within 20 minutes at baseline and within 10 to 15 minutes at subsequent time points)
7. Collect patient-reported data as frequently as necessary to meet research objectives, without overburdening patients
8. Collect patient-reported information via electronic data capture technologies whenever possible
9. Consider whether measurement equivalence has been established when mixing modes of patient-reported data collection (eg, Web, telephone, handheld device, paper, tablet computer)
10. Employ methods to minimize missing patient-reported data including education of site personnel, training of patients, and real-time monitoring of adherence with backup data collection
Data Analysis and Reporting
11. Conduct a power calculation for the key patient-reported end points when designing a study
12. Include a plan for analyzing and reporting missing patient-reported data
13. Report the proportion of patients experiencing a change from baseline demonstrated as being meaningful for each measure as well as mean group changes
14. Consider evaluating the cumulative distribution of responses and including cumulative distribution curves in publications
15. Analyze and publish results of patient-reported outcome data collection simultaneously with other clinical outcomes

Abbreviation: CER, comparative effectiveness research.

Without including PROs, studies leave out essential information about the impact of interventions or health care processes on patients. The patient experience is at the center of most CER evaluations. Self-reports provide the most direct measure of the patient experience with disease and treatment. Empiric evidence demonstrates that clinicians' reports do not adequately reflect patients' subjective experiences with care.[2-4]

It is recognized that additional financial cost and effort is involved with collection of PRO data in clinical research. Including PRO assessments in research requires methodologic expertise, infrastructure, training of site personnel and patients, and associated expense and effort. However, without direct evidence reflecting the patient experience, stakeholders including patients, clinicians, payers, investigators, and regulators will have incomplete information toward decision making. If PRO measures are not included in a study, a justification should be provided for this omission.

Recommendation 2. Include patient-reported symptoms that are appropriate to the study population, intervention, context, objectives, and setting.

Both cancer and its treatment can result in symptoms that affect patients' functional status, general health perceptions, and QOL.[23] Measuring symptoms from the patient perspective is critical to understanding the burden of cancer on people's lives. To understand what symptoms are prevalent and meaningful to patients in a given context, an investigator should conduct a literature review and/or qualitative and quantitative research with patients before conducting a study. This information, in addition to characteristics of the targeted disease and intervention of the study, should guide selection of outcomes and measures.

Numerous PRO measures have been used and evaluated in oncology, both generic and specifically focused on particular populations, interventions, or symptoms. Measure selection should be based on the needs of a study, psychometric properties of the PRO measure, and characteristics of the population. The following measures are particularly recommended because of the available evidence supporting their psychometric properties and past use in cancer clinical research (listed alphabetically):

- EORTC QLQ-C30 (EORTC Quality of Life Questionnaire)
- FACT (Functional Assessment of Cancer Therapy)
- MDASI (MD Anderson Symptom Inventory)
- PRO-CTCAE (PRO version of the Common Terminology Criteria for Adverse Events)
- PROMIS (PRO Measurement Information System)

The EORTC QLQ-C30, FACT, and MDASI are questionnaires that include core modules with a static list of commonly experienced symptoms (as well as functioning and QOL measures) and offer optional context-specific modules with additional symptoms. The PROMIS provides researchers access to short forms for a number of selected symptoms and HRQOL. These short forms vary in length to meet the needs of investigators relative to the tradeoff between response burden and precision (ie, the more items in a PRO measure, the more reliable the instrument will be). The PRO-CTCAE is designed specifically for assessing symptoms related to treatment toxicity or tolerability, and may be used to complement other measures that are intended to assess the impact of interventions on symptoms related to disease or in studies focusing on symptomatic toxicities (such as dose finding, comparative tolerability assessments, or safety surveillance).

Additional multisymptom measures that have been used and evaluated in oncology include the Edmonton Symptom Assessment Scale, Linear Analog Self-Assessment, Memorial Symptom Assessment Scale, Rotterdam Symptom Checklist, Symptom Distress Scale, and Patient Care Monitor. Different measures employ different approaches that may be appropriate in various settings, such as different recall periods or different attributes of symptoms (eg, severity, frequency, bother). In addition to measures with a static list of symptoms, studies should consider including a mechanism for collecting unsolicited symptoms from patients. If a US labeling claim is sought based on assessment of symptoms in a study, which is beyond the scope of this document, then selection of measures consistent with the FDA PRO guidance is advised.

Table 2 lists 12 symptoms that are common across advanced cancers and clinical study contexts and that frequently have a meaningful impact on the patient experience, as well as their availability in existing measurement systems. These symptoms can be related to disease or toxicities, or can be multifactorial. This core symptom list is based on prevalence and severity data from the development and implementation of several measurement systems, including the EORTC QLQ-C30, Memorial Symptom Assessment Scale, MDASI,

JCO 2012 30:4249-4255

Table 2. Common Symptoms in Advanced and Metastatic Cancers in Adults for Consideration in Clinical CER Studies and Availability in Existing Instruments

Symptom	ESAS	FACT*	LASA	MDASI*	MSAS	PCM	PRO-CTCAE*	PROMIS*	QLQ-C30*	RSCL	SDS
Anorexia	X	X†	—	X	X	X	X	—	X	X	X
Anxiety	X	X	X	X	—	X	X	X	X	X	—
Constipation	—	X†	—	X‡	X	X	X	—	X	X	—
Depression	X	X	X	X	—	X	X	X	X	X	—
Diarrhea	—	X†	—	X‡	X	X	X	—	X	X	X
Dyspnea	X	X†	—	X	X	X	X	—	X	X	X
Fatigue	X	X	X	X	X	X	X	X	X	X	X
Insomnia	X	X	X	X	X	X	X	X	X	X	X
Nausea	X	X	—	X	X	X	X	—	X	X	X
Pain	X	X	X	X	X	X	X	X	X	X	X
Neuropathy	—	X†	—	X	X	X	X	—	X§	X	—
Vomiting	—	X†	—	X	X	X	X	—	X	X	—

NOTE. Listed alphabetically. Most measurement systems include additional symptom items beyond these 12 symptoms.

Abbreviations: CER, comparative effectiveness research; ESAS, Edmonton Symptom Assessment Scale; FACIT, Functional Assessment of Chronic Illness Therapy; FACT-G, Functional Assessment of Cancer Therapy–General; LASA, Linear Analog Self-Assessment; MDASI, MD Anderson Symptom Inventory; MSAS, Memorial Symptom Assessment Scale; PCM, Patient Care Monitor; PRO, patient-reported outcome; PRO-CTCAE, PRO version of the Common Terminology Criteria for Adverse Events; PROMIS, PRO Measurement Information System; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; RSCL, Rotterdam Symptom Checklist; SDS, Symptom Distress Scale.

*These PRO instruments are particularly recommended because of their evaluated measurement properties and past use in cancer clinical research.

†Anorexia items are included in the FACT-Lymphoma and FACT-Gastric modules; constipation items are included in the FACT-Cervix, FACT-Endometrial, FACT-Hepatobiliary, FACT-Vulva, FACIT–Aromatase Inhibitor, FACIT-Palliative modules; diarrhea items are included in the FACT-Bladder, FACT-Colorectal, FACT-Gastric, FACT-Endocrine, and FACIT-Diarrhea modules; dyspnea items are included in the FACT–Breast Cancer, FACT-Endometrial, FACT-Lung, FACT-Melanoma, FACT–Bone Marrow Transplant, FACIT–Aromatase Inhibitor, FACT-B+4 (new FACT–Breast Cancer), and FACIT-Palliative modules and the FACIT–Dyspnea Scale 33 Item Bank; neuropathy items are included in the FACT/ Gynecologic Oncology Group Neurotoxicity and FACT-Taxane modules; vomiting items are included in the FACT-Ovarian, FACIT–Aromatase Inhibitor, FACT-Esophageal, and FACIT-Palliative modules.

‡Constipation items are included in the MDASI-Gastrointestinal, MDASI–Lung Cancer, MDASI–Head and Neck, MDASI–Brain Tumor, and MDASI-Spine modules; diarrhea items are included in the MDASI-Gastrointestinal, MDASI-Thyroid, MDASI–Brain Tumor, and MDASI-Spine modules.

§Sensory neuropathy items are included in the QLQ-C30 Lung Cancer 13, Ovarian Cancer 28, Myeloma 20, and Colorectal Liver Metastases 21.

Patient Care Monitor, and PRO-CTCAE; on data reported by investigators via the NCI Adverse Event Expedited Reporting System and Clinical Data Update System for all phases II and III clinical trials sponsored by the NCI between 2005 and 2009; and on adverse symptoms reported by investigators in clinical trials in the North Central Cancer Treatment Group. Notably, an NCI Clinical Trials Planning Meeting in September 2011 yielded a virtually identical list based on similar sources, structured review of clinical trial publications, and consensus via a modified Delphi process. However, these core symptoms should not stand alone as the only patient-reported symptoms that should be captured in a study; these and other symptoms should be selected based on literature review and/or feedback from patients, clinicians, and experts given the context and research application.

Recommendation 3. Include an assessment of HRQOL.

Whereas assessment of individual symptoms provides insights about specific impacts of disease and treatment, HRQOL measures can reflect the overall patient experience and its multidimensional contributors, including important non–symptom-specific areas. HRQOL measures allow an investigator to understand how an intervention affects the physical, mental, social, and spiritual aspects of a patient's life. Although measurement of HRQOL does not typically lead to drug product approval or labeling in the United States, such assessment has particular value in CER or late-phase settings, where understanding of the overall patient experience is valued by stakeholders including payers, guideline developers, clinicians, and the patients themselves.

Both multi- and single-item HRQOL measures have been used in oncology research. The choice of approach depends on the context of a trial. An advantage of single-item assessment is reduced patient burden, whereas multi-item scales can be more precise and better elucidate the state of the patient's physical/functional, mental/emotional, social, and spiritual well-being. Single-item measures with robust psychometric properties include PROMIS global items and Linear Analog Self-Assessment items, and well-developed multi-item measures include the EORTC QLQ-C30, FACT-General, and PROMIS short forms.

Recommendation 4. Consider a measure that enables cost-utility analysis.

Cost-utility analyses based on calculation of quality-adjusted life-years can be valuable in CER and are enabled by instruments specifically designed for this purpose, such as the EuroQoL EQ-5D and Health Utilities Index. These tools allow quantification in a single score of the impact of a disease or treatment on a patient's health status, with weights derived based on perspectives of a society or population. Competing interventions can then be ranked against some baseline, or comparator, intervention in terms of cost per quality-adjusted life-year gained. The EuroQoL EQ-5D is preferentially recommended by the authors because of its brevity and widespread use by European authorities.

Recommendation 5. Assure that measures have demonstrated validity (based on qualitative and quantitative research), reliability, and sensitivity in a comparable patient population (including assessment of meaningfulness of score changes and ability to detect change over time), as well as an appropriate recall period.

Any measure used in clinical research—whether a serum biomarker, radiographic evaluation, or PRO—should be demonstrated to be valid, reliable, and sensitive in a given study context or in a closely related context to assure meaningful study findings. The principles in the FDA PRO guidance, which pertain specifically to determining validity, reliability, meaningfulness of score changes and sensitivity to

ISSN 1527-7755

change, are pertinent to prospective clinical CER.[13] The Medical Outcomes Trust also provides guidance.[24]

Implementation Methods

Recommendation 6. Limit data collection so that the average patient can complete the process as quickly as possible (ideally within 20 minutes at baseline and within 10 to 15 minutes at subsequent time points).

Patients with cancer may experience fatigue and/or other symptoms, psychosocial difficulties, and time demands that make it difficult or inconvenient to complete long questionnaires. It is essential to minimize patient burden when designing patient questionnaires. Brief questionnaires assure greater completeness of data and minimize missing data from those who experience the most impairment; there is evidence of attrition of responses as questionnaires become longer than 10 to 15 minutes during a study (longer questionnaires at baseline are reasonable for collecting necessary initial data).[6,25] It is acknowledged that in some studies, longer interviews are merited periodically to gather essential information from patients, and in such cases, each individual item or module should be justified with an associated actionable hypothesis.

Recommendation 7. Collect PRO data as frequently as necessary to meet research objectives, without overburdening patients.

To understand the patient subjective experience with disease and treatment, collection of PRO data at baseline and at selected follow-up time points (which are the same for every patient) is necessary. If the goal of assessment is to understand how the patient experience changes from baseline to a particular time point (eg, symptom improvement after a particular intervention or period of observation), then a limited number of assessments may be reasonable (eg, after completion of treatment or study withdrawal, several months later, and at selected long-term time points). However, if the goal of assessment is to characterize toxicities or comparative tolerability of interventions from the patient perspective (eg, to assess the impact of treatment on nausea, diarrhea, sensory neuropathy, appetite loss, sleep disturbance), then more frequent assessments are likely necessary to capture the possible variation in experiences over time. This is because less frequent assessments may miss information about interim toxicities.

Recommendation 8. Collect PRO information via electronic data capture technologies whenever possible.

Although many PRO measures were initially developed on paper before the advent of electronic data capture technologies, there are several advantages to using electronic modes of administration. Paper forms depend on distribution by research personnel, whereas electronic forms can be automatically provided to patients. Paper forms often necessitate patients presenting to a clinic or other setting to report, or taking a paper booklet home for between-visit reporting (where it is uncertain if the patient completes the form at a requested time point). Use of electronic PRO data collection has been widely shown as feasible in academic and community oncology as well as in industry settings.[5,6,26-28] Although there are increased costs associated with creating and administering the electronic tool and with training patients, data transcription and data query/cleaning costs are saved, and electronic approaches allow for real-time monitoring of compliance, which facilitates targeted backup data collection toward fewer missing data.[28a]

Recommendation 9. Consider whether measurement equivalence has been established when mixing modes of patient-reported data collection (eg, Web, telephone, handheld device, paper, tablet computers).

Use of a PRO measure developed in one mode but subsequently used in another (eg, developed on paper but administered via Web or automated telephone/interactive voice response) is referred to as migration. There are established guidelines for assessing whether a version of a measure that has been migrated from one mode to another is acceptable in terms of its equivalence to the original or in terms of its own measurement properties.[29] In general, it has been found that that paper-to-Web migration yields between-mode equivalence comparable to the test-retest reliability of the original mode.[30] It is acknowledged that in some settings, using paper as a primary or backup data collection strategy may be unavoidable, and this should be justified in the study protocol.

Providing an interface familiar to or preferred by particular patients or populations may reduce missing data. Mixing modes is generally viewed as acceptable in clinical research if a reasonable level of between-mode equivalence has been demonstrated (eg, with a level of agreement comparable to the test-retest reliability of the initial mode in which the measure was developed).[29,30] However, mixing modes necessitates the capacity to provide training for more than one mode.

Recommendation 10. Employ methods to minimize missing patient-reported data, including education of site personnel, training of patients, and real-time monitoring of adherence with backup data collection.

In real-world populations, it is essential to employ methods to minimize missing data. Approaches commonly used include real-time alerts to site staff or a telephone bank, with a follow-up call to patients reminding them to complete items. Site staff should reach out to patients who serially do not report to ascertain and resolve reasons for nonadherence and provide encouragement. Incentives for patients to complete questionnaires and incentives for local sites to accrue patients and collect data on time (with active site monitoring by the coordinating center) are acceptable to minimize missing data.

Data Analysis and Reporting

Recommendation 11. Conduct a power calculation for the key patient-reported end points when designing a study.

To understand the adequacy of a particular study design to ascertain meaningful information about the patient experience, a dedicated a priori power calculation for the PROs of greatest interest is recommended.

Recommendation 12. Include a plan for analyzing and reporting missing patient-reported data.

A plan for addressing missing PRO data should be included in a study design or protocol, including sensitivity analyses using imputation methods. This should include a plan for analysis when an entire measure has not been completed, or when individual items in a multi-item measure are missing. Additional details about this and other methodologic challenges and limitations involved with analysis of PRO data are included in the full version of this EGD at http://cmtpnet.org.

Recommendation 13. Report the proportion of patients experiencing a change from baseline demonstrated as being meaningful for each measure, as well as mean group changes.

ISSN 1527-7755

Traditionally, analyses of PRO data have focused on comparisons of means between study groups. More granular and actionable information is provided by also reporting the proportion of participants experiencing a specific change from baseline at a predetermined time point considered meaningful to patients in the study population (ie, a responder analysis). Such information is particularly useful to individual patients and clinicians facing decisions, for whom information about mean group changes is less tangible.

Recommendation 14. Consider evaluating the cumulative distribution of responses and including cumulative distribution curves in publications.

In addition to a responder analysis, it is recommended that an analysis of the cumulative distribution of responses (ie, the proportion of patients who experience every magnitude of change in a specific measure at a time point of interest compared with baseline) be included. This approach helps elucidate the spectrum of responses across a study population. Both improvements and decrements in scores from baseline should be included. Cumulative distribution curves are increasingly included in analyses of PRO data and are described in the FDA PRO guidance.[13,31]

Recommendation 15. Analyze and publish results of PRO data collection simultaneously with other clinical outcomes.

In the past, PRO data often were analyzed and reported separately from other clinical trial outcomes and typically presented in different journals, if at all. As a result, important information about the patient subjective experience has not been accessible to stakeholders reviewing the primary publication. Over time, it has become clear that stakeholders using information from CER studies value the patient perspective, and such information is most accessible and meaningful when presented alongside other clinical outcomes. This means both including overall results of PRO data analyses in primary publications when PROs are not the primary end points and publishing a dedicated PRO results report simultaneously, ideally in the same journal. Journal editors should be sympathetic and supportive of including this important patient-centered information when study results are reported.

DISCUSSION

Measurement of PROs is increasingly common in late-phase industry trials, in NCI cooperative group trials, and in registries. There is burgeoning interest in integrating PROs into electronic health record systems and into quality of care/performance evaluation. Funding by the NIH and NCI of the PROMIS and PRO-CTCAE initiatives and PRO-related funding announcements by the PCORI, Agency for Healthcare Research and Quality, and NIH are expected to increase the use of PRO measures in nonregulatory research. This article, which is an abbreviation of the full PRO EGD (available at http://cmtpnet.org), offers guidance for improving the availability, consistency, and usefulness of information about the patient experience in clinical CER in adult oncology. By promoting the collection of PRO data and good research practices, it is intended to enhance communication, education, decision making, quality of care, and patient centeredness.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: Amy P. Abernethy, Advoset (C), Orange Leaf Associates (C), Pillars4Life (C); Keith Wenzel, Perceptive Informatics (C); Stephen A. Raymond, PHT Corporation (C)
Consultant or Advisory Role: Amy P. Abernethy, Amgen (C), Helsinn Therapeutics (C), Novartis (C), Proventys (C), Bristol-Myers Squibb (C), Pfizer (C); C. Daniel Mullins, Amgen (C), Bayer Pharmaceuticals (C), Bristol-Myers Squibb (C), Celgene (C), GlaxoSmithKline (C), Mitsubishi Tanabe Pharma (C), Novartis (C), Novo Nordisk (C), Pfizer (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** Amy P. Abernethy, Pfizer, Helsinn Therapeutics, Amgen, KangLaiTe USA, Alexion, BioVex, DARA BioSciences, Mi-Co, Eli Lilly, Endo Pharmaceuticals, Bristol-Myers Squibb, Genentech; C. Daniel Mullins, Bayer Pharmaceuticals, Pfizer **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Ethan Basch, Amy P. Abernethy, C. Daniel Mullins, Bryce B. Reeve, Mary Lou Smith, Stephen Joel Coons, Jeff Sloan, Keith Wenzel, Cynthia Chauhan, Elizabeth S. Frank, Joseph Lipscomb, Stephen A. Raymond, Merianne Spencer, Sean Tunis
Administrative support: Merianne Spencer
Provision of study materials or patients: Ethan Basch, Amy P. Abernethy, C. Daniel Mullins, Bryce B. Reeve, Mary Lou Smith, Jeff Sloan, Sean Tunis
Collection and assembly of data: Ethan Basch, Amy P. Abernethy, C. Daniel Mullins, Bryce B. Reeve, Jeff Sloan, Sean Tunis
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Mullins CD, Montgomery R, Abernethy AP, et al: Recommendations for clinical trials of off-label drugs used to treat advanced stage cancer. J Clin Oncol 30:661-666, 2012
2. Basch E: The missing voice of patients in drug-safety reporting. N Engl J Med 362:865-869, 2010
3. Fromme EK, Eilers KM, Mori M, et al: How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. J Clin Oncol 22:3485-3490, 2004
4. Pakhomov SV, Jacobsen SJ, Chute CG, et al: Agreement between patient-reported symptoms and their documentation in the medical record. Am J Manag Care 14:530-539, 2008
5. Abernethy AP, Herndon JE 2nd, Wheeler JL, et al: Feasibility and acceptability to patients of a longitudinal system for evaluating cancer-related symptoms and quality of life: Pilot study of an e/Tablet data-collection system in academic oncology. J Pain Symptom Manage 37:1027-1038, 2009
6. Basch E, Artz D, Dulko D, et al: Patient online self-reporting of toxicity symptoms during chemotherapy. J Clin Oncol 23:3552-3561, 2005
7. Detmar SB, Muller MJ, Schornagel JH, et al: Health-related quality-of-life assessments and patient-physician communication: A randomized controlled trial. JAMA 288:3027-3034, 2002
8. Detmar SB, Muller MJ, Schornagel JH, et al: Role of health-related quality of life in palliative chemotherapy treatment decisions. J Clin Oncol 20:1056-1062, 2002
9. Greenhalgh J, Meadows K: The effectiveness of the use of patient-based measures of health in

routine practice in improving the process and outcomes of patient care: A literature review. J Eval Clin Pract 5:401-416, 1999

10. Snyder CF, Blackford AL, Brahmer JR, et al: Needs assessments can identify scores on HRQOL questionnaires that represent problems for patients: An illustration with the Supportive Care Needs Survey and the QLQ-C30. Qual Life Res 19:837-845, 2010

11. Taenzer P, Bultz BD, Carlson LE, et al: Impact of computerized quality of life screening on physician behaviour and patient satisfaction in lung cancer outpatients. Psychooncology 9:203-213, 2000

12. Velikova G, Booth L, Smith AB, et al: Measuring quality of life in routine oncology practice improves communication and patient well-being: A randomized controlled trial. J Clin Oncol 22:714-724, 2004

13. US Food and Drug Administration: Guidance for industry: Patient-reported outcome measures—Use in medical product development to support labeling claims. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf

14. European Medicines Agency Committee for Medicinal Products for Human Use: Preauthorisation evaluation of medicines for human use: Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. http://www.ispor.org/workpaper/emea-hrql-guidance.pdf

15. Lipscomb J, Gotay CC, Snyder CF: Patient-reported outcomes in cancer: A review of recent research and policy initiatives. CA Cancer J Clin 57:278-300, 2007

16. National Cancer Institute: The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2008. Bethesda, MD, National Cancer Institute, NIH publication 06-6090, 2008

17. American Cancer Society: 2015 goals of the American Cancer Society. http://relay.acsevents.org/site/DocServer/ACS%20Mission%20Statement-2015%20Goals.pdf?docID=57443

18. Johnson JR, Williams G, Pazdur R: End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol 21:1404-1411, 2003

19. Centers for Medicare and Medicaid Services: Report to Congress: National strategy for quality improvement in health care—March 2011. http://www.healthcare.gov/law/resources/reports/nationalqualitystrategy032011.pdf

20. National Institutes of Health: Patient-reported outcomes measurement information system: Dynamic tools to measure health outcomes from the patient perspective. http://www.nihPROMIS.org

21. Patient Protection and Affordable Care Act. Pub Law 111-148, 111th Congress, 2010

21a. Methodology Committee of the Patient-Centered Outcomes Research Institute (PCORI): Methodological standards and patient-centeredness in comparative effectiveness research: The PCORI perspective. JAMA 307:1636-1640, 2012

22. Mullins CD, Montgomery R, Abernethy AP, et al: Recommendations for clinical trials of off-label drugs used to treat advanced-stage cancer. J Clin Oncol 30:661-666, 2012

23. Wilson JB, Cleary PD: Linking clinical variables with health-related quality of life: A conceptual model of patient outcomes. JAMA 273:59-65, 1995

24. Assessing health status and quality of life instruments: Attributes and review criteria. Qual Life Res 11:193-205, 2002

25. Abernethy AP, Herndon JE 2nd, Wheeler JL, et al: Improving health care efficiency and quality using tablet personal computers to collect research-quality, patient-reported data. Health Serv Res 43:1975-1991, 2008

26. Fortner B, Baldwin S, Schwartzberg L, et al: Validation of the Cancer Care Monitor items for physical symptoms and treatment side effects using expert oncology nurse evaluation. J Pain Symptom Manage 31:207-214, 2006

27. Fortner B, Okon T, Schwartzberg L, et al: The Cancer Care Monitor: Psychometric content evaluation and pilot testing of a computer administered system for symptom screening and quality of life in adult cancer patients. J Pain Symptom Manage 26:1077-1092, 2003

28. Basch E, Iasonos A, Barz A, et al: Long-term toxicity monitoring via electronic patient-reported outcomes in patients receiving chemotherapy. J Clin Oncol 25:5374-5380, 2007

28a. Abernethy AP, Herndon JE 2nd, Wheeler JL, et al: Improving health care efficiency and quality using tablet personal computers to collect research-quality, patient-reported data. Health Serv Res 43:1975-1991, 2008

29. Coons SJ, Gwaltney CJ, Hays RD, et al: Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force report. Value Health 12:419-429, 2009

30. Gwaltney CJ, Shields AL, Shiffman S: Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: A meta-analytic review. Value Health 11:322-333, 2008

31. Farrar JT, Dworkin RH, Max MB: Use of the cumulative proportion of responders analysis graph to present pain data over a range of cut-off points: Making clinical trial data more understandable. J Pain Symptom Manage 31:369-377, 2006

