Patient-Reported Outcomes Assessment in Cancer Trials: Taking Stock, Moving Forward


ABSTRACT

To evaluate and improve the use of cancer trial end points that reflect the patient’s own perspective, the National Cancer Institute organized an international conference, Patient-Reported Outcomes Assessment in Cancer Trials (PROACT), in 2006. The 13 preceding articles in this special issue of the Journal were commissioned in preparation for or in response to the PROACT conference, which was cosponsored by the American Cancer Society. Drawing from these articles and also commentary from the conference itself, this concluding report takes stock of what has been learned to date about the successes and challenges in patient-reported outcome (PRO) assessment in phase III, phase II, and symptom management trials in cancer and identifies ways to improve the scientific soundness, feasibility, and policy relevance of PROs in trials. Building on this synthesis of lessons learned, this article discusses specific administrative policies and management procedures to improve PRO data collection, analysis, and dissemination of findings; opportunities afforded by recent methodologic and technologic advances in PRO data collection and analysis to enhance the scientific soundness and cost efficiency of PRO use in trials; and the importance of better understanding the usefulness of PRO data to the full spectrum of cancer decision makers, including patients and families, health providers, public and private payers, regulatory agencies, and standards-setting organizations.

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INTRODUCTION

Taken together, the previous 13 articles in this special review issue have sought to illuminate, evaluate, and ultimately enhance the role of patient-reported outcome (PRO) measurement in cancer trials sponsored by the National Cancer Institute (NCI). As discussed earlier, these articles were commissioned either in preparation for or in response to the NCI-organized conference, Patient-Reported Outcomes Assessment in Cancer Trials (PROACT): Evaluating and Enhancing the Payoff to Decision Making, held September 20 to 21, 2006, in Rockville, MD. Cosponsored by the American Cancer Society; guided by a multidisciplinary scientific program committee drawn from government, academia, and industry; and attended by more than 200 researchers, clinicians, and administrators, the PROACT conference had the following specific goals: examine when, where, and how the measurement of PROs, including health-related quality of life (HRQOL), in cancer trials can yield valuable information for cancer decision making; identify best practices for the application of PRO measures across a range of NCI-sponsored trials (phase III, phase II, and symptom management) through a critical discussion of case studies developed expressly for the conference; support the NCI Clinical Trials Working Group implementation process to ensure that the most important HRQOL studies are initiated in a timely fashion in conjunction with NCI-sponsored trials; and inform the research agenda on improving the application of PRO measures in clinical trials generally.

In this article, we draw from the findings and recommendations of these PROACT reports to take stock of what has been learned to date about the successes and challenges in PRO measurement in cancer trials and to identify specific ways to improve the scientific soundness, feasibility, and policy relevance of PROs in clinical trials.

The next section identifies key determinants of the successful application of PROs in cancer trials and also those factors associated with suboptimal application. Although the potential benefits and costs of PRO use may vary with the type of cancer trial, most of the factors associated with both successful and less than successful PRO use apply to all cancer trials. Building on this synthesis of lessons
In essence, a PRO measure adds value to a cancer trial when it enables investigators to address a decision-relevant question (for example, does a new therapy deliver significant clinical benefit from the patient’s perspective?) in a scientifically sound fashion. In principle, all candidate end points, whether biomedical or patient reported, should be evaluated in this fashion. In practice, the selection of trial end points is subject to close scrutiny, whether by the NCI for the cooperative group trials it supports or by the FDA for the industry-sponsored trials it must evaluate as part of the drug product approval process. Yet, it is not uncommon for the FDA in its recent draft Guidance for Industry on PRO use in product labeling claims.16 Thus, PRO measures may include reports of disease symptoms, treatment adverse effects, functional status, or overall well-being. (It is important to keep in mind, however, that the link between a patient’s perception of well-being and the patient’s reported outcome is his/her response to some selected survey instrument, whose application is necessarily accompanied by a risk of measurement error, both random and systematic. Hence, ongoing research to improve PRO measurement reliability and validity is important.16) Likewise, PRO measures may vary in breadth, depth, and complexity, from a single-item question about some single concept (eg, presence/absence of nausea) to measures of HRQOL, which typically involve multi-item instruments for measuring multiple domains of functional status.18

These issues are important because they challenge the validity, or at least the usefulness, of measuring cancer outcomes from the patient’s own perspective. However, one of NCI’s Strategic Objectives is “to ensure the best outcomes for all, including improving the quality of life for cancer patients, survivors, and their families.”15 Thus, it would seem vitally important to measure the impact of cancer and its treatment on QOL from the perspective of those individuals living with and surviving cancer. For this objective to be realized, we need patient-reported measures of outcome that are valid, reliable, responsive, clearly interpretable, and decision relevant.

In what may now be seen as a substantial response to these concerns, NCI’s 35-member Cancer Outcomes Measurement Working Group (COMWG) concluded, after a review of hundreds of published studies, that HRQOL assessment in cancer trials is feasible, has improved significantly over time in scientific quality, can yield interpretable findings, and will bring value added to cancer care decision making under specific assumptions (eg, when there is no survival difference between competing therapies but a substantial HRQOL difference).20 The empirical base for the COMWG analyses was essentially the peer-review literature through 2002. However, these succinct published accounts of cancer trials rarely provide sufficient information to draw in-depth conclusions about the scientific quality and decisional importance of the HRQOL applications. This is especially the case in treatment trials where an HRQOL measure is unlikely to be the primary end point. Consequently, the case studies of phase III,3 phase II,2 and symptom management trials4 that were commissioned for the PROACT conference and reported in this special issue provide important additional information about the application of PRO measures in cancer trials. From a PROACT-commissioned survey of the NCI Cooperative Groups come additional reports providing unique insights regarding the issues and challenges of integrating PROs into NCI-supported cancer trials3 and finding adequate funding to support these efforts.9 The reports by scientists associated with the National Cancer Institute of Canada (NCIC),5 the European Organisation for Research and Treatment of Cancer (EORTC),6 the US pharmaceutical industry,7 and the FDA8 all contribute important additional perspectives.

On the basis of these PROACT analyses, we conclude that factors affecting the success of PRO application in cancer trials can arise during the following times: the initial determination about whether to collect PRO data in the trial; planning the PRO application; PRO data collection; analysis and interpretation of PRO data, and reporting and disseminating PRO findings. Our summary discussion of cross-cutting findings and recommendations from PROACT contributors will be organized accordingly.

**Decision to Collect PRO Data in the Trial**

In its clinical trial “Investigator’s Handbook,”21 NCI’s Division of Cancer Treatment and Diagnosis emphasizes the importance of choosing relevant end points and, in the context of phase III trials, notes that, “Of greatest medical importance, of course, are relative survival and quality of life.” In practice, NCI staff has sought to support the effective use of HRQOL measures in recent years by providing advice to cooperative group investigators on a protocol-specific basis, using consistent principles, but with recognition that official guidance has yet to evolve. Proceeding in this flexible way has likely served to reinforce the importance of HRQOL end points in proposed trials where they seem particularly germane. But whether it has promoted consistency of decision making about HRQOL across the cooperative groups, regarding either the criteria for deciding whether to measure HRQOL in a given trial or the standards for assessing and presenting HRQOL data, is a pertinent question. Also pertinent is the parallel question of whether it is actually desirable for the groups to be subject to consensus.
to a single, centralized PRO guidance, given the diversity of their disease focuses and disciplinary mix of investigators.

Therefore, it may not be surprising to find that the 12 surveyed cooperative groups evidenced considerable heterogeneity with respect to formal and informal policies and procedures regarding the inclusion of PRO end points in cancer trials. Likewise, there seemed to be significant variation in the cultural embrace of PROs. This is reflected in notable differences across groups in investigator training/mentorship in PRO use; resources made available for PRO measurement in trials either ongoing or being planned; and the presence and/or influence of HRQOL committee members on the cooperative groups’ disease site committees, where decisions about proposed end points are typically made.

Interestingly, the NCIC Clinical Trials Group (which is the principal cancer trials group for all of Canada) has pursued a somewhat different approach to decision making about the inclusion of HRQOL end points. Although it is formally left up to the individual principal investigator whether to propose a HRQOL end point, it is expected that the issue will be addressed in the study protocol and that a recommendation not to include an HRQOL end point will be explicitly justified. Moreover, it is required that there be an NCIC QOL committee liaison on each NCIC disease site committee to ensure that HRQOL issues arising with each trial are discussed and that HRQOL measurement be closely integrated into trial design.

Panelists in a roundtable discussion that concluded the PROACT conference (see Conference Agenda, http://outcomes.cancer.gov/publications/workshops/proact/) generally agreed that PROs should be included in cancer treatment trials when they address an important scientific question and the methodology for data collection is reliable and feasible; in phase II trials when this can serve to validate the PRO measure(s) and guide PRO instrument choice for subsequent phase III trials; and in virtually all symptom management trials. Still, it remains a challenge to determine the appropriate balance between intergroup flexibility and intergroup consistency in decision making about the inclusion of HRQOL end points in trials.

Whatever additional policies might be embraced by NCI in the future, it seems clear already that both intragroup and intergroup decision making about PROs could be enhanced straightforwardly by widening and deepening existing channels of communication. At the NCI level, it seems important to include (and difficult to justify not including) QOL committee liaisons on the newly introduced, disease-specific steering committees that evaluate new concepts for phase III treatment trials. In conjunction with these new steering committees, NCI is creating a new Symptom Management and Health-Related Quality of Life (SxQOL) Steering Committee that will play a pivotal role in fostering information sharing by the cooperative group QOL committees and their investigators actively involved in trials with PRO end points (see discussion below).12

Planning the Data Collection and Analysis

The focus here is on important administrative and methodologic decisions that should be (but sometimes are not) addressed before the actual collection of PRO data in the trial. An underlying theme is that PROs should be treated in similar fashion to any other trial end point; whenever PRO measures are to be included in a trial, they should be incorporated into the study design and analysis plan, as would be the case for important biomedical end points.

Several key points emerged from the PROACT analyses and conference discussion. It is essential that the selection of all trial end points, including PRO end points, be guided by clearly articulated and compelling hypotheses concerning the impact of interventions on outcomes. The importance of creating a hypothesis-driven framework for the selection of end point measures has been emphasized by the Scientific Advisory Committee of the Medical Outcomes Trust,22 NCI’s COMWG,16 an NCI-conducted analysis of HRQOL measurement in symptom management trials,23 and, most recently, the FDA in its draft Guidance for Industry on PRO application in industry-sponsored trials.17

As early as possible in the trial planning process, a carefully constructed plan for PRO data collection should be prepared and implemented. To the extent feasible, preparation for the collection of PRO end points in a phase III treatment trial should begin with the phase II trial.2

Whenever PRO measures are to be included in a trial, they should be incorporated as either primary or secondary end points from the beginning and not introduced only some time later in a companion study designed to supplement the information not identified in the original study design. All too often, such follow-on studies do not provide adequate statistical power for investigating hypotheses.

The concept measured by the PRO instrument should be relevant and specific to the population, condition, and treatment to yield clinically valid and useful information. In some cases, a short, simple (even one-question) PRO measure is appropriate and adequate; in other cases, a longer HRQOL or symptom-oriented instrument is more appropriate. Briefer instruments greatly reduce administrative and respondent burden. There is evidence that simple single-item PRO measure responses can be prognostic of patient survival.4 Often, however, single-item PRO measures cannot capture the duration, frequency, content breadth, and degree of perceived bother associated with the patient’s health condition. The degree of administrative and respondent burden may not be prohibitive because most frequently used multidimensional instruments today can be completed by respondents in 5 to 20 minutes and yield more precise scores than single-item measures.24 A well-planned PRO investigation will consider such trade-offs in advance and make a selection of PRO instrumentation that balances perceived benefits and costs.

PRO Data Collection

There is a strong consensus among PROACT contributors that PRO data collection should be carried out with the same degree of administrative oversight, attention to detail, and dedication to complete and accurate information as would be accorded to the trial’s biomedical end points. There may be defensible reasons for certain treatment trials to include no PROs among primary and secondary end points, but if the decision is made to designate a PRO as a study end point, there is little justification for then tolerating substantial amounts of missing, inaccurate, or poor quality data.

However, over the years, the most serious practical problem in the application of PRO measures in cancer trials has been missing data, arising either from patient dropout or failure to capture complete and accurate information from patients still enrolled onto the trial. The importance of this concern is emphasized in the FDA draft Guidance for Industry on PRO use in industry-sponsored trials17 and was cited in an earlier FDA analysis as an
important reason why QOL measures have not been influential in product-labeling decisions in cancer.\textsuperscript{25} However, evidence from the PROACT case studies does suggest that the more recent cancer trials may be working effectively to reduce the incidence of missing PRO data.\textsuperscript{27,28} These trials seem to be benefiting from improvements in several areas, including choice of PRO end points, study design, the knowledge and commitment of clinical research associates (CRAs), procedures for data collection, and the monitoring of data collection sites to promote timely and complete reporting of PRO measures.\textsuperscript{21}

PROACT contributors from both the NCIC and the EORTC emphasize that better education and training of CRAs and trial investigators can lead to substantial improvements in the quality and timeliness of PRO data collection.\textsuperscript{5,6} Similarly, creating standardized approaches to collect, report, and follow-up on missing PRO observations can improve data quality while also reducing the resource cost and administrative burden of data collection. For example, such standardization can help ensure that patients do not have to work through separate informed consent documents, at different points in time, for PROs and other study end points.

### PRO Data Analysis

It has been argued that PRO data pose no greater statistical challenges, in principle, than other biomedical outcomes data and should be analyzed with the same care and rigor.\textsuperscript{26} We believe a case can be made for this contention as long as at least two conditions are met. First, missing PRO data must not create substantial systematic measurement error. Second, there must be adequate consensus regarding what constitutes a minimum important difference (MID) in the PRO measure, so that one can gauge whether a statistically significant change also represents a clinically important difference in patient status. In fact, how to operationally define the MID has been subject to ongoing debate in recent years.\textsuperscript{27,28} At present, there is support in the literature for using multiple approaches to identify the MID. These could include anchor-based methods (wherein the PRO is posited to move in a predictable way with another outcome measure whose MID is comparatively well understood) and distribution-based methods (wherein the MID is defined in terms of how large a change score is in relationship to the statistical dispersion [standard deviation] of all scores). Recent PRO studies, using either one method or the other or some combination of the two, have defined the MID to be anywhere from one-third to one-half standard deviation of the observed change in scores.\textsuperscript{28}

To the extent that PRO findings from a trial can be clearly interpreted vis-à-vis parallel results on well-known biomedical end points used in trial (for example, the PRO and biomedical end points are significantly correlated in plausible ways), the construct validity of the PRO measure is supported, and its salience to the clinical community may be enhanced.

Of course, it ought to be the case that biomedical end points are held to these standards of minimal missing data and clearly interpretable meaning for small changes in the end point. In reality, most statistically significant changes in a biomedical outcome, such as disease-free survival, are treated as clinically significant, no matter how small.

A critically important member of the PRO analysis team is the statistician assigned to the cancer trial. There were recurring observations in the PROACT analyses and commentary at the conference that statisticians are often not well integrated into the planning and analysis of PRO measures in NCI-sponsored trials. This may arise because of inadequate planning and funding for the statistical analysis of PRO data, or it may reflect skepticism among some statisticians about whether PRO measures are valid, meaningful, and useful end points compared with traditional biomedical outcomes.

### Reporting and Disseminating PRO Findings

Frequently, the main biomedical and PRO findings from cancer trials will be reported in different scientific journals.\textsuperscript{29} The report focusing on survival, disease-free survival, or other biomedical end points may appear in a cancer or general medical journal likely read by clinicians, whereas the report presenting PRO findings may be published in a methods-oriented journal more likely to be read by measurement scientists. Another common reporting scenario is that biomedical outcome and PRO findings will appear in the same article but with the PRO analysis discussed quickly and superficially because of space constraints and the desire to focus on the trial’s primary (biomedical) end points. Either way, the clinical oncology community may not receive a clear and balanced picture of the trial’s PRO findings.

A much preferable scenario is for the trial’s non-PRO and PRO results to be published in the same journal but reported in separate, complementary reports, ideally appearing in the same issue. A prime example is the reporting of results from the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene trial comparing tamoxifen and raloxifene for breast cancer prevention, with the study’s overall findings and a separate analysis of PRO results appearing in consecutive papers in the Journal of the American Medical Association.\textsuperscript{29,30} Another effective dissemination strategy is to report the trial’s overall findings and PRO analyses in two journals that are both widely read by the clinical oncology community, as illustrated in a study comparing approaches for delivering chemotherapy to ovarian cancer patients.\textsuperscript{31,32}

In general, authors must be cognizant of their readership and strive to report PRO results in a way that enhances comprehension of the relevance of the findings. Given the critical role that clinicians play in identifying evidence-based treatment options for patients, PRO researchers should attempt to use reporting standards familiar to physicians, such as percent improvement or percent decline, number needed to treat for benefit, or comparison of scores to relevant population norms.
relevance of PRO measurement in cancer trials. Indeed, some of these policies and procedures are already well under discussion.

**NCI's SxQOL Steering Committee**

Created as part of the NCI Clinical Trials Working Group implementation process, the new SxQOL Steering Committee has been assigned several important initial responsibilities. These include convening state-of-the-science meetings to identify critical questions, unmet needs, and priorities for PRO applications in NCI clinical trials (treatment and symptom management trials); reviewing and prioritizing symptom management intervention trials conducted through the Community Clinical Oncology Program (CCOP); reviewing the inclusion of HRQOL as an end point in cooperative group clinical trials; and developing criteria for the review of HRQOL studies that may compete for the yet-to-be determined Correlative Science and Quality of Life set-aside funds, which were recommended by the Clinical Trials Working Group.

With a membership expected to include representatives from CCOP research bases, community oncologists, patient advocates, and NCI-funded investigators in HRQOL and palliative care, the SxQOL Steering Committee is planned to work closely with the other existing disease-specific steering committees and the Investigational Drug Steering Committee to promote the effective inclusion of PROs in NCI-sponsored clinical trials.

The SxQOL Steering Committee should serve as a forum for cooperative groups and CCOP research bases to encourage the sharing of expertise and the development of common standards. Although the NCI has fostered the inclusion of HRQOL through the Quality of Life Intergroup (which brings together representatives from the cooperative groups and CCOP research bases, both in person annually and throughout the year via LISTSERV, to discuss HRQOL applications), this new steering committee can facilitate greater standardization through the prospective review of PROs included in the clinical trials. Specific areas for consideration would include educational and training materials for group investigators and CRAs; PRO surveys or instruments developed for specific trials and not yet available in published form; and best practice approaches for planning, collecting, and analyzing PRO data.

This SxQOL Steering Committee is one clear sign of NCI’s commitment to high-quality application of PROs in cancer clinical trials. Building on the lessons learned from PROACT, such application should include a hypothesis-driven trial design with PRO measures integrated into the study design, the appropriate choice of instrument and the timing of the assessments, a sound strategy that minimizes the risk of missing data, a strong statistical analysis plan that provides an integrated assessment of the biomedical and PRO end points, and an effective publication strategy that ensures the clinical oncology community is well informed about both the biomedical and the PRO findings of the trial.

As suggested earlier, the ability for PROs to impact decision making in cancer clinical trials depends on the quality of the measurement tools used to capture patient data, the timing of the HRQOL assessments within the trial, adherence by research sites to appropriate data collection procedures, and the reporting of PRO results in ways that are meaningful to stakeholders. In this section, we examine how innovations in psychometric science and the technology of data collection, transmission, and analysis can enhance PRO measurement in cancer trials. These advances in the state of the science should serve to complement the efforts by NCI and a host of other agencies and organizations worldwide to rationalize the entire process of PRO data use in trials. We discuss, in turn, innovations in PRO data collection and transmission, recent efforts to apply the patient-reported concept to the standard terminology criteria used in cancer trials, and new approaches to strengthening patient adherence in PRO data collection.

**Improving the Quality and Cost Efficiency of PRO Data Collection in Trials**

Recent work in PRO instrument development has taken advantage of innovations in psychometrics, health survey methods, and information technologies. In addition, efforts to field these PRO measures in clinical trials have led to a better understanding of the importance of appropriate timing in HRQOL assessment to capture treatment effects while also minimizing missing data.

Many of the recent innovations in HRQOL assessment have entailed a shift from paper to electronic modes of data collection (ie, E-PROs) and capitalizing on the unique opportunities that computers and the Internet provide for collecting and transmitting data. E-PRO assessment can make HRQOL questionnaires accessible to people with limited physical or financial resources. The font of the questionnaire can be adjusted automatically for people with limited vision, and the questions can automatically switch to different languages for non-English speakers. Interactive voice response software provides access to individuals with limited reading ability, to the blind, and to people without computers but who have access to telephones. Missing HRQOL data can be reduced through automated reminders to patients. Human data entry errors observed on paper questionnaires can also be greatly reduced by computer assessment. E-PRO data can be instantly transmitted and summarized for researchers even in distant locations. That said, a trial integrating different HRQOL assessment modalities (eg, paper-based and computer-based forms) will need to consider the possible measurement bias introduced by mixing assessment modes.

PRO questionnaires, particularly those measuring HRQOL, have undergone considerable refinement in recent years in response to a call from the clinical oncology research community for standardized, brief, valid, and precise tools to capture the burden of cancer and treatment. To answer this need, developers have been using methods from the fields of qualitative research, cognitive aspects of survey methodology, and psychometrics. Qualitative methods seek to provide a full understanding of the domains and issues affecting cancer patients. Cognitive aspects of survey methodology examines the cognitive factors that may influence the quality of responses obtained through self-report. Psychometrics lays the groundwork for empirically testing the developer’s theoretical framework (conceptual model) that underlies the questionnaire and examining instrument measurement properties. It provides the means to refine the instrument or to link the measurement scales between two or more PRO instruments to compare or to combine results from multiple studies.

Currently, an area of intense interest in PRO questionnaire development is the use of item banks to provide a foundation for deriving short forms and for carrying out computerized-adaptive testing.
(CAT). Item banking incorporates the methodologies described earlier to build a large pool of items that have been tested to ensure their relevance, psychometric robustness, and clarity. Each item bank measures a single outcome domain such as depression or pain severity. Under an item response theory framework, each item within a domain is calibrated with a set of statistical properties to allow researchers to select any set of items from the bank to match the characteristics of the study population (eg, the items posed to a clinically depressed population would be more oriented to the efficient measurement of clinical depression than the items posed to the general health population). Scores from any set of items can be compared or combined with scores from any other set of items from the same item bank.

The most ambitious and scientifically rigorous effort to bring item banking into reality is the National Institutes of Health–supported initiative to develop a Patient-Reported Outcomes Measurement Information System (PROMIS).10 The goals of the PROMIS project are to build a set of publicly available item banks for measuring patient-reported symptoms (eg, pain, fatigue, depression) and HRQOL domains (eg, physical function, social role participation) relevant to a variety of chronic diseases studied in randomized clinical trials. Additional work supported expressly by NCI will focus on the outcome domains of illness impact, sexual function, sleep/wake function, and cognitive function. When available, these item banks can be used to select short-form HRQOL measures or to assess a patient’s health status via CAT. CAT provides efficient and precise HRQOL measurement by choosing, for each respondent, the most informative set of questions by selecting each question based on the pattern of responses to all previously administered questions. In other words, CAT allows PRO assessments to be individually tailored to the patients participating in the study. Although CAT technology shows promise, the PROMIS short forms will initially see greater use in clinical trials because the same set of items are administered to all patients (thus not departing too far from the standard paradigm of PRO measurement). CAT assessment in trials will likely grow in application if and when validity studies have demonstrated that different sets of items from the same bank produce equivalent results, thus providing support for a central feature of the CAT methodology.

New methodologies like PROMIS enhance our ability not only to improve the use of PROs within specific clinical trials, but also to compare PROs across clinical trials, especially when applications draw items from similarly constructed item banks. This technology will enable the field to build on experience in the same way that research has done with more traditional standard end points, like mortality and survival.

**Improving the Clinical Relevance of PROs:**

**The Patient-Reported Common Terminology Criteria for Adverse Events**

There have been recent promising developments in the use of PROs to complement clinician-reported drug toxicity in clinical trials.13,36,37 Currently in NCI-sponsored trials, the mandated instrument for this purpose is the NCI’s Common Terminology Criteria for Adverse Events.38 Clinical staff obtain, interpret, and report patient symptoms rated by five grades reflecting the severity of the adverse event. Of the 1,059 terms in the Common Terminology Criteria for Adverse Events, approximately 24% of the symptoms may be enhanced by PRO data.13 Integrating a PRO symptom assessment system into the routine clinician reporting of adverse events could greatly improve drug toxicity monitoring and become the standard in cancer treatment trials.

**Strengthening Adherence to PRO Data Collection Plans**

The timing of PRO data collection within a trial is critical for capturing treatment effects. Each time point when PRO data are collected needs to be justified and should be selected to match the purpose of the study and characteristics of the sample.3 Automated reminders to CRAs and perhaps also to patients will decrease missing data. Another major source of missing PRO data within multisite trials arises from reporting delinquencies at the sites. Clinical trial groups at NCI14 and EORTC15 have implemented quality control procedures that include regular review of data submission and compliance during a trial. All participating sites are monitored for compliance with these policies.

**Who Uses PRO Data from Cancer Trials? Understanding and Enhancing Decision Relevance**

As a review of the thousands of citations in the COMWG’s 32-chapter book, *Outcomes Assessment in Cancer: Measures, Methods, and Applications*,29 will show, there is a large, rapidly growing, and increasingly sophisticated literature on the psychometric development and research application of HRQOL across the cancer continuum. However, a closer look at these COMWG literature citations will also suggest that there is only a small, still nascent effort by HRQOL investigators to understand and improve the way that patients, providers, payers, regulators, and other policy makers actually use these measures in decision making. The need to better understand the role that PRO measurement plays (or could play) within various cancer research and policy application arenas was emphasized in a recent report.39

Specifically, although the PROACT case studies provided important new insights into the scientific strengths and limitations of PRO applications in cancer trials, they were not intended to identify the possible impact of trial findings on subsequent cancer care decision making by patients and clinicians, third-party payers, and others. To do that would require research, still possibly case-study focused, whose center of gravity moves from the cancer trials community to those specific decision-making arenas. The report in this issue by Rock et al,8 documenting the role of PROs in FDA product approval to date, provides an important example of how this might be done. We could benefit significantly from parallel studies about whether and how PRO findings from trials influence the day-to-day decisions that patients and providers make about choice of therapy, medical care organizations make about clinical practice policies, and public and private third-party payers make about coverage of specific cancer interventions.

Such studies would explore the actual and potential contributions of a variety of factors on the perceived decision relevance of PRO data and on ways to enhance the usefulness of information that conveys the patient’s perspective. For example, to what extent are PRO specialists, or outcomes researchers generally, represented in the forums and arenas where clinical policies and coverage...
decisions are made? Do media reports on important cancer trials give due weight to QOL findings, if available, in addition to results about patient survival? (To be sure, press accounts will likely be influenced by the way the trial findings are initially reported by investigators in print and at conferences, which, in turn, will be influenced by the trial’s designated primary and secondary end points.) To what extent has PRO measurement made its way into medical school curricula or fellowship training programs? How strong and influential are the connections among cancer decision makers at all levels and the major professional organizations emphasizing PRO research (eg, the International Society for Quality of Life Research or the International Society for Pharmacoeconomics and Outcomes Research)? In sum, we need a new synergism wherein the PRO measurement literature informs the decision maker, who in turn influences the direction of the cancer outcomes research literature.24

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In this article, we discuss patient-reported outcome (PRO) assessment in cancer trials and challenges relying solely on static multi-item HRQOL instruments. Although individual assessment of symptomatic adverse events, physical function, and disease symptoms can take advantage of the strengths of emerging contemporary instruments to provide a flexible, reasonably comprehensive, yet concise picture of the core patient experience in cancer trials, continued efforts must be undertaken to identify the optimal PRO strategy for single-arm trials and to characterize and mitigate effects of open-label.