Integrating Patient-Reported Outcomes Into Cancer Symptom Management Clinical Trials Supported by the National Cancer Institute–Sponsored Clinical Trials Networks

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Patient-reported outcomes (PROs) are often the primary end point in symptom management trials. The scientific field of PROs is evolving, as evidenced by the US Food and Drug Administration’s February 2007 release of a draft guidance for using PROs in effectiveness claims for drug labeling. This article presents issues encountered during use of PROs in National Cancer Institute–sponsored symptom management trials. Selected trials are presented that exemplify the challenges often seen in symptom management trials, and solutions are described. The examples presented include defining the appropriate end point, selecting and validating assessments, and answering the research questions through statistical analysis and interpretation. Progress has been made in addressing some of the unique challenges of PRO-based symptom management research. Many challenges still remain, but a foundational body of work now exists for more consistent and rigorous application of PROs into symptom management trials. There remains a need for more research in several methodologic aspects of design, analysis, and interpretation of symptom management trials.

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 Trials for Bone and Brain Metastases

Symptom management trials present a unique challenge in that the precise end point of interest is often difficult to define.3,5 Symptom management protocols, especially those with palliative intent, often are directed towards relieving or preventing patient suffering. Multiple trials developed by the Radiation Therapy Oncology Group (RTOG) for symptoms associated with bone metastases and brain metastases provide insight into the utility of PROs in these settings.

The first of six RTOG bone metastases treatment trials discussed here was conducted in 1974 (RTOG 7402).16 This study randomly assigned patients to several different radiation therapy fractionation schedules, such as 30 Gy in 10 fractions or 40.5 Gy in 15 fractions. The primary end point of the trial was the patient-reported pain at the treatment site, defined as a score composed of the frequency of pain (on a 0 to 3 scale, representing less than once a day, once a day, several times a day, or constant, respectively) multiplied by the intensity of the pain (on a 0 to 3 scale, representing none, mild, moderate, or severe, respectively). Pain medication use was monitored on a similar scale. This scale was created for the trial, and although similar in form and in content to other assessment instruments validated in different patient populations, it underwent no formal validation before its use in the trial. This study was one of the first clinical trials to demonstrate the feasibility of collecting this information directly from cancer patients.

A similar patient-reported pain scale was then used in RTOG 7810, a phase I/II trial of hemibody irradiation for widespread bone metastases.17 A new end point of net pain relief was introduced, which was defined as the duration of pain relief as normalized to the length of survival.

Pain relief treatments often consist of a mixture of interventions including narcotics, analgesics, and radiation therapy. A particular problem arises if pain is the only component of the primary end point because a patient experiencing no pain while taking high-dose narcotics will have a better pain score than a patient on no analgesics experiencing a low level of pain. RTOG also conducted a phase I/II study of fractionated hemibody irradiation (RTOG 8822).18 The primary end point was the maximum-tolerated dose of fractionated hemibody irradiation, as determined by the occurrence of any severe toxicity recorded by the NCI Common Toxicity Criteria (CTC). The only other outcome measures reported were time to new disease and time to new treatment. No PROs were included, despite all of the patients having the inclusion criteria of at least moderate pain on entry. The rationale for not documenting the response of the pain to treatment was not reported.

The next study for the palliation of bone metastases was RTOG 9714, a randomized trial of single- and multiple-fraction radiation therapy.19 A rigid end point of complete pain relief (ie, no pain and no narcotic use) was chosen as the PRO for this study. This trial abandoned the previous trials’ approach of focusing only on the treated sites and focused on a global end point, which may not be sensitive for a localized outcome. However, the limitations of the scales used in the trials previously described were avoided. The specific pain measure used was the Brief Pain Inventory.20 Secondary end points were also patient reported and included HRQOL, which was measured by the Functional Assessment of Cancer Therapy (FACT),21 and health status, which was measured by the Health Utilities Index.22 An ongoing RTOG trial, RTOG 0517, is comparing the use of bisphosphonates with or without a single dose of a bone-absorbed radionuclide (strontium-89 or samarium-153). Again, an objective and composite end point was chosen for the primary end point (skeletal events, including re-treatment or fractures). However, PROs are included as secondary end points. The Brief Pain Inventory will measure pain, and the FACT-General and the EuroQol will measure HRQOL.23

Brain metastases have also been a scientific focus within the RTOG. The first trials compared various fractionation schedules and had observer-oriented primary end points using the Neurologic Function Classification.24 The Neurologic Function Classification is as follows: 1, able to work, neurologic findings minor or absent; 2, able to be at home, although nursing care may be required; neurologic findings present but not serious; 3, requires hospitalization and medical care, with major neurologic findings; and 4, requires hospitalization and is in a serious physical or neurologic state, including coma.

The rapid deterioration and short survival of most patients with brain metastases presents a challenge for the use of PROs in symptom management trials involving this patient population. Patient compliance decreases as their medical and neurologic condition deteriorates.

The RTOG has tried a variety of approaches to address this challenge. A phase II trial of twice-a-day radiation for patients with brain metastases, RTOG 8528, used an end point that was still observer oriented, using an improvement in the Neurologic Function Class, improvement of the brain imaging, or a decrease in needed corticosteroids. The follow-up phase III trial, RTOG 9104, used survival as its primary end point and included the Mini-Mental State Examination (MMSE) as a secondary end point. Although the MMSE was completed by the patient, it was scored by an observer and, therefore, is not, strictly speaking, a PRO.24 Subsequent RTOG research attempted to use end points that reflected patients’ experiences. To achieve this goal, a battery of neurocognitive assessments previously validated in cancer patients was constructed to create instruments that were sufficiently sensitive and specific but not overly burdensome to the patient. RTOG 0018 was one phase II trial that evaluated the ability of patients with brain metastases to complete this neurocognitive testing battery. The results demonstrated that it was feasible for patients to complete the battery with a high degree of compliance.25

The primary lesson learned from this series of trials is that outcome measures of palliative care protocols can benefit from obtaining data directly from patients. The challenge is to incorporate the patient’s experience using measures that are valid and have a high degree of completion. Furthermore, the end points must sufficiently reflect patients’ conditions so that they can adequately measure the effects of interventions. To date, the palliative care protocols have not completely achieved these goals but have made progress.

Describing the Relationship Between Overall HRQOL and Individual Symptoms: Megestrol Acetate for Anorexia in Head and Neck and Lung Cancer Patients Receiving Radiation Therapy

A challenge in defining end points for symptom management trials is the conceptual overlap between HRQOL and symptoms. A particular challenge arises in situations when studies alleviate symptoms but do not impact HRQOL, or vice versa.

The Comprehensive Cancer Center of Wake Forest University (CCCFWU) CCOP Research Base encountered this challenge in a series of their symptom management trials aimed at treating anorexia.
Two phase III randomized controlled trials were performed, one in lung cancer patients (CCCWFU 98199)\(^{26}\) and the other in head and neck cancer patients (CCCWFU 97300),\(^{27}\) to assess the effect of prophylactic megestrol acetate (MA) on weight concurrent with and for 12 weeks after definitive radiation therapy. The combined results from a meta-analysis of both trials regarding weight loss are presented in Figure 1. In contrast to a slight increase in mean weekly weight for patients receiving MA of 0.01 lb (95% CI, −0.39 to 0.4 lb; \(P = .98\)), patients receiving placebo experienced a mean weekly weight loss of 0.56 lb (95% CI, −0.98 to −0.15 lb; \(P = .001\)).

There were no significant differences in HRQOL between patients receiving placebo and those receiving MA. Furthermore, although overall HRQOL was similar between treatment groups, the symptom of anorexia was improved in the MA arm (\(P = .008\)). Although one symptom might be ameliorated, it may not be associated with an alteration in overall HRQOL. Study investigators concluded that prophylactic MA significantly reduces weight loss in lung and head and neck cancer patients receiving at least 50 Gy of radiation therapy.

Similar findings were reported by the NCCTG in trials of epoetin-\(\alpha\) for alleviating fatigue in advanced cancer patients.\(^{28}\) Although hemoglobin values improved, PROs related to fatigue and HRQOL did not change. In several hot flash studies, the NCCTG has reported that patients who report reductions of greater than 50% in hot flash activity do not indicate a substantial change in HRQOL.\(^{4,29}\) Defining end points for symptom management trials often involves developing and validating a new measurement approach and defining what is meant by a clinically significant outcome. The NCCTG conducted a two-period, placebo-controlled, cross-over clinical trial involving 120 menopausal breast cancer survivors randomly assigned to receive either vitamin E or placebo for alleviation of hot flashes.\(^{30}\) This trial is representative of many trials that evaluate hot flash interventions using hot flash activity as reported by the patient (see Sloan et al\(^{30}\) for a list). The trial was the first in a series and was initiated when no accepted assessment for hot flash activity existed. A diary was constructed and concurrently validated for the ability to consistently measure a woman’s hot flash activity.\(^{31,32}\)

The study illustrates the need for considering clinical significance (beyond statistical significance) in reporting results from symptom management trials. The primary analysis for the first period of the cross-over design indicated that patients did not experience any difference in hot flash frequency between the placebo and vitamin E treatment arms (25% \(\times 22\%\), respectively; \(P = .90\)).\(^{30}\) Analysis of the full cross-over design, however, indicated that patients treated with vitamin E averaged one hot flash fewer per day than patients receiving placebo (roughly four \(\times\) five per day, respectively, from a baseline activity of about eight hot flashes per day; \(P < .05\)). The study was powered to detect a difference of at least one hot flash per day, which turned out to be close to the observed effect size. Although statistically significant, the results posed a question. Is it worth it to the individual to take the vitamin E and have one less hot flash? The investigators concluded that the “clinical magnitude of this reduction was marginal.”\(^{30}\) Although the \(P\) value is an important interpretation tool, the statistical analysis and results should reflect clinically meaningful outcomes and patient values.

**Selecting Appropriate Assessments: Ginger for Nausea**

Once end points have been defined, another considerable challenge is to operationalize the definitions by selecting an appropriate method of assessment. The researcher must balance the idealized need to collect sufficient information against the reality that PRO assessment represents an additional burden to cancer patients. One way to deal with this challenge is exemplified by the University of Rochester Cancer Center (URCC) Research Base, which conducted a phase II/III randomized, controlled clinical trial of ginger for nausea caused by chemotherapy for cancer (URCC 0114). A 4-day home record of nausea was supplemented by the FACT-General QOL assessment and a symptom inventory to capture the adverse effects of ginger. Figure 2 displays the simple nausea scale used, which was easy for the patients to complete.

Figure 3 illustrates the straightforward manner in which the symptom inventory, adapted from one created at The University of Texas M.D. Anderson Cancer Center, was constructed.\(^{33}\) Pain and fatigue are illustrated in Figure 3, but other symptoms were also captured in this manner. The only caveat to the inclusion of different symptoms in this inventory is that the terminology used for each symptom must be understandable by the patient. For example, one would not ask a patient to rate their peripheral neuropathy but, rather, the numbness or tingling in their hands and feet.

The URCC Research Base prefers assessment methods that keep measures and study design as short and as simple as possible. There is great utility in giving a symptom measure multiple times, and they have found that single items to assess symptom severity work best. Where there is not an obviously optimal symptom measure, the use of competing questionnaires assessing the symptom(s) of interest provide the required data to assess efficacy of the agent under study while also providing data to inform future trials of the same symptom. The URCC Research Base has published peer-reviewed empirical articles in the last 6 years that have included single-item assessments, typically at multiple time points.\(^{34,35}\) The URCC Research Base has provided ample evidence that simple symptom assessments allow for a direct approach to the evaluation of symptom ameliorative agents.
Comparing Single-Item and Multiple-Item Assessments for the Same Symptom: Fatigue During Chemotherapy

Much has been written about the relative merits of single-item and multi-item assessments. Single-item assessments represent an efficient method for assessing overall HRQOL domains but cannot capture the detail provided by multiple-item assessments. However, multiple-item assessments do not necessarily add clarifying information, as evidenced by a study involving the prevalence and treatment of fatigue in cancer patients receiving chemotherapy (URCC 1996P). The primary objective in that study was to assess the degree to which an antidepressant drug (paroxetine) could reduce patient fatigue during chemotherapy treatment. Measures included the Multidimensional Assessment of Fatigue (MAF), the Profile of Mood States (POMS), the Fatigue Symptom Checklist, and the Center for Epidemiologic Studies Depression Scale (published elsewhere). The primary outcome measure reported was question 1 from the MAF, a 5-point semantic rating scale asking patients to indicate to what degree they had experienced fatigue during the previous week. Table 1 indicates that the correlation among study measures for fatigue was strong; most of the more complex measures are highly correlated with the simple, single MAF question. The single-item measure of fatigue also exhibited less overlap with the assessment of depression, as indicated by its lower correlations with the POM-Degression/Dejection and the Center for Epidemiologic Studies Depression Scale. The utility of a single-item fatigue assessment was confirmed in a separate phase III trial of modafinil using similar study measures.

Similar results have been seen for other end points in symptom management trials. For example, normative data are now available for a single-item measure of overall HRQOL that has been used in numerous symptom management trials. Research has further indicated that a score of 5 or less on the 0 to 10 scale used for this assessment of overall HRQOL is indication of the need for clinical intervention, that a movement of 2 points is a clinically meaningful change, and that a healthy individual typically will provide a score of 7 to 9.

**Table 1.**

<table>
<thead>
<tr>
<th>Not at all Nauseated</th>
<th>Moderately Nauseated</th>
<th>Extremely Nauseated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of Treatment</td>
<td>1st Day Following Treatment</td>
<td>2nd Day Following Treatment</td>
</tr>
<tr>
<td>(day of week)</td>
<td>(day of week)</td>
<td>(day of week)</td>
</tr>
<tr>
<td>Morning</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Afternoon</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Evening</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Nighttime</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Fig 2. The nausea scale used by the University of Rochester Cancer Center Research Base.

Fig 3. An example of a symptom inventory. The University of Rochester Cancer Center (URCC) Research Base Information Needs Assessment form.
Supplementing the CTC With PROs: Oxaliplatin-Related Peripheral Neuropathy

Symptom management trials have relied heavily on physicians to report patient symptoms, typically via the NCI CTC or, subsequently, the Common Terminology Criteria for Adverse Events. The CTC has a long history as a tool for reporting adverse events. The CTC specifies grading scales for hundreds of symptoms, typically assessed by a physician. For most end points relevant to a symptom management trial, the CTC provides definitions for an ordinal grading as follows: 0, none; 1, mild; 2, moderate; 3, severe; 4, life threatening; and 5, lethal.

A recent treatment study of the NCCTG dealing with oxaliplatin-related peripheral neuropathy indicated that supplementing the CTC with simple PROs provided valuable clinically relevant information. The PROs involved numerical analog scale (NAS) assessments similar to the format already seen in Figure 3. The NAS asked patients to report their perceived level of peripheral neuropathy (numbness/tingling in their hands and feet) by circling an integer from 0 (not at all) to 10 (as bad as it can be). Six hundred ninety-six patients randomly assigned to receive oxaliplatin in the practice-changing NCCTG/In-tergroup study N9741 provided data on the incidence and severity of peripheral neuropathy experienced via biweekly CTC assessments and NAS measurements taken every 12 weeks. Peripheral neuropathy via the NAS was defined as a worsening of 2 points from baseline. Time to onset of peripheral neuropathy via the NAS was defined as the time from baseline to the first 2-point worsening (from baseline) and was defined via the CTC as the time from baseline to the first report of grade 2 or higher (ie, grade 2+) peripheral neuropathy and the time from baseline to the first report of grade 3 or higher (ie, grade 3+) peripheral neuropathy. Two hundred seventy-six patients (40%) reported peripheral neuropathy via the NAS compared with only 99 patients (14%) with a reported incidence of CTC grade 3+ peripheral neuropathy. Figure 4 further demonstrates that the time to onset of peripheral neuropathy via the NAS was substantially less than the time to onset of peripheral neuropathy via the CTC for patients who had not perceived a clinically meaningful change in their peripheral neuropathy, with the NAS being more sensitive to the patient’s perceptions. This is clinically important for potentially identifying a need for dose adjustment earlier or considering a prophylactic intervention to prevent the peripheral neuropathy from escalating to the level of a serious adverse event.

A grade 3+ CTC report is typically the predating factor in considering oxaliplatin dose modification. If one were to use incidence of a grade 2+ CTC peripheral neuropathy as an indicator event, this would be giving the CTC an unfair advantage because a grade 2 event is not typically considered as a trigger for dose modification. Even with this modification to the CTC usage, the time to onset of CTC grade 2+ peripheral neuropathy was still substantially longer than time to onset of peripheral neuropathy via the NAS for patients with onset within the first 6 months of random assignment (Fig 4). The incidence rate of recording a CTC grade 2+ peripheral neuropathy was 37% and, therefore, closer to the incidence rate of 40% observed by the NAS. However, there was, at best, moderate concor-dance between the CTC and NAS approaches to identifying which patients were actually experiencing troublesome peripheral neuropathy (65%, Cohen’s κ = .26). Hence, the extra people who were identified by the report of a CTC grade 2 event were, for the most part, patients who had not perceived a clinically meaningful change in their peripheral neuropathy via the NAS. The CTC and NAS PRO would seem to be measuring two different aspects of oxaliplatin-related peripheral neuropathy, with the NAS being more sensitive to the patient’s perceptions. This is clinically important for potentially identifying a need for dose adjustment earlier or considering a prophylactic intervention to prevent the peripheral neuropathy from escalating to the level of a serious adverse event.

Table 1. Correlations Among Various Measures of Fatigue

<table>
<thead>
<tr>
<th>Measure of Fatigue</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Multidimensional Assessment of Fatigue question 1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Multidimensional Assessment of Fatigue total score</td>
<td>0.94</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Fatigue Symptom Checklist</td>
<td>0.67</td>
<td>0.73</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Profile of Mood States–Fatigue/Inertia</td>
<td>0.81</td>
<td>0.85</td>
<td>0.77</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5. Profile of Mood States–Depression/Dejection</td>
<td>0.47</td>
<td>0.52</td>
<td>0.61</td>
<td>0.60</td>
<td>1</td>
</tr>
<tr>
<td>6. Center for Epidemiologic Studies Depression Scale</td>
<td>0.60</td>
<td>0.67</td>
<td>0.71</td>
<td>0.70</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Listening to Patient Comments: Sucralfate for Stomatitis

Having defined appropriate end points and chosen the optimal assessment approach, the final major challenge remains analyzing and interpreting the results. Standard statistical methods deal with many
of the research questions posed by symptom management trials. Nonetheless, several statistical considerations involved in symptom management trials require particular attention. The intent-to-treat principle of including all patients in the analysis who are subjected to treatment and yet do not provide data is a particularly challenging aspect of symptom management trials. This is exemplified in a trial reported by Martenson et al of a placebo-controlled study of 100 patients testing sucralfate for alleviating stomatitis. In the initial analysis, \( P = .06 \) in favor of sucralfate when comparing the maximum grade of stomatitis for patients receiving sucralfate versus placebo. However, twice as many patients went off study early on the sucralfate arm. Investigation of the patient comments among those who did not complete the trial revealed that all but three patients on the sucralfate arm went off study because the treatment made them gag. If these patients were added to the analysis as treatment failures, the primary analysis \( P \) value would still be .06, but now, it would favor placebo over sucralfate. This study provided the lesson that, in symptom management trials, it is important to make sure you are asking the appropriate question.

**Incorporating Mood As a Covariate: Antidepressants for Hot Flash Activity**

Assessing the burden of symptoms in cancer patients without considering depression is difficult. Early in the 1990s, it became apparent that newer antidepressants that selectively inhibit serotonin reuptake (selective serotonin reuptake inhibitors) might reduce hot flash activity. Loprinzi et al reported that venlafaxine administered in doses less than that approved to treat depression reduced hot flashes. The issue was differentiating activity specific to hot flash reduction from perception or mood. An important covariate, the Beck Depression Inventory, was used to address this issue. The adjusted analysis indicated that the mood changes were both statistically and clinically nonsignificant. Therefore, the effect of the venlafaxine on hot flash activity could be reasonably ascribed to true impact on the number of hot flashes experienced.

Consistency of PRO assessments over the series of hot flash studies carried out by the NCCCTG allowed for a meta-analysis that yielded several implications for future study design. Specifically, a scientifically supportable response criterion based on empirical data was defined as a 50% reduction in hot flash activity for individual patients. Furthermore, a sample size of only 25 patients was determined to be efficient for pilot hot flash studies.

**Examining Symptom Clusters: Donepezil for Cognitive Function in Irradiated Brain Tumor Patients**

Recently, researchers have attempted to analyze clusters of end points in an effort to interpret the multiplicative nature of PROs. Cognitive function, for example, is a simple collective concept to express but is a complex composite end point when incorporated into a clinical trial.

The Wake Forest University CCOP Research Base encountered this challenge when they conducted an open-label phase II study, CCCWFU 97100, which treated irradiated brain tumor patients with donepezil, an FDA-approved reversible acetylcholinesterase inhibitor used to treat mild to moderate dementia of the Alzheimer’s type. In addition to extensive cognitive assessments, this trial included the FACT-Brain for assessing HRQOL and the POMS for assessing mood, illustrating the need for multiple symptom assessments to answer a composite research hypothesis.

**Dealing With Missing Data: Radiofrequency Ablation for Bone Metastases**

An important consideration for conducting a successful symptom management trial is the proper management of missing data. In recent years, several methods have been advanced to both prevent and account for missing data in an experimental design. Despite these statistical advances, missing data continue to be a major problem facing symptom management trials. PROs, which are reliant on patients being able and willing to provide a response, are often the primary end point in symptom management trials. The best method for handling missing data is prevention, which requires careful consideration during the design and implementation stages of a clinical trial. Good planning is essential to avoid missing data, paying particular attention to the data collection burden of instrument selection. Research has shown that the amount of missing data is directly proportional to the number of items the patients is asked to complete.

Once missing data are present, the key issue is whether a systematic bias in the pattern of the missing data is associated with a particular treatment or whether the pattern of missing data is consistent across treatments. For example, experience has demonstrated that the best performers are the patients who tend to provide more complete data in symptom management trials. Patients who do not provide complete data often do so because they become too ill to participate. As a result, the PRO data in symptom management trials tend to overestimate the well-being of the patient population. Hence, analysis of PRO data in symptom management trials must take the presence of missing data into consideration. Various imputation methods have been proposed to deal with this issue.
A symptom management trial that dealt with missing data issues examined radiofrequency ablation for pain from bone metastases. Missing data were anticipated as a result of the nature of the intervention and the desire to track pain longitudinally. A number of preventive measures were put in place. First, the number of assessments involved was scrutinized, and only items that were absolutely essential were included. Second, study assistants specified at each clinical site collected the PRO assessment data. Third, the assessments were organized into carefully designed high-quality print booklets that included a message to the participants from the investigator and a contact number for them to use for any questions or concerns. These efforts kept the missing data well below 10% for any end point. Current research suggests that keeping missing PRO data below the 10% threshold is essential for confidence in the findings of most studies, assuming that appropriate statistical imputation techniques are applied. This conclusion reinforces the importance of careful planning and execution of PROs in clinical trials to minimize missing data in the first place.

CONCLUSION

The goal of this article was to examine the application of PROs in symptom management cancer clinical trials. Examples were drawn from specific NCI-sponsored symptom management trials that either involved methodologic techniques or furthered the knowledge base of applications of PROs for cancer-related symptoms. These areas of research continue to evolve.

The clinical trials described in this article demonstrate that incorporating PROs in symptom management trials presents challenges in study design, analysis, and interpretation. Many challenges still remain, but a foundational body of work now exists for more consistent and rigorous application of PROs in future symptom management trials. Recent publications and workshops, such as Patient-Reported Outcomes Assessment in Cancer Trials, have attempted to delineate the key issues now facing researchers who want to incorporate the patient’s subjective experience into cancer clinical trials. Further methodologic advances similar to those presented in this article are needed to ensure that PROs have the requisite scientific integrity for continued and expanded use in symptom management clinical trials.

REFERENCES


AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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