

ARTICLE

Recommended Patient-Reported Core Set of Symptoms to Measure in Adult Cancer Treatment Trials

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Background The National Cancer Institute's Symptom Management and Health-Related Quality of Life Steering Committee held a clinical trials planning meeting (September 2011) to identify a core symptom set to be assessed across oncology trials for the purposes of better understanding treatment efficacy and toxicity and to facilitate cross-study comparisons. We report the results of an evidence-synthesis and consensus-building effort that culminated in recommendations for core symptoms to be measured in adult cancer clinical trials that include a patient-reported outcome (PRO).

Methods We used a data-driven, consensus-building process. A panel of experts, including patient representatives, conducted a systematic review of the literature (2001–2011) and analyzed six large datasets. Results were reviewed at a multistakeholder meeting, and a final set was derived emphasizing symptom prevalence across diverse cancer populations, impact on health outcomes and quality of life, and attribution to either disease or anticancer treatment.

Results We recommend that a core set of 12 symptoms—specifically fatigue, insomnia, pain, anorexia (appetite loss), dyspnea, cognitive problems, anxiety (includes worry), nausea, depression (includes sadness), sensory neuropathy, constipation, and diarrhea—be considered for inclusion in clinical trials where a PRO is measured. Inclusion of symptoms and other patient-reported endpoints should be well justified, hypothesis driven, and meaningful to patients.

Conclusions This core set will promote consistent assessment of common and clinically relevant disease- and treatment-related symptoms across cancer trials. As such, it provides a foundation to support data harmonization and continued efforts to enhance measurement of patient-centered outcomes in cancer clinical trials and observational studies.

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Beyond traditional measures of therapeutic response (ie, survival and tumor response), the efficacy and toxicity of an intervention can be more fully interpreted through evaluation of disease- and treatment-related symptoms. Toxicities often develop several weeks after starting cancer treatment, and many are subjective (eg, fatigue, headache, neuropathy) and thus best captured by patient self-report (1).

Symptom screening offers an opportunity to improve care quality for patients participating in clinical trials (2), thereby improving treatment adherence and clinical outcomes, particularly in our contemporary treatment environment where use of oral agents is increasing (3,4). Identification of a core set of symptoms and/or health-related quality-of-life (HRQOL) domains to be measured across trials could enhance clinical and population research and improve supportive care (5).

The lack of an agreed-upon core set of symptoms to be collected in adult oncology treatment trials reflects the heterogeneity of cancer types and effects of treatments on patients' lives. For example, treatments for localized prostate cancers are associated with diarrhea, urinary incontinence, and impotence (6–9), whereas treatments for head and neck cancers are associated with mucositis, xerostomia, dysphagia, weight loss, and speech alterations (10,11). However, several symptoms, including fatigue, pain, insomnia, gastrointestinal symptoms, anxiety, and depressed mood, are commonly experienced across different cancer sites and treatment modalities (12–16).

Systematic assessment of a core symptom set across all trials where patient-reported endpoints are included would 1) encourage the inclusion of the patient's perspective consistently across clinical trials and facilitate comparative effectiveness research; 2) enhance our understanding of the impact of cancer and its treatment on patients'

lives, which in turn may help identify effective treatment and supportive care strategies; and 3) enhance data harmonization across trials, permitting integrated data analysis and meta-analysis. Ultimately, this would lead to more efficient and robust research approaches.

Several national organizations, including the Center for Medical Technology Policy (17), the Food and Drug Administration (18), the Patient-Centered Outcomes Research Institute (19), the National Quality Forum (20), the American Society of Clinical Oncology (21), and the International Society for Quality of Life Research (22,23) have issued statements establishing the importance of PROs as an essential outcome metric in clinical research and to guide decision-making in clinical practice and evaluations of care quality. A number of these guidance documents also recommend that a consistent core set of PROs be included in electronic health records, registries, and national population surveillance initiatives.

We undertook a data-driven, consensus-building process that included a systematic review of the published literature, analysis across several large datasets, and a multistakeholder meeting to identify a recommended core set of symptoms across disease sites to be assessed in cancer clinical trials that include a PRO.

Methods

Through a US National Cancer Institute's (NCI's) Clinical Trials Planning Meeting (CTPM), a panel of stakeholders, including researchers, clinicians, and patient representatives, was convened to develop recommendations. A systematic, multistep iterative process was used over an 18-month period that included: 1) a systematic literature review to determine the prevalence and severity of symptoms across published studies; 2) an analysis of two NCI trial databases that contained clinician reporting of symptomatic adverse events, together with four large datasets measuring patient-reported symptoms in diverse cancer populations across the United States and Europe; and 3) a multistakeholder CTPM to review the evidence and build consensus.

A subset of the stakeholders (represented by authors of this article) served as an expert panel, conducting the literature review and data analysis and drafting the initial recommendations to be discussed at the multistakeholder CTPM. After the meeting, the expert panel synthesized the CTPM's conclusions and finalized a proposed list of core symptoms across disease sites.

Three additional expert panels were constituted for the CTPM to address core symptom and HRQOL domains for three specific cancer sites (head and neck, prostate, ovarian). Although symptom and HRQOL domains to be assessed in clinical trials are proposed by the site-specific expert panels, for reasons of feasibility, the expert panel that was convened to address the core set across all diseases limited their scope of work to symptoms.

Systematic Literature Review

The initial step in this process, a systematic review of the literature, is described elsewhere (24). Search terms included "multiple symptoms" and "cancer" and was limited to adults (aged 18 years or older) and to reports published in English between 2001 and 2011. This strategy identified 55 publications, including the Kim et al. systematic review of the symptom experience reported in adult cancer studies published from 1990 to 2007 (14). A limitation of the work of Kim et al. (14)

is that their review was restricted to studies that used one of three PRO measures: the Symptom Distress Scale (25), the M. D. Anderson Symptom Inventory (26), and the Memorial Symptom Assessment Scale (27). Eighteen research articles were included in the Kim et al. (14) review, representing a total of 3506 patients with a mean age of 59 years (range = 47–67 years) and 48% of whom were women.

The Reilly et al. review (24) extended the work by Kim et al. (14) by synthesizing 21 additional US-based and multinational studies and by including studies that used any PRO measure of symptoms. The pooled sample characteristics of Kim et al. (14) and Reilly et al. (24) were fairly comparable; the Reilly et al. review (24) reflected pooled data of 4067 cancer patients, of whom 62% were women with a mean age of 58 years (range = 18–97 years). Reilly et al. identified 47 symptoms that were ranked by prevalence and severity (24).

Primary Data Sources

Six large research datasets (see Table 1) were obtained, including data from two NCI clinician-reported adverse event reporting systems, three PRO measure validation studies (28–31), and one symptom assessment observational study (32). Within each dataset, the prevalence, severity, or importance of symptoms across a variety of cancer populations was tabulated. The characteristics, emphasis, and limitations of each of these datasets are described in the [Supplementary Methods](#) (available online) and summarized in Table 1.

These six datasets offered diversity and representativeness with respect to demographics, disease site and stage, participation in clinical trials, and receipt of contemporary oncology treatment regimens. In addition, these datasets reflected a variety of symptom assessment measures, thereby increasing confidence in the generalizability of our conclusions.

Symptom prevalence and severity were then tabulated using findings from the systematic literature review and the primary datasets. Based on the literature review and analysis of the datasets, a panel of experts (represented by the authors of this article) came to consensus on a first draft of recommendations for symptoms to be measured across disease sites to be presented for stakeholder input. Additional criteria considered by the expert panel in proposing a provisional core set of symptoms are provided in Table 2.

Multistakeholder CTPM

To solicit multistakeholder input on the draft recommendations, in September 2011, the NCI's Symptom Management and Health-Related Quality of Life Steering Committee sponsored a CTPM to address two aims: 1) identify a recommended core set of patient-reported symptoms to be assessed in cancer clinical trials and 2) identify a core set of site-specific symptoms and/or HRQOL domains that should be assessed in clinical trials for head and neck, prostate, and ovarian cancers. The meeting included interdisciplinary investigators in cancer outcomes research and clinical trials, representing expertise in developmental therapeutics, cancer symptom and HRQOL assessment, measurement methodology, and statistics, as well as representatives from the patient advocacy community, clinical trial cooperative group administration, the pharmaceutical industry, the NCI, and the US Food and Drug Administration.

At the CTPM, the four expert panels (one tasked with identifying the cross-cutting patient-reported symptoms and three others tasked with identifying PRO domains for head and neck, prostate, and

Table 1. Characteristics of datasets*

Characteristic	CDUS/AdEERS	EORTC	SOAPP	PRO-CTCAE	FACT
Data type	Clinician-reported adverse events in NCI clinical trial systems database (CDUS and AdEERS)	Patient-reported symptom data from EORTC trials and other research studies. These data were also used to derive QLQ-C30 reference values	Patient-reported symptom data from cooperative group study	Patient-reported symptom data from instrument validation study in cancer	Patient-reported symptom importance for monitoring
Measure	CTCAE	EORTC-QLQ-C30	MDASI	PRO-CTCAE	FACT-G and other HRQOL questions
Measure type	Clinician-reported	Patient-reported	Patient-reported	Patient-reported	Patient-reported
Sample size	449672 AE reports	23553 patients	3123 patients	595 patients	533 patients
Years of data	2004–2008	1992–2006	2006–2008	January–August 2011	2011
Cancer cite	Multiple cancer sites (details not available)	14% lung, 14% prostate, 12% breast, 12% other, 8% colorectal, 8% esophagus/stomach, 5% gynecological, 5% melanoma, 5% unknown, 4% myeloma, 3% head & neck, 2% leukemia, 2% liver, 2% lymphoma, 2% testicular, 1% brain, 1% kidney, 1% pancreas; <1% each of bladder, bone, and sarcoma	50% breast, 23% colorectal, 17% lung, 10% prostate	21% breast, 20% lung, 17% head or neck, 12% prostate, 7% colorectal, and 23% other cancer types	10% breast, 10% ovarian, 9% brain, 9% colorectal, 9% head and neck, 9% hepatobiliary, 9% kidney, 9% lung, 9% lymphoma, 9% prostate, 6% bladder
Disease stage	Not available	20% stage I–II; 34% stage III–IV; 20% recurrent/metastatic disease	38% advanced disease	Not available	100% stage III–IV
ECOG PS rating	Not available	Not available	ECOG 0: 57% ECOG 1: 36% ECOG 2–4: 7%	ECOG 0–1: 77% ECOG 2–4: 23%	ECOG 0: 23% ECOG 1: 48% ECOG 2: 25% ECOG 3: 4%
Sex	Not available	46% female	70% female	53% female	48% female
Age	Not available	>54% aged 60 years or older	Median of 61 years	Mean of 59 years	Mean of 59 years

* AE = adverse event; CDUS = Clinical Data Update System; AdEERS = Adverse Event Expedited Reporting System; CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organization for the Research and Treatment of Cancer; FACT = Functional Assessment of Cancer Therapy; FACT-G = Functional Assessment of Cancer Therapy-General; HRQOL = health-related quality of life; MDASI = MD Anderson Symptom Inventory; NCI = National Cancer Institute; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer - Quality of Life Questionnaire - Core 30; SOAPP = Symptom Outcomes and Practice Patterns study.

Table 2. Criteria for inclusion of a symptom in the proposed core set

- Rank ordered within the top 10 symptoms based on prevalence, severity, and/or importance ratings in at least two data sources
- Present across diverse cancer populations
- Attributable to either disease or to anticancer treatment
- Sensitive to change
- Measurable from the patient perspective

ovarian cancers) reported results of the systematic literature reviews and presented the rank-ordering of the prevalence or importance of the PRO domains based on analysis of the datasets. From the literature review and the empirically derived rankings, a provisional list of symptoms to be measured across all disease sites was proposed for discussion. To be included in the provisional list, the symptom must have met the criteria listed in [Table 2](#). Feedback from CTPM participants was collected for subsequent review by the expert panels.

Expert Panel Deliberations After the Meeting and Endorsement by Relevant NCI Committees

After the consensus meeting, the expert panel finalizing the cross-cutting patient-reported symptoms met monthly by teleconference between February 2011 and August 2012. The literature synthesis, analysis of data, and stakeholder CTPM feedback were considered on a symptom-by-symptom basis to identify a parsimonious final core symptom set. To be included in this final core set, the symptom

must have met the criteria listed in [Table 2](#) and be endorsed by participants at the stakeholder meeting. The expert panel also recommended that the core set be as small as possible to limit respondent burden. In their deliberations, the expert panel also established that the core symptom set should be assessed alongside other hypothesis-driven disease- and treatment-targeted symptom, functioning, and HRQOL domains, when appropriate.

The recommended core symptom set for adult cancer treatment trials was endorsed by NCI's Symptom Management and Health-Related Quality of Life Steering Committee, Clinical and Translational Research Operations Committee, and Clinical Trials and Translational Research Advisory Committee.

Results

Data from the systematic literature review and datasets were summarized and presented to the stakeholder CTPM attendees charged with synthesis of the information and decision-making to prioritize the core symptoms. After the CTPM, the provisional list was finalized by the expert panel, who took into account the five criteria listed in [Table 2](#).

Prevalence and Severity of Symptoms

[Table 3](#) integrates the results of the synthesis across the literature reviews and dataset analyses, detailing the top-ranked symptoms identified from each source based on prevalence, severity, or importance. Terminology mapping from the Medical Dictionary for Regulatory Activities was used to determine synonymous symptom terms across studies that used different nomenclature (eg, dyspnea = shortness of breath; anorexia = decreased appetite).

Final Core Set of Symptoms

The 12 symptoms included in the final core set are listed above the horizontal, bold line in [Table 3](#) and include the following: fatigue, insomnia, pain, anorexia, dyspnea, cognitive problems (includes memory or concentration impairment), anxiety (includes worry), nausea, depression, sensory neuropathy, constipation, and diarrhea. Notwithstanding their prevalence, severity, and/or importance, symptoms that were prevalent in particular subpopulations but not across all diagnostic groups (eg, cough) that might introduce fixed effects because of prior treatment (alopecia) or that reflect nonspecific effects of a variety of medications or comorbidities (eg, dry mouth, drowsiness) were not included in the core list. For parsimony, and because it was reflected in the top 10 most prevalent, severe, or important symptoms in only one dataset, vomiting was excluded from the final set.

Discussion

In many clinical trials, the patients' overall response to therapy may entail the reduction of disease-specific symptoms as well as the development of symptomatic treatment-related complications. Thus, the inclusion of patient reporting provides enhanced understanding of the overall treatment effect. Although there is growing scientific interest in the inclusion of PRO assessments in cancer trials ([33–36](#)), to date, no consensus has been reached with regard to the optimal core set of symptoms that should be considered for

measurement across clinical trials. The consensus-building process described here included a systematic literature review, analysis and synthesis across several large datasets, a multistakeholder meeting with academic, community, government, and patient representation, and an expert panel synthesis and summary of the information.

The result is a recommended core set of 12 symptoms to be considered for inclusion in NCI-sponsored treatment trials that include PROs. It is hoped that both the methodology we used and our study results will help to inform similar strategic planning in other organizations internationally ([37–39](#)) and complement recently proposed guidance for PRO reporting in cancer clinical trials ([40–42](#)). Cancer clinical trials conducted through the NCI Canada Clinical Trials Group and the European Organization for the Research and Treatment of Cancer have developed a systematic approach to the inclusion of PROs in their trials ([43,44](#)).

The principal limitation of this work is the dependence on existing publications and datasets. For a majority of these sources, the number and characteristics of the symptoms being assessed was constrained as a function of the questionnaire that was used. However, other data sources we examined ([30](#)) used qualitative work to identify important symptoms in an open-ended and patient-centered fashion. Our source materials may also have introduced a risk of bias because they may not fully reflect the patient experience of less common cancers or of treatments developed after 2008. Although this work is limited to adult populations, parallel work is identifying important symptoms in pediatric oncology populations ([45](#)). We also acknowledge that symptoms are not the only important HRQOL concern to consider in clinical trials. The group recognizes that physical, mental, and social functioning are other important potential outcomes to measure.

A quandary was whether to restrict the core set to those symptoms that are direct consequences of a specific cancer-directed therapy (eg, nausea, neuropathy). Ultimately, we elected to include the direct effects of treatment and aspects of the patient experience (eg, anxiety, fatigue) that reflect general disease effects but that also may vary as a function of treatment-related toxicity or the worsening or improvement of tumor-related symptoms (ie, symptomatic therapeutic response). In addition to being prevalent and important symptoms, anxiety and depression represent aspects of the cancer experience that may be worsened or improved by cancer-directed therapy, and we argue that capturing such change is relevant to trial-level interpretations of treatment benefits and burdens ([46,47](#)) and can provide valuable information to explain trial dropout, nonadherence, toxicity-related treatment delays, and missing data ([48](#)) or for subgroup analysis ([49](#)).

Several important considerations accompany these recommendations. These recommendations are not a directive to measure symptoms or any PRO in every trial. As with any other trial endpoint, PROs should be included when they are expected to contribute meaningfully to addressing a trial's research questions. The inclusion of a PRO should be well justified and hypothesis driven and should include an analysis plan that details how the results will inform interpretation of therapeutic or toxicity endpoints or how the data will develop new knowledge about the patient experience with a particular treatment approach. These recommendations address the value of a common, consistent, patient-reported symptom documentation across cancer

Table 3. Symptom summaries across literature reviews and secondary data sources (selected core symptoms above horizontal line)*

Symptom	Literature reviews						Data sources										
	Reilly et al.†			Kim et al.‡			CDUS/AdEERS§		EORTC		SOAPP¶		PRO-CTCAE#		FACT**		
	Prevalence %	rank	Severity mean	Prevalence %	rank	Prevalence %	rank	Prevalence %	rank	Prevalence %	rank	Prevalence %	rank	Prevalence %	rank	Importance %	rank
Fatigue	60	1	4.6	62	1	6.2	2	32	2	34	1	58	1	48	1		
Insomnia	49	2	4.2	41	4	0.6	17	25	4	27	2	35	3	16	5		
Pain	48	3	3.4	40	5	7.7	1	25	3	19	5	42	2	11	6		
Anorexia	45	5	3.9	32	3	2.2	5	18	6	17	9	34	4	6	7		
Dyspnea	44	6	2.8	26	12	1.8	7	15	7	15	7	19	15	4	8		
Cognitive problems	44	7	3.1	25	13			14	10	17	9	21	13	3	11		
Anxiety	41	9		54	2			32	1	19	5	31	6	26	3		
Nausea	40	10	2.5	21	15	3.3	3	9	12	12	12	22	12	21	4		
Depression			2.7	39	6			19	5	17	9	26	10	27	2		
Neuropathy				29	10	1.9	6			19	5	19	16				
Constipation				27	11	1.4	11	14	9			30	7	4	9		
Diarrhea				16	17	3.1	4	6	13			25	11	4	10		
Dry mouth	48	4	3.5	42	3			15	8	19	5	32	5				
Irritability				37	7												
Drowsiness				36	8					22	3						
Coughing				26	12	1.0	13										
Taste alteration				23	14	0.6	19					28	9				
Itching				23	14												
Dizziness				20	16	0.5	20										
Vomiting				13	18	1.7	8	14	14	20	4	8	19				
Alopecia						1.5	9					30	7				
Headache												20	14				

Blanks indicate either the symptom was not measured in the study or not reported.

* Selected core symptoms are shown above the horizontal line. CDUS/AdEERS = Clinical Data Update System/Adverse Event Expedited Reporting System; EORTC = European Organization for the Research and Treatment of Cancer; FACT = Functional Assessment of Cancer Therapy; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; SOAPP = Symptom Outcomes and Practice Patterns study.

† Reilly et al. (24) literature review of 21 published studies from 2001 to 2011.

‡ Kim et al. (14) literature review of 18 published studies from 1990 to 2007.

§ Reported percentages are percentage of all clinician-reported adverse events (n = 449672).

|| Reported percentages of 23 553 cancer patients reporting "quite a bit" or "very much," reflecting moderate to severe symptom intensity.

¶ Reported percentages of 3106 cancer patients reporting moderate to severe symptom severity.

Reported percentages of 595 patients reporting frequency of occasionally or more for diarrhea; somewhat or more for amount of hair loss; and moderate or higher severity for the remaining 17 symptoms.

** Reported percentages of 533 cancer patients ranking symptoms as most concerning.

clinical trials. Consistent use will provide a standardized reporting approach to evaluate symptoms to promote discovery and test hypotheses, facilitate data harmonization, and allow for cross-trial comparisons and meta-analyses.

Second, specific contexts will warrant evaluation of additional symptoms and HRQOL domains beyond this core symptom set. These contexts may be shaped by cancer type, disease stage, treatment type, or other characteristics of a study population or a particular study design. For example, as a component of the current initiative, additional HRQOL domains for use alongside the core symptoms in three specific disease settings (ovarian, prostate, and head and neck cancers) were identified and are reported in this issue of the Journal (50–52).

Third, there exists an array of available PRO measures to assess symptoms in oncology research (53,54), and these measures have been developed through varying approaches (29,30,54,55). This initiative does not prescribe which specific measure(s) should be used to assess the core symptoms, nor does it recommend the intervals at which symptom data should be collected or advocate for particular approaches to parameterizing, analyzing, or interpreting symptom outcomes (36,56–58). This initiative also does not specify which symptom characteristic(s) (eg, frequency, severity/intensity, bother) should be measured and does not specify whether summative scores, subscale scores, composite endpoints, or symptom clusters offer the best approach to representing symptoms (56,59). Thus, adoption of these symptom domains for measurement across trials will not fully resolve all aspects of measurement heterogeneity (36,42). Continued research is needed to refine and validate in specific treatment contexts symptom measures that encompass these 12 core symptoms and to define which symptom attributes most precisely and efficiently capture diverse symptom experiences. Research is also needed to develop novel analytic approaches to integrate symptoms into the evaluation of therapeutic response and treatment toxicity (36).

Lastly, parsimonious and efficient data collection techniques (eg, conditional branching, computerized-adaptive testing) are essential to optimize response rates and reduce missing data due to participant nonresponse, particularly for follow-up data and in populations at the end of life (60,61). With 12 core symptoms, several additional context-specific symptoms, and items to represent HRQOL and functional status, an item count near 25 items is conceivable. For most patients, completing this number of items by paper-, computer-, or phone-based systems takes less than 10 minutes and is generally well tolerated, even among those with severe symptoms, advanced disease, or impaired performance status (62–64). Additional feasibility investigations are needed to gauge the burden of data collection for clinical trial investigators responsible for ensuring that patients complete the scheduled PROs, burden to the cooperative groups for monitoring data quality and missing data, and burden to statistical centers for additional data management and analysis of PROs. It will also be important to assess how practical this is across the disease and treatment continuum and to identify cost-effective technologies and follow-up strategies to minimize missing data.

The overall goal of this initiative is to advance the science of PRO measurement and enhance our understanding of the patient experience with disease and treatment as reported directly by

patients. The contemporary emphasis on evidence-driven health-care delivery and a research context where data sharing, data pooling, and interoperability of datasets are essential make this effort particularly timely. Combining studies and datasets based on common metrics is increasingly important in determining efficacy, toxicity, and safety and for making comparisons across treatment options. Ultimately, increased consistency of symptom assessment across trials will contribute to building a more comprehensive evidence base, allow for linkage of PROs to biomarkers and clinical outcomes, and provide an opportunity to improve care quality by promoting increased attention to quality-of-life concerns and facilitating integration of supportive care (65) for cancer clinical trial participants.

References

1. Ederly M, Fojo T. Is there room for improvement in adverse event reporting in the era of targeted therapies? *J Natl Cancer Inst.* 2008;100(4):240–242.
2. Berry DL. Patient-reported symptoms and quality of life integrated into clinical cancer care. *Semin Oncol Nurs.* 2011;27(3):203–210.
3. Gebbia V, Bellavia G, Ferrau F, Valerio MR. Adherence, compliance and persistence to oral antineoplastic therapy: a review focused on chemotherapeutic and biologic agents. *Expert Opin Drug Saf.* 2012;11(Suppl 1):S49–S59.
4. Gotay C, Dunn J. Adherence to long-term adjuvant hormonal therapy for breast cancer. *Expert Rev Pharmacoecon Outcomes Res.* 2011;11(6):709–715.
5. Oberguggenberger A, Hubalek M, Sztankay M, et al. Is the toxicity of adjuvant aromatase inhibitor therapy underestimated? Complementary information from patient-reported outcomes (PROs). *Breast Cancer Res Treat.* 2011;128(2):553–561.
6. Cockle-Hearne J, Faithfull S. Self-management for men surviving prostate cancer: a review of behavioural and psychosocial interventions to understand what strategies can work, for whom and in what circumstances. *Psychooncology.* 2010;19(9):909–922.
7. Hsiao CP, Loescher LJ, Moore IM. Symptoms and symptom distress in localized prostate cancer. *Cancer Nurs.* 2007;30(6):E19–E32.
8. Penson DF. Quality of life following prostate cancer treatments. *Curr Urol Rep.* 2000;1(1):71–77.
9. Singh J, Trabulsi EJ, Gomella LG. The quality-of-life impact of prostate cancer treatments. *Curr Urol Rep.* 2010;11(3):139–146.
10. Kubrak C, Olson K, Jha N, et al. Nutrition impact symptoms: key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. *Head Neck.* 2010;32(3):290–300.
11. Lokker ME, Offerman MP, van der Velden LA, de Boer MF, Pruyn JF, Teunissen SC. Symptoms of patients with incurable head and neck cancer: prevalence and impact on daily functioning. *Head Neck.* 2013;35(6):868–876.
12. Gilbertson-White S, Aouizerat BE, Jahan T, Miaskowski C. A review of the literature on multiple symptoms, their predictors, and associated outcomes in patients with advanced cancer. *Palliat Support Care.* 2011;9(1):81–102.
13. Johnsen AT, Petersen MA, Pedersen L, Groenvold M. Symptoms and problems in a nationally representative sample of advanced cancer patients. *Palliat Med.* 2009;23(6):491–501.
14. Kim JEE, Dodd MJ, Aouizerat BE, Jahan T, Miaskowski C. A review of the prevalence and impact of multiple symptoms in oncology patients. *J Pain Symptom Manage.* 2009;37(4):715–736.
15. Linden W, Vodermaier A, Mackenzie R, Greig D. Anxiety and depression after cancer diagnosis: prevalence rates by cancer type, gender, and age. *J Affect Disord.* 2012;141(2–3):343–351.
16. Rangwala F, Zafar SY, Abernethy AP. Gastrointestinal symptoms in cancer patients with advanced disease: new methodologies, insights, and a proposed approach. *Curr Opin Support Palliat Care.* 2012;6(1):69–76.
17. Center for Medical Technology Policy. Recommendations for incorporating patient-reported outcomes (PROs) into clinical comparative

- effectiveness research (CER) in adult oncology. http://www.cmtpnnet.org/docs/resources/PRO_EGD.pdf. Accessed April 30, 2013.
18. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>. Accessed April 30, 2013.
 19. PCORI. PCORI methodology standards. <http://www.pcori.org/assets/PCORI-Methodology-Standards.pdf>. Accessed April 30, 2013.
 20. NQF. Patient-reported outcomes in performance measurement. http://www.qualityforum.org/Publications/2012/12/Patient-Reported_Outcomes_in_Performance_Measurement.aspx. Accessed April 30, 2013.
 21. Basch E, Abernethy AP, Mullins CD, et al. Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. *J Clin Oncol*. 2012;30(34):4249–4255.
 22. Reeve BB, Wyrwich KW, Wu AW, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. *Qual Life Res*. 2013;22(8):1889–1905.
 23. Ahmed S, Berzon RA, Revicki DA, et al. The use of patient-reported outcomes (PRO) within comparative effectiveness research: implications for clinical practice and health care policy. *Med Care*. 2012;50(12):1060–1070.
 24. Reilly CM, Bruner DW, Mitchell SA, et al. A literature synthesis of symptom prevalence and severity in persons receiving active cancer treatment. *Support Care Cancer*. 2013;21(6):1525–1550.
 25. McCorkle R, Young K. Development of a symptom distress scale. *Cancer Nurs*. 1978;1(5):373–378.
 26. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer*. 2000;89(7):1634–1646.
 27. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *Eur J Cancer*. 1994;30A(9):1326–1336.
 28. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365–376.
 29. European Organisation for Research and Treatment of Cancer Quality of Life Group. EORTC QLQ-C30 reference values. http://groups.eortc.be/qol/sites/default/files/img/newsletter/reference_values_manual2008.pdf. Accessed January 25, 2013.
 30. Cella D, Rosenbloom SK, Beaumont JL, et al. Development and validation of 11 symptom indexes to evaluate response to chemotherapy for advanced cancer. *J Natl Compr Canc Netw*. 2011;9(3):268–278.
 31. Bruner DW, Hanisch LJ, Reeve BB, et al. Stakeholder perspectives on implementing the National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Transl Behav Med*. 2011;1(1):110–122.
 32. Fisch MJ, Lee JW, Weiss M, et al. Prospective, observational study of pain and analgesic prescribing in medical oncology outpatients with breast, colorectal, lung, or prostate cancer. *J Clin Oncol*. 2012;30(16):1980–1988.
 33. Bruner DW. Outcomes research in cancer symptom management trials: the Radiation Therapy Oncology Group (RTOG) conceptual model. *J Natl Cancer Inst Monogr*. 2007;2007(37):12–15.
 34. Lipscomb J, Donaldson MS, Hiatt RA. Cancer outcomes research and the arenas of application. *J Natl Cancer Inst Monogr*. 2004;2004(33):1–7.
 35. Bruner DW, Bryan CJ, Aaronson N, et al. Issues and challenges with integrating patient-reported outcomes in clinical trials supported by the National Cancer Institute-sponsored clinical trials networks. *J Clin Oncol*. 2007;25(32):5051–5057.
 36. Cleeland CS, Sloan JA, Cella D, et al. Recommendations for including multiple symptoms as endpoints in cancer clinical trials: a report from the ASCPRO (Assessing the Symptoms of Cancer Using Patient-Reported Outcomes) Multisymptom Task Force. *Cancer*. 2013;119(2):411–420.
 37. Howell D, Fitch M, Bakker D, et al. Core domains for a person-focused outcome measurement system in cancer (PROMS-Cancer Core) for routine care: a scoping review and Canadian Delphi Consensus. *Value Health*. 2013;16(1):76v87.
 38. Macefield RC, Avery KN, Blazeby JM. Integration of clinical and patient-reported outcomes in surgical oncology. *Br J Surg*. 2013;100(1):28–37.
 39. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials*. 2012;13:132.
 40. Brundage M, Blazeby J, Revicki D, et al. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. *Qual Life Res*. 2013;22(6):1161–1175.
 41. Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA*. 2013;309(8):814–822.
 42. Kyte DG, Draper H, Ives J, Liles C, Gheorghe A, Calvert M. Patient reported outcomes (PROs) in clinical trials: is “in-trial” guidance lacking? A systematic review. *PLoS One*. 2013;8(4):e60684.
 43. Brundage M, Osoba D, Bezjak A, et al. Lessons learned in the assessment of health-related quality of life: selected examples from the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2007;25(32):5078–5081.
 44. Bottomley A, Aaronson NK, European Organisation for Research and Treatment of Cancer. International perspective on health-related quality-of-life research in cancer clinical trials; the European Organisation for Research and Treatment of Cancer experience. *J Clin Oncol*. 2007;25(32):5082–5086.
 45. Reeve BB, Withycombe JS, Baker JN, et al. The first step to integrating the child's voice in adverse event reporting in oncology trials: a content validation study among pediatric oncology clinicians. *Pediatr Blood Cancer*. 2013;60(7):1231–1236.
 46. Kenna HA, Poon AW, de los Angeles CP, et al. Psychiatric complications of treatment with corticosteroids: review with case report. *Psychiatry Clin Neurosci*. 2011;65(6):549–560.
 47. Sjoquist KM, Friedlander ML, O'Connell RL, et al. Hope, quality of life, and benefit from treatment in women having chemotherapy for platinum-resistant/refractory recurrent ovarian cancer: the gynecologic cancer intergroup symptom benefit study. *Oncologist*. 2013;18(11):1221–1228.
 48. Hoppe S, Rainfray M, Fonck M, et al. Functional decline in older patients with cancer receiving first-line chemotherapy. *J Clin Oncol*. 2013;31(31):3877–3882.
 49. Joseph LA, Routledge JA, Burns MP, et al. Value of the Hospital Anxiety and Depression Scale in the follow up of head and neck cancer patients. *J Laryngol Otol*. 2013;127(3):285–294.
 50. Donovan KA, Donovan HS, Cella D, et al. Recommended patient-reported core set of symptoms and other quality of life domains to measure in ovarian cancer treatment trials. *J Natl Cancer Inst*. 2014;106(7): dju128 doi:10.1093/jnci/dju128.
 51. Chen RC, Chang P, Vetter RJ, et al. Recommended patient-reported core set of symptoms to measure in prostate cancer treatment trials. *J Natl Cancer Inst*. 2014;106(7): dju132 doi:10.1093/jnci/dju132.
 52. Chera BS, Eisbruch A, Murphy BA, et al. Recommended patient-reported core set of symptoms to measure in head and neck cancer treatment trials. *J Natl Cancer Inst*. 2014;106(7): dju127 doi:10.1093/jnci/dju127.
 53. Kaasa S, Loge JH, Fayers P, et al. Symptom assessment in palliative care: a need for international collaboration. *J Clin Oncol*. 2008;26(23):3867–3873.
 54. Kirkova J, Davis MP, Walsh D, et al. Cancer symptom assessment instruments: a systematic review. *J Clin Oncol*. 2006;24(9):1459–1473.
 55. Cleeland CS, Sloan JA, ASCPRO Organizing Group. Assessing the Symptoms of Cancer Using Patient-Reported Outcomes (ASCPRO): searching for standards. *J Pain Symptom Manage*. 2010;39(6):1077–1085.
 56. Kirkova J, Aktas A, Walsh D, Davis MP. Cancer symptom clusters: clinical and research methodology. *J Palliat Med*. 2011;14(10):1149–1166.
 57. Nguyen J, Cramarossa G, Bruner D, et al. A literature review of symptom clusters in patients with breast cancer. *Expert Rev Pharmacoecon Outcomes Res*. 2011;11(5):533–539.
 58. Wyrwich KW, Norquist JM, Lenderking WR, Acaster S, ISOQOL. Methods for interpreting change over time in patient-reported outcome measures. *Qual Life Res*. 2013;22(3):475–483.
 59. Hinds PS, Schum L, Srivastava DK. Is clinical relevance sometimes lost in summative scores? *West J Nurs Res*. 2002;24(4):345–353.

60. Hagen NA, Biondo PD, Brasher PM, Stiles CR. Formal feasibility studies in palliative care: why they are important and how to conduct them. *J Pain Symptom Manage*. 2011;42(2):278–289.
61. Rolstad S, Adler J, Ryden A. Response burden and questionnaire length: is shorter better? A review and meta-analysis. *Value Health*. 2011;14(8):1101–1108.
62. Basch E, Iasonos A, Barz A, et al. Long-term toxicity monitoring via electronic patient-reported outcomes in patients receiving chemotherapy. *J Clin Oncol*. 2007;25(34):5374–5380.
63. Hjermstad MJ, Lie HC, Caraceni A, et al. Computer-based symptom assessment is feasible in patients with advanced cancer: results from an international multicenter study, the EPCRC-CSA. *J Pain Symptom Manage*. 2012;44(5):639–654.
64. Khanna D, Krishnan E, Dewitt EM, Khanna PP, Spiegel B, Hays RD. The future of measuring patient-reported outcomes in rheumatology: Patient-Reported Outcomes Measurement Information System (PROMIS). *Arthritis Care Res (Hoboken)*. 2011;63(S11):S486–S490.
65. Meyers FJ, Linder J, Beckett L, Christensen S, Blais J, Gandara DR. Simultaneous care: a model approach to the perceived conflict between investigational therapy and palliative care. *J Pain Symptom Manage*. 2004;28(6):548–556.

Notes

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