

# Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms

Paul G. Kluetz<sup>1</sup>, Ashley Slagle<sup>2</sup>, Elektra J. Papadopoulos<sup>2</sup>, Laura Lee Johnson<sup>3</sup>, Martha Donoghue<sup>1</sup>, Virginia E. Kwitkowski<sup>1</sup>, Wen-Hung Chen<sup>2</sup>, Rajeshwari Sridhara<sup>3</sup>, Ann T. Farrell<sup>1</sup>, Patricia Keegan<sup>1</sup>, Geoffrey Kim<sup>1</sup>, and Richard Pazdur<sup>1</sup>

## Abstract

Cancer clinical trials have relied on overall survival and measures of tumor growth or reduction to assess the efficacy of a drug. However, benefits are often accompanied by significant symptomatic toxicities. The degree to which a therapy improves disease symptoms and introduces symptomatic toxicity affects how patients function in their daily lives. These concepts are important contributors to health-related quality of life (HRQOL). In this article, we discuss patient-reported outcome (PRO) assessment in cancer trials and challenges relying solely on static multi-item HRQOL instruments. We propose focusing on three separate measures of well-defined concepts: symptomatic adverse events, physical function, and disease-related symptoms, which are key

contributors to the effect of a therapy on HRQOL. Separate measures of these three concepts may facilitate the incorporation of emerging contemporary instruments that can tailor the PRO assessment strategy to different trial contexts. Irrespective of the PRO measures used, continued improvement in trial design and conduct is crucial to decrease missing data and optimize the quality of PRO information. International stakeholder collaboration and continued research into optimal practices for PRO and other clinical outcome assessments are necessary to advance a common framework for generating and reporting rigorous patient-centered data from cancer clinical trials. *Clin Cancer Res*; 22(7); 1553–8. ©2016 AACR.

## Introduction

Oncology drug development has benefitted from an ability to visualize malignancies, whether by radiographic means or microscopic evaluation of the blood or bone marrow. However, although objective endpoints such as response rate, progression-free survival, and overall survival (OS) have aided our ability to evaluate anticancer drugs, the availability of these endpoints has, in some ways, reduced the incentive to rigorously evaluate clinical outcome assessments in oncology trials. There is an increasing realization that accurate measurement of how patients feel and function can provide important additional information to assess the benefits and risks of cancer therapies. Oncology trials have standardized and iteratively improved the measures of

radiographic endpoints using RECIST (1) and clinician-reported safety data using Common Terminology Criteria for Adverse Events (CTCAE; ref. 2). There is now a need to reexamine the measurement tools available to assess key health-related contributors to the quality of life of patients in oncology clinical trials. In this article, we offer our perspective on patient-reported outcomes (PRO) and propose a PRO strategy that focuses on separate measures of well-defined concepts—symptomatic adverse events, physical function, and disease-related symptoms—that are key contributors to the effect of a therapy on health-related quality of life (HRQOL).

PROs are reports of the status of a patient's health condition that come directly from the patient, without interpretation of the patient's response by a clinician or anyone else (3). A PRO measure can be used to assess concepts that may be narrow (e.g., pain intensity) or broad (e.g., HRQOL). HRQOL is a multidomain concept representing the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life (3). The PRO effort in oncology has primarily focused on measuring HRQOL in the clinical trial setting. Instruments used to measure HRQOL are typically large multidomain assessments, in the order of 30 or more questions, that attempt to evaluate the many different contributors to this broad concept.

Many of the commonly used cancer-targeted HRQOL measures were developed in a prior therapeutic era dominated by cytotoxic chemotherapy (4–6). These instruments share some strengths, including available language translations and a familiarity among investigators and trial sponsors generated from years of

<sup>1</sup>Office of Hematology and Oncology Products, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland. <sup>2</sup>Clinical Outcome Assessment Staff, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland. <sup>3</sup>Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland.

**Note:** This is a U.S. Government work. There are no restrictions on its use.

**Corresponding Author:** Paul G. Kluetz, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, WO22 Room 2223, Silver Spring, MD 20993. E-mail: paul.kluetz@fda.hhs.gov

doi: 10.1158/1078-0432.CCR-15-2035

©2016 American Association for Cancer Research.

incorporation in cancer trials. However, while work has been done to support the use of these measures in different contexts using multiple disease modules, the instruments and their modules are largely "static"; the questions are the same, irrespective of the disease stage or therapies being studied. This lack of flexibility, particularly with respect to symptomatic toxicities, can be problematic in an era of novel therapies with multiple mechanistic classes and unique symptomatic adverse events.

The use of HRQOL as a primary objective in cancer trials is further complicated by the need to measure domains considered distal from the effect of the drug on the patient and the patient's disease, such as social and family well-being, to completely capture this broad concept. Although questions addressing social and family well-being are important to patients and contribute to HRQOL, many non-drug-related contributors to social and family status can confound existing HRQOL measures. These issues may make an HRQOL endpoint less sensitive to the positive or negative effects of an investigational therapy on the patient.

### Focusing on Core Concepts That Are Key Contributors to HRQOL

We have begun to consider an approach that focuses PRO analyses on key elements of HRQOL by concentrating on the individual measurement of three well-defined concepts that are more proximal to a therapy's effect on the patient and the patient's disease: symptomatic adverse events, physical function, and, where appropriate, a measure of the key symptoms of the disease (Fig. 1). Individually measuring concepts such as symptomatic adverse events can take advantage of contemporary PRO measurement tools that are becoming available. Additional focused clinical outcome assessments unique to a particular malignancy, such as cognitive function in patients with brain tumors or performance-based measures of function (e.g., swallowing in patients with esophageal cancer), may also be important depending on the trial context and objectives.

Focused individual measurement of symptomatic adverse events, physical function, and disease-related symptoms can take advantage of newly developed instruments that can provide increased flexibility to adapt to differing disease and therapy contexts. PRO instruments that appear to be well-suited to this approach include two publicly funded efforts: the PRO version of the CTCAE (PRO-CTCAE) for the description of symptomatic adverse events (7) and the Patient Reported Outcomes Measurement Information System (PROMIS) physical function assessments (8). Each of these instruments contains a library of items and questions, a subset of which can be selected to fit the side-effect profile of the therapy and the baseline functional status of the population.

#### Symptomatic adverse events

Daily oral administration of cancer therapies and prolonged treatment duration have become increasingly common. The assessment of safety may be augmented by a systematic and longitudinal PRO assessment of symptomatic adverse events (9). The NCI PRO-CTCAE is an item library of 78 symptomatic toxicities derived from the CTCAE reporting system developed through a consortium of PRO researchers, clinical investigators, trial sponsors, patient advocates, and the FDA (7). PRO-CTCAE provides a standard yet flexible approach to describe symptomatic adverse events as they are experienced and reported by patients

themselves. The instrument continues to be systematically evaluated, and a recent article reports favorable validity, reliability, and responsiveness in a large group of cancer patients undergoing treatment (10). A small set of symptomatic adverse events relevant to the therapies under study could be selected from the PRO-CTCAE library and the results presented as descriptive data in FDA drug labeling, complementary to routine clinician-reported CTCAE safety data.

The selection of which symptomatic adverse events to measure from the PRO-CTCAE library during the design of a trial is critically important to provide an unbiased presentation of the most important symptomatic toxicities for the therapies being assessed. Importantly, the PRO-CTCAE has the ability for a "write-in" open-ended question, allowing patients to report symptomatic toxicities not selected for routine assessment. Issues being addressed to allow for broader implementation of PRO-CTCAE include the need for language translations, clarifying optimal trial design issues including assessment frequency, determining how or whether real-time PRO-CTCAE data should inform clinical care, and identifying standard analyses and informative methods to present PRO-CTCAE results. Further work is required to consider ways to incorporate PRO-CTCAE as one element of a clinical trial design that would be suitable for evaluation of comparative tolerability in cancer trials.

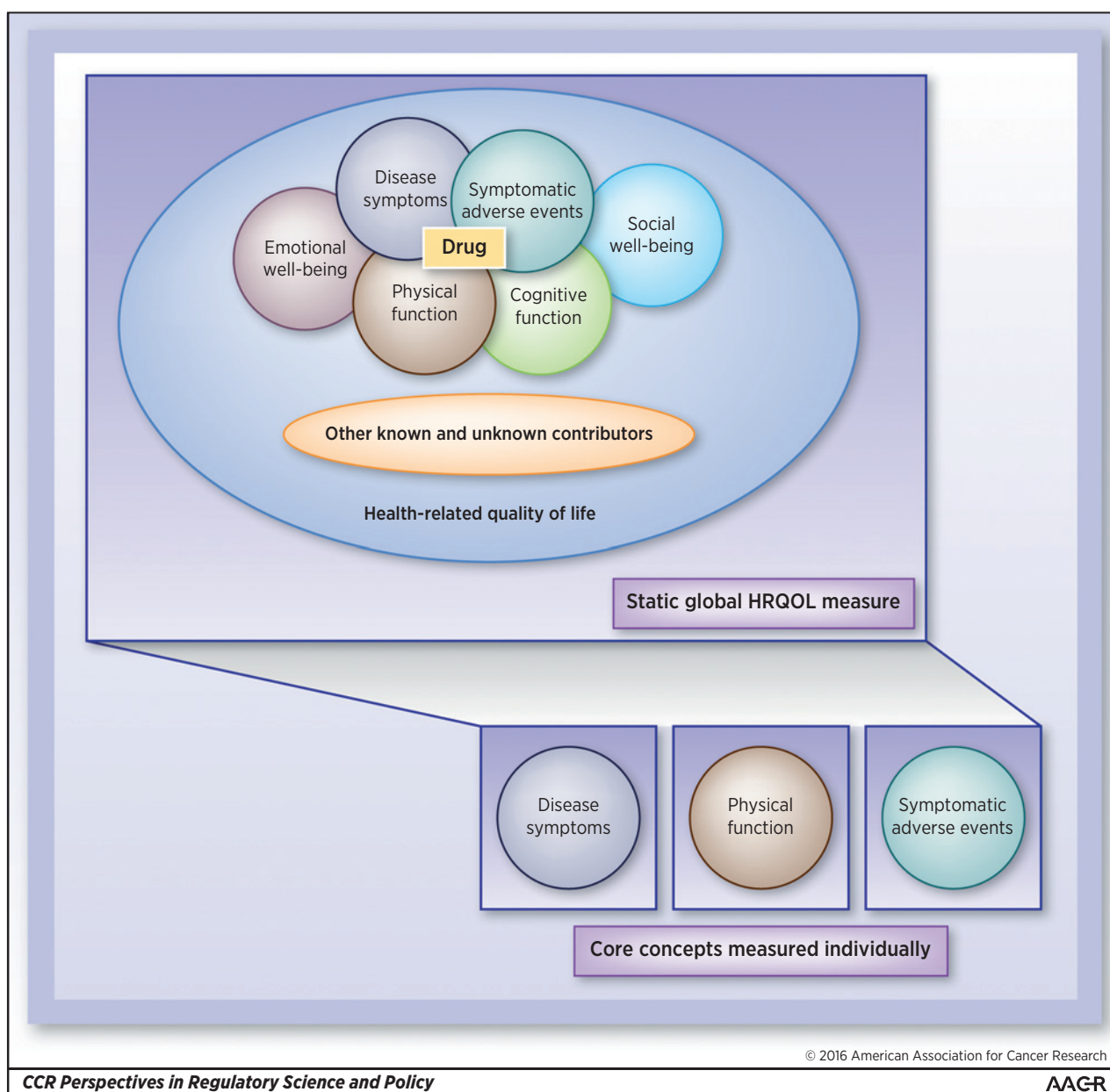
#### Patient-reported physical function

The concept of physical function or the ability to perform activities of daily living is an important aspect of quality of life for cancer patients (11). Physical function can be affected by both disease symptoms and treatment-related adverse events and is included as a domain in most patient-reported HRQOL measures. Although patient-reported physical function impacts are clinically meaningful in and of themselves, different measures of physical function or performance status assessed by investigators (12) and by PRO measures (13) have also been shown to be prognostic for survival across several cancer populations.

Although several options exist for the measurement of physical function in cancer patients, the PROMIS physical function instrument is a domain-based item bank developed using modern psychometric theory, containing questions assessing physical function across a range of baseline functional status. One can either build tailored static short forms (8) or utilize computerized adaptive testing (CAT), either of which can accommodate a broad range of patient functioning and mitigate problems with the ability to detect change at the far ends of the severity continuum (i.e., floor and ceiling effects; ref. 14). Efforts are also under way to use CAT with other instruments to measure physical function in cancer trials (15). Operationalizing the administration of CAT in large multinational trials may be challenging, and additional work is needed to better understand the strengths and limitations of CAT. Finally, although this article focuses on PRO, the use of actigraphy and other noninvasive monitoring of the activity of patients during clinical trial participation is an area of active investigation and could augment PRO results for physical functioning in cancer trials (16).

#### Disease-related symptoms

Several challenges exist in assessing disease-related symptoms in cancer trials. One challenge is the overlap between disease-related symptoms and symptomatic adverse events. For instance,

**Figure 1.**

Core concepts that are key contributors to HRQOL: symptomatic adverse events, physical function, and disease symptoms. The concept of HRQOL is broad and complex. Most current measures attempt to quantify this concept in a single static multi-item instrument with several domains. Focusing analyses on the separate measurement of three well-defined core concepts that are important contributors to HRQOL (disease symptoms, physical function, and symptomatic adverse events) can allow for the use of emerging contemporary instruments, providing a more adaptable PRO strategy across the wide range of oncology disease and therapy contexts.

anorexia is a common advanced cancer symptom but can also be caused by many anticancer therapies. Nonetheless, PRO disease symptom scores have been used successfully in oncology, including the Myelofibrosis Total Symptom Score, which provided key support for the FDA approval of Jakafi (ruxolitinib, Incyte; ref.17). Efforts have been undertaken to identify the key symptoms to measure in several malignant diseases, such as prostate, head and neck, and ovarian cancers (11, 18, 19), and measurement tools continue to be developed and refined.

Several symptoms, including pain, anorexia, and fatigue, appear to be common in patients with advanced cancer as disease progression occurs (20). Although there may be overlap with treatment side effects, these three symptoms may be able to form the basis of many advanced cancer symptom scores. Additional symptoms may be included based on unique characteristics of each disease, such as abdominal symptoms in gastrointestinal malignancies. For example, the Critical Path Institute PRO Consortium is developing a non-small cell lung cancer symptom

assessment questionnaire that has been submitted to the FDA qualification program that includes these three common advanced cancer symptoms (pain, fatigue, and anorexia) in addition to common lung cancer symptoms of dyspnea and cough (21). Further development and patient input are needed to generate new or modify existing disease symptom scores. Selected symptoms should be meaningful to patients, linked to the underlying malignancy, and have the potential to be responsive to effective therapies.

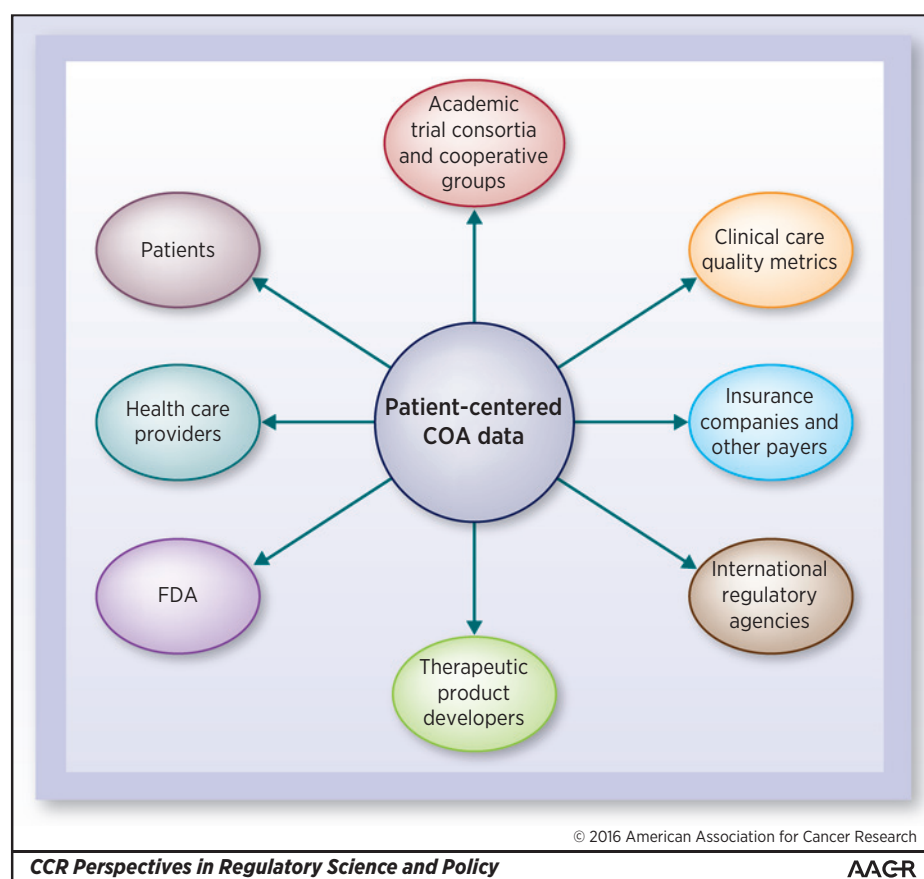
Improvement in disease symptoms can provide important supportive evidence of treatment benefit. However, it must be noted that symptom improvement observed with an anticancer therapy in the absence of evidence of radiographic tumor shrinkage, delay in tumor progression, or benefit in survival provides evidence more consistent with a supportive care indication. The risk tolerance for supportive care therapies is different than for anticancer therapies, and this would be considered when assessing the risks and benefits of a new cancer indication.

Many cancer trials enroll asymptomatic or minimally symptomatic patient populations. The endpoint for these trials may be an analysis of the appearance or worsening of symptoms (time-to-event endpoints), which is more challenging than a symptom palliation endpoint. Trials enriched for symptomatic populations, or supportive data from prespecified subgroup analysis of symptomatic patients, may provide more robust evidence of disease symptom improvement. In either case, if a claim of superiority in disease symptom improvement (or delay in deterioration) is sought, that hypothesis should be tested within the main statistical hierarchy of the clinical trial.

## Meeting the Need for Accurate and Meaningful Patient-Centered Data

In 2012, the FDA Safety and Innovation Act was enacted, and as part of this legislation, the FDA committed to holding public patient-focused drug development meetings with patients who live with a specific disease. During the lung cancer meeting held on June 28, 2013, diverse opinions were expressed between patients regarding endpoints viewed as clinically meaningful. Some patients suggested debilitating symptoms, treatment side effects, and other components of their quality of life were most important, whereas others expressed that an improvement in OS would be most meaningful (22). Although the drug development community has provided robust survival and radiographic data, rigorous collection and analysis of data-informing symptoms and function are less common. Accurate and carefully collected PRO data focusing on key components of HRQOL would provide information to supplement our conventional imaging- and survival-based endpoints to fully inform patients facing cancer treatment decisions.

It should be acknowledged that oncology trials can provide unique challenges for PRO measurement. Many cancer trials are open-label and often receive accelerated approval based on single-arm trials. Although FDA guidance has provided information regarding optimal PRO instrument development and trial design considerations for labeling claims (3), flexibility will be needed to address the unique challenges encountered in oncology trials. Although individual assessment of symptomatic adverse events, physical function, and disease symptoms can take advantage of



**Figure 2.** Multiple cancer drug development stakeholders utilize clinical outcome assessments such as PRO data for differing purposes. International stakeholder collaboration is necessary to identify PRO strategies that address the needs of all parties.



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 trial designs. Regardless of the instruments used or concepts being measured, conveying the importance of the completion of PRO measures to patients, investigators, and research staff may reduce missing data and improve data quality. Additional areas that will require collaborative work include the standardization of both data analysis and presentation of PRO information.

The FDA is only one stakeholder. Patient-centered data from large multinational trials must satisfy multiple parties, including international regulatory agencies, government payers, and private health care plans (Fig. 2). Adding contemporary instruments like the PRO-CTCAE to a battery of questions from unmodified large, static HRQOL and health utility measures is likely to result in a degree of duplication and increased patient burden. Further collaboration between international stakeholders is necessary to review the strengths and limitations of existing and emerging PRO tools to identify efficient strategies to obtain patient-centered data that can satisfy all parties. Further discussion will be critical regarding whether modifications could be made to existing HRQOL instruments to reduce duplication and patient burden by selecting global items or parsimonious domains that assess some of the broader concepts, such as social well-being, emotional well-being, or overall global impression of health, as exploratory supportive data, when such concepts are not the primary objective of the clinical trial (23). The goal should be to achieve a comprehensive evaluation of the patient experience most affected by the therapy, while maximizing the relevance of individual questions and minimizing overall burden and duplication.

## Conclusions

Clinical outcome assessments, such as PRO, can provide important data to support the safety and efficacy of a cancer treatment. Accordingly, we should expect a similar degree of scientific rigor to be applied to the PRO strategy as is expected in assessing conventional measures such as radiographic tumor

assessments. Individual measurement of patient-reported symptomatic adverse events, physical function, and disease symptoms provides important patient-centered data on key components of HRQOL and may be more sensitive to a therapy's effect on the disease and the patient. Several recently developed instruments can be tailored to an individual trial context and can be updated iteratively. Optimization of trial design and conduct to minimize missing data and mitigate bias as well as identification of standard methods to analyze and present PRO data must be undertaken. Although separate measurement of the three core concepts may provide data more applicable to U.S. regulatory requirements, the FDA is only one of the several stakeholders relying on patient-centered data from oncology clinical trials. Collaboration among international stakeholders must aim to balance the needs of all parties and work to increase question relevance and reduce duplication and patient burden. Rigorous patient-focused symptom and function data are needed in cancer clinical trials, and it is critical that we reevaluate available tools and practices to carefully select the most important concepts to measure, and measure them well.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** P.G. Kluetz, A. Slagle, L.L. Johnson, R. Sridhara, R. Pazdur

**Development of methodology:** R. Sridhara

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** R. Sridhara

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** L.L. Johnson, R. Sridhara, P. Keegan, G. Kim, R. Pazdur

**Writing, review, and/or revision of the manuscript:** P.G. Kluetz, A. Slagle, E. J. Papadopoulos, L.L. Johnson, M. Donoghue, V.E. Kwitkowski, W.-H. Chen, R. Sridhara, A.T. Farrell, P. Keegan, G. Kim, R. Pazdur

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** R. Sridhara, R. Pazdur

**Study supervision:** P.G. Kluetz

Received November 13, 2015; revised December 22, 2015; accepted December 24, 2015; published OnlineFirst January 12, 2016.

## References

- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz L, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
- Common terminology criteria for adverse events (CTCAE) version 4.0 [PDF on the Internet]. Bethesda, MD: National Cancer Institute; 2001 [cited 2015 Jul 14]. Available from: [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).
- Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims [PDF on the internet]. Silver Spring, MD: U.S. Food and Drug Administration; 2009 [cited 2015 Jul 14]. Available from: <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>.
- Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;11:570–9.
- Niezgoda HE, Pater JL. A validation study of the domains of the core EORTC quality of life questionnaire. *Qual Life Res* 1993;2:319–25.
- Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle M, Morrissey M, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer* 2000;89:1634–46.
- Basch E, Reeve BB, Mitchell SA, Clauser S, Minasian L, Dueck A, et al. Development of the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Natl Cancer Inst* 2014 Sep 29;106(9).
- Jensen RE, Potosky AL, Reeve BB, Hahn E, Cella D, Fries J, et al. Validation of the PROMIS physical function measures in a diverse US population-based cohort of cancer patients. *Qual Life Res* 2015;24:2333–44.
- Thanarajasingam G, Hubbard JM, Sloan JA, Grothey A. The imperative for a new approach to toxicity analysis in oncology clinical trials. *J Natl Cancer Inst* 2015 Aug 1;107(10).
- Dueck AC, Mendoza TR, Mitchell SA, Reeve BB, Castro K, Rogak L, et al. National Cancer Institute PRO-CTCAE Study Group. Validity and reliability of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *JAMA Oncol* 2015;1:1051–9.
- Donovan KA, Donovan HS, Cella D, Gaines M, Penson R, Plaxe S, et al. Recommended patient-reported core set of symptoms and quality-of-life domains to measure in ovarian cancer treatment trials. *J Natl Cancer Inst* 2014 Jul 8;106(7).

Kluetz et al.

12. Sorensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. *B J Cancer* 1993; 67:773–5.
13. Izano M, Satariano WA, Hiatt RA, Braithwaite D. The impact of functional limitations on long-term outcomes among African-American and white women with breast cancer: a cohort study. *BMJ Open* 2013;3:e003232.
14. Rose M, Bjorner JB, Gandek B, Bruce B, Fries JF, Ware JE Jr. The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency. *J Clin Epidemiol* 2014;67:516–26.
15. Petersen MA, Groenvold M, Aaronson NK, Chie W, Conroy T, Costantini A, et al. Development of computerized adaptive testing (CAT) for the EORTC QLQ-C30 physical functioning dimension. *Qual Life Res* 2011;20:479–90.
16. Fouladiun M, Korner U, Gunnebo L, Sixt-Ammilon P, Bosaeus I, Lundholm K. Daily physical-rest activities in relation to nutritional state, metabolism, and quality of life in cancer patients with progressive cachexia. *Clin Cancer Res* 2007;13:6379–85.
17. Deisseroth A, Kaminskas E, Grillo J, Chen W, Saber H, Lu H, et al. U.S. Food and Drug Administration approval: ruxolitinib for the treatment of patients with intermediate and high-risk myelofibrosis. *Clin Cancer Res* 2012;18:3212–7.
18. Chen RC, Chang P, Vetter RJ, Lukka H, Stokes W, Sanda M, et al. Recommended patient-reported core set of symptoms to measure in prostate cancer treatment trials. *J Natl Cancer Inst* 2014 Jul 8;106(7).
19. Chera BS, Eisbruch A, Murphy BA, Ridge J, Gavin P, Reeve BB, et al. Recommended patient-reported core set of symptoms to measure in head and neck cancer treatment trials. *J Natl Cancer Inst* 2014 Jul 8;106(7).
20. Reeve BB, Mitchell SA, Dueck AC, Basch E, Cella D, Reilly CM, et al. Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. *J Natl Cancer Inst* 2014 Jul 8;106(7).
21. Clinical outcome assessment qualification submissions [about 5 screens] [cited 2015 Jul 14]. Available from: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm450689.htm>.
22. The voice of the patient: lung cancer [PDF on the Internet]. Rockville, MD: U.S. Food and Drug Administration; 2013 [cited 2015 Aug 25]. Available from: <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM379698.pdf>.
23. Sloan JA, Aaronson N, Cappelleri JC, Fairclough DL, Varricchio C; Clinical Significance Consensus Meeting, Group. Assessing the clinical significance of single items relative to summated scores. *Mayo Clinic Proc* 2002;77:479–87.

# Clinical Cancer Research

## Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms

Paul G. Kluetz, Ashley Slagle, Elektra J. Papadopoulos, et al.

*Clin Cancer Res* 2016;22:1553-1558. Published OnlineFirst January 12, 2016.

**Updated version** Access the most recent version of this article at:  
doi:[10.1158/1078-0432.CCR-15-2035](https://doi.org/10.1158/1078-0432.CCR-15-2035)

**Cited articles** This article cites 13 articles, 4 of which you can access for free at:  
<http://clincancerres.aacrjournals.org/content/22/7/1553.full#ref-list-1>

**Citing articles** This article has been cited by 3 HighWire-hosted articles. Access the articles at:  
<http://clincancerres.aacrjournals.org/content/22/7/1553.full#related-urls>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, use this link  
<http://clincancerres.aacrjournals.org/content/22/7/1553>.  
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.